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(54) Title: ANTI-TUMOR ASSOCIATED ANTIGEN ANTIBODIES AND USES THEREOF

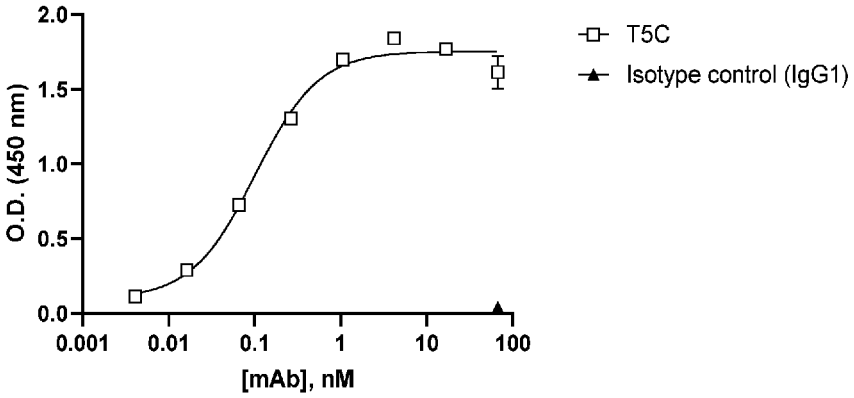

FIG. 1

(57) Abstract: Anti-TAA antibodies and antigen-binding fragments thereof are described. Also described are nucleic acids encoding the antibodies, compositions comprising the antibodies, and methods of producing the antibodies and using the antibodies for treating or preventing diseases such as cancer and/or an inflammatory disease.

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ANTI-TUMOR ASSOCIATED ANTIGEN ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/021,215, filed on May 7, 2020; U.S. Provisional Application No. 62/706,131, filed on August 3, 2020; U.S. Provisional Application No. 63/198,420, filed on October 16, 2020; and U.S. Application No. 63/131,394, filed on December 29, 2020. Each disclosure is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to monoclonal anti-tumor associated antigen (TAA) antibodies, nucleic acids and expression vectors encoding the antibodies, recombinant cells containing the vectors, and compositions comprising the antibodies. Methods of making the antibodies, and methods of using the antibodies to treat diseases including cancer and inflammatory diseases and/or associated complications are also provided.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

[0003] This application contains a sequence listing, which is submitted electronically via EFS-Web as an ASCII formatted sequence listing with a file name "065799.34WO1 Sequence Listing" and a creation date of April 28, 2021 and having a size of 150 kb. The sequence listing submitted via EFS-Web is part of the specification and is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0004] A "tumor-associated antigen (TAA)," refers to any cell surface peptide and/or antigen or a combination of a cell surface peptide and/or antigen and its post-translational modifying moiety (such as glycosylation) that are present at a higher level in a tumor than in normal tissues. Some of the tumor-associated antigens present specifically in tumors are also known as tumor-specific antigens (TSAs). Examples of tumor-associated antigens are viral proteins encoded by oncogenic viruses; mutated oncoproteins or tumor suppressors; normal proteins overexpressed on and/or in tumor cells; post-translational modifications of cell surface proteins; oncofetal proteins, whose expression are normally restricted in developmental stages but not in adult tissues; and cell-type specific proteins, whose expression are limited to unessential tissues.

[0005] Tax-interacting protein 1 (TIP-1, also known as Tax1bp3 or glutaminase-interacting protein, GIP) is a PDZ (PSD-95/Discs large/ZO-1 homologous) domain-containing intracellular protein (124 amino acids in human and mouse). The single PDZ domain encompassing residues

13-112 of the 124-amino acid protein (Olalla, et al., FEBS Lett 2001; 488:116-122) is the only functional and structural unit that can be identified in TIP-1, suggesting that TIP-1 is unique among PDZ-containing proteins and may carry out its function solely through protein-protein interactions. TIP-1 interacts with many intracellular proteins through the PDZ domain, including glutaminase L, β-Catenin, FAS, HTLV Tax, HPV E6, Rhotekin and Kir 2.3 (Zoetewey et al., Biochemistry 2011; 50:3528-3539). However, the precise biological function of TIP-1 remains unclear. Elevated TIP-1 expression was detected in human invasive breast cancer cells and shown to be linked to tumor cell adhesion, migration and pulmonary metastasis (Han et al., Biochem Biophys Res Commun 2012; 422:139-145). Recently, it was found that TIP-1 is translocated to the surface of cancer cells upon induction by irradiation (Yan et al., Oncotarget 2016; 7:43352-43362), suggesting TIP-1 could be a cancer neoantigen upon induction. Thus, an anti-TIP-1 monoclonal antibody (mAb) can be used to target cancer cells with selectivity and to serve as a potential therapeutic.

[0006] Glypican-3 (GPC3) is a GPI-anchored cell surface glycoprotein containing a 66 KDa core protein and two heparan sulfate (HS) glycosaminoglycan polysaccharide chains. It belongs to the glypican family, which has 6 members (GPC1 to GPC6). GPC3 is an oncofetal protein that's only expressed during embryonic development but is overexpressed in > 70% hepatocellular carcinoma (HCC) (Baumhoer, D., et al., Am J Clin Pathol. 2008 Jun; 129(6):899-906). The restricted expression in cancer cells makes GPC3 a tumor specific antigen (TSA) that can be exploited to target cancer cells by monoclonal antibody-based therapies. In addition to its tumor specific expression, GPC3 may also promote tumor growth. GPC3 can regulate the Wnt signaling pathways. The core protein of GPC3 interacts with Wnt and functions as a coreceptor to activate frizzled (FZD) and downstream signaling via β-catenin and YAP (Capurro, MI, et al., Cancer Res. 2005 Jul 15; 65(14):6245-54). Indeed, the Wnt signaling is frequently activated in HCCs (Khalaf, AM., J Hepatocell Carcinoma. 2018; 5:61-73). Thus, GPC3 is a promising therapeutic target to treat HCC and any other cancers overexpressing GPC3.

BRIEF SUMMARY OF THE INVENTION

[0007] In one general aspect, the invention relates to isolated monoclonal antibodies or antigen-binding fragments thereof that specifically bind TAAs such as TIP-1 and GPC3.

[0008] Provided are isolated monoclonal antibodies or antigen-binding fragments thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably human GPC3.

[0009] Provided are isolated monoclonal antibodies or antigen-binding fragments thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably human GPC3.

[0010] Provided are isolated monoclonal antibodies or antigen-binding fragments thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 3, 4, 5, 6, 7, and 8, respectively.

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

[0011] Provided are isolated monoclonal antibodies or antigen-binding fragments thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 9, 10, 11, 12, 13, and 14, respectively.

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

[0012] In certain embodiments, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, 71, or 1, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, 72, or 2.

[0013] In certain embodiments, the isolated monoclonal antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;

(b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107

(c) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;

(d) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;

(e) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;

(f) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58;

(g) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72; or

(h) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

[0014] In certain embodiments, the isolated monoclonal antibody or antigen-binding fragment thereof binds to a TAA and is capable of inducing effector-mediated tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and/or complement-dependent cytotoxicity (CDC); and/or mediating the recruitment of conjugated drugs; and/or forming a bispecific antibody with another monoclonal antibody or antigen-binding fragment thereof with cancer-killing effect.

[0015] In certain embodiments, the isolated monoclonal antibody or antigen-binding fragment thereof is chimeric.

[0016] In certain embodiments, the isolated monoclonal antibody or antigen-binding fragment thereof is human or humanized. In certain embodiments, the humanized monoclonal antibody or

antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

[0017] In certain embodiments, the humanized monoclonal antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
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(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
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(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
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(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

[0018] Also provided are isolated bispecific antibodies comprising the monoclonal antibodies or antigen-binding fragments thereof of the invention.

[0019] Also provided are isolated nucleic acids encoding the monoclonal antibodies or antigen-binding fragments thereof or bispecific antibodies of the invention.

[0020] Also provided are vectors comprising the isolated nucleic acids encoding the monoclonal antibodies or antigen-binding fragments thereof or bispecific antibodies or antigen-binding fragments thereof of the invention.

[0021] Also provided are host cells comprising the vectors comprising the isolated nucleic acids encoding the monoclonal antibodies or antigen-binding fragments thereof or bispecific antibodies or antigen-binding fragments thereof of the invention.

[0022] In certain embodiments, provided is a pharmaceutical composition comprising an isolated monoclonal antibody or antigen-binding fragment thereof or an isolated bispecific

antibody or antigen-binding fragment thereof of the invention and a pharmaceutically acceptable carrier.

[0023] Also provided are methods of specifically targeting a TAA (e.g., TIP-1 or GPC3), on a cancer cell surface in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the invention.

[0024] Also provided are methods of treating cancer in a subject in need thereof, comprising administering to the subject the pharmaceutical compositions of the invention. The cancer can be any liquid or solid cancer, for example, it can be selected from, but not limited to, a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

[0025] Also provided are methods of treating an inflammatory disease in a subject in need thereof, comprising administering to the subject a pharmaceutical composition of the invention.

[0026] Also provided are methods of producing a monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof of the invention, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof, and recovering the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof from the cell or culture.

[0027] Also provided are methods of producing a pharmaceutical composition comprising a monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof of the invention, comprising combining the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

[0028] Also provided are methods of determining the level of a TAA (e.g., TIP-1 or GPC3) in a subject. The methods comprise (a) obtaining a sample from the subject; (b) contacting the sample with an antibody or antigen-binding fragment thereof of the invention; and (c) determining the level of a TAA in the subject. In certain embodiments, the sample is a tissue

sample. The tissue sample can, for example, be a cancer tissue sample. In certain embodiments, the sample is a blood sample.

[0029] In another general aspect, the invention relates to a chimeric antigen receptor (CAR) construct that induces T cell mediated cancer killing, wherein the CAR construct comprises at least one antigen binding domain that specifically binds human GPC3, a hinge region, a transmembrane region, and an intracellular signaling domain.

[0030] Provided are isolated polynucleotides comprising a nucleic acid sequence encoding a chimeric antigen receptor (CAR). The CAR can comprise (a) an extracellular domain comprising at least one antigen binding domain that specifically binds GPC3; (b) a hinge region; (c) a transmembrane region; and (d) an intracellular signaling domain.

[0031] In certain embodiments, the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

[0032] In certain embodiments, the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

[0033] In certain embodiments, the antigen binding domain comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, or 71, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, or 72.

[0034] In certain embodiments, the antigen binding domain comprises:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;
b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;
c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;
f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58; or
g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72.

[0035] In certain embodiments, the antigen binding domain is humanized and comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

[0036] In certain embodiments, the antigen binding domain is humanized and comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;

(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;

(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or

(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

[0037] In certain embodiments, the antigen binding domain is a single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3.

[0038] In certain embodiments, the antigen binding domain is a humanized single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3. In certain embodiments, the humanized single chain variable fragment (scFv) comprises a polypeptide sequence at least 95% identical to any one of SEQ ID NOs:167-182.

[0039] In certain embodiments, the chimeric antigen receptor (CAR) comprises one or more antigen binding domains.

[0040] In certain embodiments, the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

[0041] Also provided are chimeric antigen receptors (CARs) encoded by the isolated polynucleotides of the invention.

[0042] Also provided are vectors comprising the isolated polynucleotides comprising nucleic acids encoding the CARs of the invention.

[0043] Also provided are host cells comprising the vectors of the invention.

[0044] In certain embodiments, the host cell is a T cell, preferably a human T cell. In certain embodiments, the host cell is a NK cell, preferably a human NK cell. The T cell or NK cell can, for example, be engineered to express the CAR of the invention to treat diseases such as cancer.

[0045] Also provided are methods of making a host cell expressing a chimeric antigen receptor (CAR) of the invention. The methods comprise transducing a T cell or a NK cell with a vector comprising the isolated nucleic acids encoding the CARs of the invention.

[0046] Also provided are methods of producing a CAR-T cell or CAR-NK cell of the invention. The methods comprise culturing T cells or NK cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of the

invention under conditions to produce the CAR-T cell or CAR-NK cell, and recovering the CAR-T cell or CAR-NK cell.

[0047] Also provided are methods of generating a population of RNA-engineered cells comprising a chimeric antigen receptor (CAR) of the invention. The methods comprise contacting a cell with the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of the invention, wherein the isolated polynucleotide is an *in vitro* transcribed RNA or synthetic RNA.

[0048] Also provided are methods of treating cancer in a subject in need thereof, comprising administering to the subject the CAR-T cells and/or CAR-NK cells of the invention. The cancer can be any liquid or solid cancer, for example, it can be selected from, but not limited to, a lung cancer, a gastric cancer, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

[0049] In certain embodiments, the methods of treating cancer in a subject in need thereof further comprise administering to the subject in need thereof an agent that increases the efficacy of a cell expressing a CAR molecule.

[0050] In certain embodiments, the methods of treating cancer in a subject in need thereof further comprise administering to the subject in need thereof an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule.

[0051] In certain embodiments, the methods of treating cancer in a subject in need thereof further comprise administering to the subject in need thereof an agent that treats the disease associated with GPC3.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] The foregoing summary, as well as the following detailed description of preferred embodiments of the present application, will be better understood when read in conjunction with the appended drawings. It should be understood, however, that the application is not limited to the precise embodiments shown in the drawings.

[0053] FIG. 1 shows the binding of purified chimeric anti-TIP-1 mAb T5C (VH and VL regions of mouse mAb T5 fused to the constant regions of human IgG1 heavy chain and kappa light chain, respectively) to immobilized TIP-1 in an ELISA assay. The antigen was human TIP-1 tagged with Myc at the C-terminus (Origene, CAT#: TP304776).

[0054] FIGs. 2A-2G show the binding of purified chimeric anti-GPC3 mAbs (VH and VL regions of the mouse anti-GPC3 mAbs fused to the constant regions of human IgG1 heavy chain and kappa light chain, respectively) to GPC3. FIGs. 2A-2B, binding of anti-GPC3 mAbs to immobilized human GPC3 [FLAG-huGPC3-His; human GPC3 (25-559) fusion protein with FLAG at the N-terminus and His tag at the C-terminus)] in an ELISA assay; FIGs. 2C-2E, binding of anti-GPC3 mAbs to a HEK293 stable cell line expressing human GPC3 using FACS analysis; FIGs. 2F-2G, binding of anti-GPC3 mAbs at 26 nM to control HEK293 cells (no exogenously introduced GPC3 expression) using FACS analysis. Isotype control, a negative control antibody; secondary antibody only, only secondary antibody was added in the assay as negative control.

[0055] FIGs. 3A-3O show the binding of humanized anti-GPC3 mAbs to a HEK293 stable cell line expressing human GPC3 using FACS analysis. Isotype control, a negative control antibody; 2nd antibody only, only secondary antibody was added in the assay as negative control. M3-C, the chimeric version of M3; the same naming rule is used for 26A1, 36F8, 39E1, 43B9, and F7.

[0056] FIGs. 4A-4E show the binding of anti-GPC3 scFv molecules to a HEK293 stable cell line expressing human GPC3 using FACS analysis. Isotype control, a negative control antibody; 2nd antibody only, only secondary antibody was added in the assay as negative control.

DETAILED DESCRIPTION OF THE INVENTION

[0057] Various publications, articles and patents are cited or described in the background and throughout the specification; each of these references is herein incorporated by reference in its entirety. Discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is for the purpose of providing context for the invention. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to any inventions disclosed or claimed.

[0058] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification.

[0059] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0060] Unless otherwise stated, any numerical values, such as a concentration or a concentration range described herein, are to be understood as being modified in all instances by the term "about." Thus, a numerical value typically includes ± 10% of the recited value. For example, a concentration of 1 mg/mL includes 0.9 mg/mL to 1.1 mg/mL. Likewise, a concentration range of 1% to 10% (w/v) includes 0.9% (w/v) to 11% (w/v). As used herein, the

use of a numerical range expressly includes all possible subranges, all individual numerical values within that range, including integers within such ranges and fractions of the values unless the context clearly indicates otherwise.

[0061] Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the invention.

[0062] As used herein, the terms "comprises," "comprising," "includes," "including," "has," "having," "contains" or "containing," or any other variation thereof, will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers and are intended to be non-exclusive or open-ended. For example, a composition, a mixture, a process, a method, an article, or an apparatus that comprises a list of elements is not necessarily limited to only those elements but can include other elements not expressly listed or inherent to such composition, mixture, process, method, article, or apparatus. Further, unless expressly stated to the contrary, "or" refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true (or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0063] As used herein, the conjunctive term "and/or" between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two elements are conjoined by "and/or," a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term "and/or" as used herein. Concurrent applicability of more than one of the options is also understood to fall within the meaning, and therefore satisfy the requirement of the term "and/or."

[0064] As used herein, the term "consists of," or variations such as "consist of" or "consisting of," as used throughout the specification and claims, indicate the inclusion of any recited integer or group of integers, but that no additional integer or group of integers can be added to the specified method, structure, or composition.

[0065] As used herein, the term "consists essentially of," or variations such as "consist essentially of" or "consisting essentially of," as used throughout the specification and claims, indicate the inclusion of any recited integer or group of integers, and the optional inclusion of

any recited integer or group of integers that do not materially change the basic or novel properties of the specified method, structure or composition. See M.P.E.P. § 2111.03.

[0066] As used herein, "subject" means any animal, preferably a mammal, most preferably a human. The term "mammal" as used herein, encompasses any mammal. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, monkeys, humans, etc., more preferably a human.

[0067] The words "right," "left," "lower," and "upper" designate directions in the drawings to which reference is made.

[0068] It should also be understood that the terms "about," "approximately," "generally," "substantially," and like terms, used herein when referring to a dimension or characteristic of a component of the preferred invention, indicate that the described dimension/characteristic is not a strict boundary or parameter and does not exclude minor variations therefrom that are functionally the same or similar, as would be understood by one having ordinary skill in the art. At a minimum, such references that include a numerical parameter would include variations that, using mathematical and industrial principles accepted in the art (e.g., rounding, measurement or other systematic errors, manufacturing tolerances, etc.), would not vary the least significant digit.

[0069] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences (e.g., anti-TAA antibodies and polynucleotides that encode them, TAA polypeptides and TAA polynucleotides that encode them, chimeric antigen receptors (CARs) comprising antigen binding domains specific for GPC3 and polynucleotides that encode them), refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection.

[0070] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0071] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, Adv. Appl. Math. 1981; 2:482, by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol. 1970; 48:443, by the search for similarity method of Pearson & Lipman, Proc. Nat'l. Acad. Sci. USA 1988; 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in

the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally, Current Protocols in Molecular Biology, F.M. Ausubel et al., eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., 1995 Supplement (Ausubel)).

[0072] Examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., J. Mol. Biol. 1990; 215: 403-410 and Altschul et al., Nucleic Acids Res. 1997; 25: 3389-3402, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al, supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased.

[0073] Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 1989; 89:10915).

[0074] In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin & Altschul, Proc. Nat'l. Acad. Sci. USA 1993; 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is

less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[0075] A further indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions.

[0076] As used herein, the term "isolated" means a biological component (such as a nucleic acid, peptide or protein) has been substantially separated, produced apart from, or purified away from other biological components of the organism in which the component naturally occurs, i.e., other chromosomal and extrachromosomal DNA and RNA, and proteins. Nucleic acids, peptides and proteins that have been "isolated" thus include nucleic acids and proteins purified by standard purification methods. "Isolated" nucleic acids, peptides and proteins can be part of a composition and still be isolated if the composition is not part of the native environment of the nucleic acid, peptide, or protein. The term also embraces nucleic acids, peptides and proteins prepared by recombinant expression in a host cell as well as chemically synthesized nucleic acids.

[0077] As used herein, the term "polynucleotide," synonymously referred to as "nucleic acid molecule," "nucleotides" or "nucleic acids," refers to any polyribonucleotide or polydeoxyribonucleotide, which can be unmodified RNA or DNA or modified RNA or DNA. "Polynucleotides" include, without limitation single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that can be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short nucleic acid chains, often referred to as oligonucleotides.

[0078] As used herein, the term "vector" is a replicon in which another nucleic acid segment can be operably inserted so as to bring about the replication or expression of the segment.

[0079] As used herein, the term "host cell" refers to a cell comprising a nucleic acid molecule of the invention. The "host cell" can be any type of cell, e.g., a primary cell, a cell in culture, or a cell from a cell line. In one embodiment, a "host cell" is a cell transfected with a nucleic acid molecule of the invention. In another embodiment, a "host cell" is a progeny or potential progeny of such a transfected cell. A progeny of a cell may or may not be identical to the parent cell, e.g., due to mutations or environmental influences that can occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

[0080] The term "expression" as used herein, refers to the biosynthesis of a gene product. The term encompasses the transcription of a gene into RNA. The term also encompasses translation of RNA into one or more polypeptides, and further encompasses all naturally occurring post-transcriptional and post-translational modifications. The expressed antibody can be within the cytoplasm of a host cell, into the extracellular milieu such as the growth medium of a cell culture or anchored to the cell membrane.

[0081] As used herein, the terms "peptide," "polypeptide," or "protein" can refer to a molecule comprised of amino acids and can be recognized as a protein by those of skill in the art. The conventional one-letter or three-letter code for amino acid residues is used herein. The terms "peptide," "polypeptide," and "protein" can be used interchangeably herein to refer to polymers of amino acids of any length. The polymer can be linear or branched, it can comprise modified amino acids, and it can be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art.

[0082] The peptide sequences described herein are written according to the usual convention whereby the N-terminal region of the peptide is on the left and the C-terminal region is on the right. Although isomeric forms of the amino acids are known, it is the L-form of the amino acid that is represented unless otherwise expressly indicated.

Chimeric Antigen Receptor (CAR)

[0083] As used herein, the term "chimeric antigen receptor" (CAR) refers to a recombinant polypeptide comprising at least an extracellular domain that binds specifically to an antigen or a target, a transmembrane domain and an intracellular T cell receptor-activating signaling domain.

Engagement of the extracellular domain of the CAR with the target antigen on the surface of a target cell results in clustering of the CAR and delivers an activation stimulus to the CAR-containing cell. CARs redirect the specificity of immune effector cells and trigger proliferation, cytokine production, phagocytosis and/or production of molecules that can mediate cell death of the target antigen-expressing cell in a major histocompatibility (MHC)-independent manner.

[0084] In one aspect, the CAR comprises an antigen binding domain, a hinge region, a costimulatory domain, an activating domain and a transmembrane region. In one aspect, the CAR comprises an antigen binding domain, a hinge region, two costimulatory domains, an activating domain and a transmembrane region. In one aspect, the CAR comprises two antigen binding domains, a hinge region, a costimulatory domain, an activating domain and a transmembrane region. In one aspect, the CAR comprises two antigen binding domains, a hinge region, two costimulatory domains, an activating domain and a transmembrane region.

[0085] As used herein, the term "signal peptide" refers to a leader sequence at the amino-terminus (N-terminus) of a nascent CAR protein, which co-translationally or post-translationally directs the nascent protein to the endoplasmic reticulum and subsequent surface expression.

[0086] As used herein, the term "extracellular antigen binding domain," "extracellular domain," or "extracellular ligand binding domain" refers to the part of a CAR that is located outside of the cell membrane and is capable of binding to an antigen, target or ligand.

[0087] As used herein, the term "hinge region" refers to the part of a CAR that connects two adjacent domains of the CAR protein, e.g., the extracellular domain and the transmembrane domain.

[0088] As used herein, the term "transmembrane domain" refers to the portion of a CAR that extends across the cell membrane and anchors the CAR to cell membrane. It is sometimes referred to as "transmembrane region".

Costimulatory Domains

[0089] As used herein, chimeric antigen receptors can incorporate costimulatory (signaling) domains to increase their potency. A costimulatory (signaling) domain can be derived from a costimulatory molecule. Costimulatory molecules are cell surface molecules other than antigen receptors or their ligands that are required for an efficient immune response. Costimulatory domains can be derived from costimulatory molecules, which can include, but are not limited to, CD28, CD28T, OX40, 4-1BB/CD137, CD2, CD3 (alpha, beta, delta, epsilon, gamma, zeta), CD4, CD5, CD7, CD9, CD16, CD22, CD27, CD30, CD33, CD37, CD40, CD45, CD64, CD80, CD86, CD134, CD137, CD154, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1; CD11a and CD18), CD247, CD276 (B7-H3), LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), NKG2C, Ig alpha

(CD79a), DAP10, Fc gamma receptor, MHC class I molecule, TNFR, integrin, signaling lymphocytic activation molecule, BTLA, Toll ligand receptor, ICAM-1, CDS, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD8 alpha, CD8 beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, ITGAE, CD103, ITGAL, CD1a, CD1b, CD1c, CD1d, ITGAM, ITGAX, ITGB1, CD29, ITGB2 (CD18), ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD 160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD83 ligand, cytokine receptor, activating NK cell receptors, or fragments or any combination thereof.

Activating Domains

[0090] As used herein, chimeric antigen receptors can comprise activating domains. Activating domains can include, but are not limited to, CD3. CD3 is an element of the T cell receptor on native T cells and has been shown to be an important intracellular activating element in CARs. In a preferred embodiment, the CD3 is CD3 zeta.

Hinge region

[0091] As described herein, the chimeric antigen receptor can comprise a hinge region. This is a portion of the extracellular domain, sometimes referred to as a "spacer" region. A variety of hinges can be employed in accordance with the invention, including costimulatory molecules, as discussed above, immunoglobulin (Ig) sequences, or other suitable molecules to achieve the desired special distance from the target cell. In some embodiments, the entire extracellular region comprises a hinge region.

Transmembrane region

[0092] As used herein, chimeric antigen receptors (CARs) can comprise a transmembrane region/domain. The CAR can be designed to comprise a transmembrane domain that is fused to the extracellular domain of the CAR. It can similarly be fused to the intracellular domain of the CAR. In one embodiment, the transmembrane domain that is naturally associated with one of the domains in a CAR is used. In some instances, the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex. The transmembrane domain may be derived either from a natural or from a synthetic source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. Transmembrane regions of particular use in this invention can be derived from (i.e., comprise or engineered from), but are not limited to, CD28,

CD28T, OX40, 4-1BB/CD137, CD2, CD3 (alpha, beta, delta, epsilon, gamma, zeta), CD4, CD5, CD7, CD9, CD16, CD22, CD27, CD30, CD33, CD37, CD40, CD45, CD64, CD80, CD86, CD134, CD137, CD154, programmed death-1 (PD-1), inducible T cell costimulator (ICOS), lymphocyte function-associated antigen-1 (LFA-1; CD11a and CD18), CD247, CD276 (B7-H3), LIGHT (tumor necrosis factor superfamily member 14; TNFSF14), NKG2C, Ig alpha (CD79a), DAP10, Fc gamma receptor, MHC class I molecule, TNFR, integrin, signaling lymphocytic activation molecule, BTLA, Toll ligand receptor, ICAM-1, CDS, GITR, BAFFR, LIGHT, HVEM (LIGHTR), KIRDS2, SLAMF7, NKp80 (KLRF1), NKp44, NKp30, NKp46, CD19, CD8 alpha, CD8 beta, IL-2R beta, IL-2R gamma, IL-7R alpha, ITGA4, VLA1, CD49a, IA4, CD49D, ITGA6, VLA-6, CD49f, ITGAD, ITGAE, CD103, ITGAL, CD1a, CD1b, CD1c, CD1d, ITGAM, ITGAX, ITGB1, CD29, ITGB2 (CD18), ITGB7, NKG2D, TNFR2, TRANCE/RANKL, DNAM1 (CD226), SLAMF4 (CD244, 2B4), CD84, CD96 (Tactile), CEACAM1, CRTAM, Ly9 (CD229), CD 160 (BY55), PSGL1, CD100 (SEMA4D), CD69, SLAMF6 (NTB-A, Lyl08), SLAM (SLAMF1, CD150, IPO-3), BLAME (SLAMF8), SELPLG (CD162), LTBR, LAT, GADS, SLP-76, PAG/Cbp, CD19a, CD83 ligand, cytokine receptor, activating NK cell receptors, an immunoglobulin protein, or fragments or any combination thereof.

Immune Cells

[0093] According to particular aspects, the invention provides cells that are immune cells that comprise the isolated polynucleotides or vectors comprising the isolated polynucleotides comprising the nucleotide sequence encoding the CAR are provided herein. The immune cells comprising the isolated polynucleotides and/or vectors of the invention can be referred to as "engineered immune cells." Preferably, the engineered immune cells are derived from a human (are of human origin prior to being made recombinant).

[0094] The engineered immune cells can, for example, be cells of the lymphoid lineage. Non-limiting examples of cells of the lymphoid lineage can include T cells and Natural Killer (NK) cells. T cells express the T cell receptor (TCR), with most cells expressing α and β chains and a smaller population expressing γ and δ chains. T cells useful as engineered immune cells of the invention can be $CD4^+$ or $CD8^+$ and can include, but are not limited to, T helper cells ($CD4^+$), cytotoxic T cells (also referred to as cytotoxic T lymphocytes, CTL; $CD8^+$ cells), and memory T cells, including central memory T cells, stem-like memory T cells, and effector memory T cells, natural killer T cells, mucosal associated invariant T cells, and $\gamma\delta$ T cells. Other exemplary immune cells include, but are not limited to, macrophages, antigen presenting cells (APCs), or any immune cell that expresses an inhibitor of a cell-mediated immune response, for example, an immune checkpoint inhibitor pathway receptor (e.g., PD-1). Precursor cells of immune cells that can be used according to the invention, include, hematopoietic stem and/or progenitor cells.

Hematopoietic stem and/or progenitor cells can be derived from bone marrow, umbilical cord blood, adult peripheral blood after cytokine mobilization, and the like, by methods known in the art. The immune cells are engineered to recombinantly express the CARs of the invention.

[0095] Immune cells and precursor cells thereof can be isolated by methods known in the art, including commercially available methods (see, e.g., Rowland Jones et al., Lymphocytes: A Practical Approach, Oxford University Press, NY 1999). Sources for immune cells or precursors thereof include, but are not limited to, peripheral blood, umbilical cord blood, bone marrow, or other sources of hematopoietic cells. Various techniques can be employed to separate the cells to isolated or enrich desired immune cells. For instance, negative selection methods can be used to remove cells that are not the desired immune cells. Additionally, positive selection methods can be used to isolate or enrich for the desired immune cells or precursors thereof, or a combination of positive and negative selection methods can be employed. If a particular type of cell is to be isolated, e.g., a particular T cell, various cell surface markers or combinations of markers (e.g., CD3, CD4, CD8, CD34) can be used to separate the cells.

[0096] The immune cells or precursor cells thereof can be autologous or non-autologous to the subject to which they are administered in the methods of treatment of the invention. Autologous cells are isolated from the subject to which the engineered immune cells recombinantly expressing the CAR are to be administered. Optionally, the cells can be obtained by leukapheresis, where leukocytes are selectively removed from withdrawn blood, made recombinant, and then retransfused into the donor. Alternatively, allogeneic cells from a non-autologous donor that is not the subject can be used. In the case of a non-autologous donor, the cells are typed and matched for human leukocyte antigen (HLA) to determine the appropriate level of compatibility. For both autologous and non-autologous cells, the cells can optionally be cryopreserved until ready for use.

[0097] Various methods for isolating immune cells that can be used for recombinant expression of the CARs of the invention have been described previously, and can be used, including, but not limited to, using peripheral donor lymphocytes (Sadelain et al., Nat. Rev. Cancer 2003; 3:35-45; Morgan et al., Science 2006; 314:126-9), using lymphocyte cultures derived from tumor infiltrating lymphocytes (TILs) in tumor biopsies (Panelli et al., J. Immunol. 2000; 164:495-504; Panelli et al., J. Immunol. 2000; 164:4382-92) and using selectively *in vitro* expanded antigen-specific peripheral blood leukocytes employing artificial antigen-presenting cells (AAPCs) or dendritic cells (Dupont et al., Cancer Res. 2005; 65:5417-427; Papanicolaou et al., Blood 2003; 102:2498-505). In the case of using stem cells, the cells can be isolated by methods well known in the art (see, e.g., Klug et al., Hematopoietic Stem Cell Protocols,

Humana Press, NJ 2002; Freshney et al., Culture of Human Stem Cells, John Wiley & Sons 2007).

[0098] According to particular embodiments, the method of making the engineered immune cells comprises transfecting or transducing immune effector cells isolated from an individual such that the immune effector cells express one or more CAR(s) according to embodiments of the invention. Methods of preparing immune cells for immunotherapy are described, e.g., in WO2014/130635, WO2013/176916 and WO2013/176915, which are incorporated herein by reference. Individual steps that can be used for preparing engineered immune cells are disclosed, e.g., in WO2014/039523, WO2014/184741, WO2014/191128, WO2014/184744 and WO2014/184143, which are incorporated herein by reference.

[0099] In a particular embodiment, the immune effector cells, such as T cells, are genetically modified with CARs of the invention (e.g., transduced with a viral vector comprising a nucleic acid encoding a CAR) and then are activated and expanded *in vitro*. In various embodiments, T cells can be activated and expanded before or after genetic modification to express a CAR, using methods as described, for example, in US6352694, US6534055, US6905680, US6692964, US5858358, US6887466, US6905681, US7144575, US7067318, US7172869, US7232566, US7175843, US5883223, US6905874, US6797514, US6867041, US2006/121005, which are incorporated herein by reference. T cells can be expanded *in vitro* or *in vivo*. Generally, the T cells of the invention can be expanded by contact with a surface having attached thereto an agent that stimulates a CD3/TCR complex-associated signal and a ligand that stimulates a co-stimulatory molecule on the surface of the T cells. As non-limiting examples, T cell populations can be stimulated as described herein, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD3 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore, or by activation of the CAR itself. For co-stimulation of an accessory molecule on the surface of the T cells, a ligand that binds the accessory molecule is used. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. Conditions appropriate for T cell culture include, e.g., an appropriate media (e.g., Minimal Essential Media or RPMI Media 1640 or, X-vivo 5 (Lonza)) that can contain factors necessary for proliferation and viability, including serum (e.g., fetal bovine or human serum), cytokines, such as IL-2, IL-7, IL-15, and/or IL-21, insulin, IFN-g, GM-CSF, TGFβ and/or any other additives for the growth of cells known to the skilled artisan. In other embodiments, the T cells can be activated and stimulated to proliferate with feeder cells and appropriate antibodies and cytokines using methods such as those described in US6040177, US5827642, and WO2012129514, which are incorporated herein by reference.

[00100] Antibodies and Antigen binding domains

[00101] The invention generally relates to isolated anti-TAA antibodies (e.g., anti-TIP-1 or anti-GPC3 antibodies), chimeric antigen receptors (CARs), nucleic acids and expression vectors encoding the antibodies and CARs, recombinant cells containing the vectors, and compositions comprising the antibodies, CARs, and recombinant cells expressing the CARs. Methods of making the antibodies and CARs, and methods of using the antibodies and CARs to treat diseases including cancer and inflammatory diseases. The antibodies and antigen binding domains of the CARs of the invention possess one or more desirable functional properties, including, but not limited to, high-affinity binding to TAAs, high specificity to TAAs, the ability to stimulate complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and/or antibody-dependent cellular-mediated cytotoxicity (ADCC) against cells expressing TAAs, and the ability to inhibit tumor growth in subjects and animal models when administered alone or in combination with other anti-cancer therapies.

[00102] In a general aspect, the invention relates to isolated monoclonal antibodies or antigen-binding fragments thereof that bind TAAs (e.g., TIP-1 or GPC3).

[00103] As used herein, the term "antibody" is used in a broad sense and includes immunoglobulin or antibody molecules including human, humanized, composite and chimeric antibodies and antibody fragments that are monoclonal or polyclonal. In general, antibodies are proteins or peptide chains that exhibit binding specificity to a specific antigen. Antibody structures are well known. Immunoglobulins can be assigned to five major classes (i.e., IgA, IgD, IgE, IgG and IgM), depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4. Accordingly, the antibodies of the invention can be of any of the five major classes or corresponding sub-classes. Preferably, the antibodies of the invention are IgG1, IgG2, IgG3 or IgG4. Antibody light chains of vertebrate species can be assigned to one of two clearly distinct types, namely kappa and lambda, based on the amino acid sequences of their constant domains. Accordingly, the antibodies of the invention can contain a kappa or lambda light chain constant domain. According to particular embodiments, the antibodies of the invention include heavy and/or light chain constant regions from rat or human antibodies. In addition to the heavy and light constant domains, antibodies contain an antigen-binding region that is made up of a light chain variable region and a heavy chain variable region, each of which contains three domains (i.e., complementarity determining regions 1-3; CDR1, CDR2, and CDR3). The light chain variable region domains are alternatively referred to as LCDR1, LCDR2, and LCDR3, and the heavy chain variable region domains are alternatively referred to as HCDR1, HCDR2, and HCDR3.

[00104] As used herein, the term an "isolated antibody" refers to an antibody which is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds to a TAA (e.g., TIP-1 or GPC3) is substantially free of antibodies that do not bind to the same TAA (e.g., TIP-1 or GPC3)). In addition, an isolated antibody is substantially free of other cellular material and/or chemicals.

[00105] As used herein, the term "monoclonal antibody" 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. The monoclonal antibodies of the invention can be made by the hybridoma method, phage display technology, single lymphocyte gene cloning technology, or by recombinant DNA methods. For example, the monoclonal antibodies can be produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, such as a transgenic mouse or rat, having a genome comprising a human heavy chain transgene and a light chain transgene.

[00106] As used herein, the term "antigen-binding fragment" and/or "antigen binding domain" refers to an antibody fragment such as, for example, a diabody, a Fab, a Fab', a F(ab')2, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a $(dsFv)_2$, a bispecific dsFv (dsFv-dsFv'), a disulfide stabilized diabody (ds diabody), a single-chain antibody molecule (scFv), a single domain antibody (sdab) an scFv dimer (bivalent diabody), a multispecific antibody formed from a portion of an antibody comprising one or more CDRs, a camelized single domain antibody, a nanobody, a domain antibody, a bivalent domain antibody, or any other antibody fragment that binds to an antigen but does not comprise a complete antibody structure. An antigen-binding fragment is capable of binding to the same antigen to which the parent antibody or a parent antibody fragment binds. According to particular embodiments, the antigen-binding fragment comprises a light chain variable region, a light chain constant region, and an Fd segment of the heavy chain. According to other particular embodiments, the antigen-binding fragment comprises Fab and F(ab'). An antigen binding domain is capable of binding to the same antigen to which the parent antibody binds. According to particular embodiments, the antigen binding domain comprises a single-chain antibody molecule (scFv).

[00107] As used herein, the term "single-chain antibody" refers to a conventional single-chain antibody in the field, which comprises a heavy chain variable region and a light chain variable region connected by a short peptide of about 15 to about 20 amino acids. As used herein, the term "single domain antibody" refers to a conventional single domain antibody in the field, which comprises a heavy chain variable region and a heavy chain constant region or which comprises only a heavy chain variable region.

[00108] As used herein, the term "human antibody" refers to an antibody produced by a human or an antibody having an amino acid sequence corresponding to an antibody produced by a human made using any technique known in the art. This definition of a human antibody includes intact or full-length antibodies, fragments thereof, and/or antibodies comprising at least one human heavy and/or light chain polypeptide.

[00109] As used herein, the term "humanized antibody" and/or "humanized antigen binding domain" refers to a non-human antibody and/or non-human antigen binding domain that is modified to increase the sequence homology to that of a human antibody and/or a human antigen binding domain, such that the antigen-binding properties of the antibody and/or antigen binding domain are retained, but its antigenicity in the human body is reduced.

[00110] As used herein, the term "chimeric antibody" and/or "chimeric antigen binding domain" refers to an antibody and/or antigen binding domain wherein the amino acid sequence of the immunoglobulin molecule is derived from two or more species. The variable region of both the light and heavy chains often corresponds to the variable region of an antibody and/or antigen binding domain derived from one species of mammal (e.g., mouse, rat, rabbit, etc.) having the desired specificity, affinity, and capability, while the constant regions correspond to the sequences of an antibody and/or antigen binding domain derived from another species of mammal (e.g., human) to avoid eliciting an immune response in that species.

[00111] As used herein, the term "multi-specific antibody" refers to an antibody that comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, *e.g.*, the same protein (or subunit of a multimeric protein). In an embodiment, the first and second epitopes overlap or substantially overlap. In an embodiment, the first and second epitopes do not overlap or do not substantially overlap. In an embodiment, the first and second epitopes are on different antigens, *e.g.*, different proteins (or different subunits of a multimeric protein). In an embodiment, a multi-specific antibody comprises a third, fourth, or fifth immunoglobulin variable domain. In an embodiment, a multi-specific antibody is a bispecific antibody molecule, a tri-specific antibody molecule, or a tetra-specific antibody molecule.

[00112] As used herein, the term "bispecific antibody" refers to a multi-specific antibody that binds no more than two epitopes or two antigens. A bispecific antibody is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment, the first and second epitopes are on the same antigen, *e.g.*, the same

protein (or subunit of a multimeric protein). In an embodiment, the first and second epitopes overlap or substantially overlap. In an embodiment, the first and second epitopes are on different antigens, *e.g.*, different proteins (or different subunits of a multimeric protein). In an embodiment, a bispecific antibody comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment, a bispecific antibody comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment, a bispecific antibody comprises a scFv, or fragment thereof, having binding specificity for a first epitope, and a scFv, or fragment thereof, having binding specificity for a second epitope. In an embodiment, the first epitope is located on a TAA of this invention and the second epitope is located on PD-1, PD-L1, TIM-3, LAG-3, CTLA-4, EGFR, HER-2, CD19, CD20, CD33, CD3, CD73, CD47, TIP-1, GPC3, apelin, DLL3, folate receptor alpha, Claudin 18.2 and/or other tumor associated immune suppressors or surface antigens. In an embodiment, the first and the second epitopes are located on the same TAA of this invention.

[00113] As used herein, an antibody and/or antigen binding domain that "specifically binds to a TAA" refers to an antibody and/or antigen binding domain that binds to the TAA, preferably the human TAA (e.g., TIP-1 or GPC3), with a KD of 1×10^{-7} M or less, preferably 1×10^{-8} M or less, more preferably 5×10^{-9} M or less, 1×10^{-9} M or less, 5×10^{-10} M or less, or 1×10^{-10} M or less. The term "KD" refers to the dissociation constant, which is obtained from the ratio of Kd to Ka (i.e., Kd/Ka) and is expressed as a molar concentration (M). KD values for antibodies and/or antigen binding domains can be determined using methods in the art in view of the present disclosure. For example, the KD of an antibody and/or antigen binding domains can be determined by using surface plasmon resonance, such as by using a biosensor system, e.g., a Biacore® system, or by using bio-layer interferometry technology, such as an Octet RED96 system.

[00114] The smaller the value of the KD of an antibody and/or antigen binding domain, the higher affinity that the antibody and/or antigen binding domain binds to a target antigen.

[00115] According to a particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof or a chimeric antigen receptor (CAR) comprising an antigen binding domain, wherein the monoclonal antibody or antigen-binding fragment thereof or antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), a HCDR2, a HCDR3, a light chain complementarity determining region 1 (LCDR1), a LCDR2, and a LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antibody or antigen-binding fragment thereof or antigen binding domain thereof specifically binds GPC3, preferably human GPC3.

[00116] According to a particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof or a chimeric antigen receptor (CAR) comprising an antigen binding domain, wherein the monoclonal antibody or antigen-binding fragment thereof or antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), a HCDR2, a HCDR3, a light chain complementarity determining region 1 (LCDR1), a LCDR2, and a LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antibody or antigen-binding fragment thereof or antigen binding thereof specifically binds GPC3, preferably human GPC3.

[00117] According to a particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), a HCDR2, a HCDR3, a light chain complementarity determining region 1 (LCDR1), a LCDR2, and a LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 3, 4, 5, 6, 7, and 8, respectively.

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

[00118] According to a particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), a HCDR2, a HCDR3, a light chain complementarity determining region 1 (LCDR1), a LCDR2, and a LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 9, 10, 11, 12, 13, and 14, respectively.

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

[00119] According to another particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof or a chimeric antigen receptor (CAR) comprising an antigen binding domain, wherein the monoclonal antibody or antigen-binding fragment thereof or antigen binding domain comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NOs: 85, 106, 15, 29, 43, 57, 71, or 1, or a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to one of SEQ ID NOs: 86, 107, 16, 30, 44, 58, 72, or 2. According to one preferred embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof or antigen binding domain thereof of the invention comprises a heavy chain variable region having the polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, 71, or 1, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, 72, or 2, respectively.

[00120] According to another particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof or antigen binding domain thereof of the invention, comprising:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;
b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;
c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;
f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58;

g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72; or

h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

[00121] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 3, 4, 5, 6, 7, and 8, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:1, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:2. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1; and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

[00122] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:15, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:16. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15; and a light chain variable region having the polypeptide sequence of SEQ ID NO:16.

[00123] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:29, and a light chain variable region having a polypeptide sequence at

least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:30. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29; and a light chain variable region having the polypeptide sequence of SEQ ID NO:30.

[00124] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:43, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:44. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43; and a light chain variable region having the polypeptide sequence of SEQ ID NO:44.

[00125] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:57, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:58. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57; and a light chain variable region having the polypeptide sequence of SEQ ID NO:58.

[00126] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99%

identical to SEQ ID NO:71, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:72. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71; and a light chain variable region having the polypeptide sequence of SEQ ID NO:72.

[00127] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:85, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:86. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85; and a light chain variable region having the polypeptide sequence of SEQ ID NO:86.

[00128] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:106, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:107. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106; and a light chain variable region having the polypeptide sequence of SEQ ID NO:107.

[00129] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 9, 10, 11, 12, 13, and 14, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least

85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:1, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:2. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1; and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

[00130] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:15, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:16. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15; and a light chain variable region having the polypeptide sequence of SEQ ID NO:16.

[00131] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:29, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:30. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29; and a light chain variable region having the polypeptide sequence of SEQ ID NO:30.

[00132] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding

fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:43, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:44. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43; and a light chain variable region having the polypeptide sequence of SEQ ID NO:44.

[00133] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:57, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:58. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57; and a light chain variable region having the polypeptide sequence of SEQ ID NO:58.

[00134] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:71, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:72. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71; and a light chain variable region having the polypeptide sequence of SEQ ID NO:72.

[00135] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 93, 94, 95, 96, 97 and 98,

respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:85, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:86. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85; and a light chain variable region having the polypeptide sequence of SEQ ID NO:86.

[00136] In one embodiment, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof, comprising HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, having the polypeptide sequences of SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively. In another embodiment, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:106, and a light chain variable region having a polypeptide sequence at least 85%, preferably 90%, more preferably 95% or more, such as 95%, 96%, 97%, 98%, or 99% identical to SEQ ID NO:107. Preferably, the isolated monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106; and a light chain variable region having the polypeptide sequence of SEQ ID NO:107.

[00137] According to another particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof of the invention, wherein the antibody or antigen-binding fragment thereof is chimeric.

[00138] According to another particular aspect, the invention relates to an isolated monoclonal antibody or antigen-binding fragment thereof of the invention, wherein the antibody or antigen-binding fragment thereof is human or humanized.

[00139] According to another particular aspect, the humanized monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

[00140] According to another particular aspect, the humanized monoclonal antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

[00141] According to another particular aspect, the antigen binding domain is humanized and comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to SEQ ID NO: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

[00142] According to another particular aspect, the antigen binding domain is humanized and comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;
(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or (75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

[00143] According to another particular aspect, the antigen binding domain is a single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3.

[00144] In certain embodiments, the encoded antigen binding domain is a humanized single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3. In certain embodiments, the antigen binding domain is a humanized single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3. In certain embodiments, the humanized single chain variable fragment (scFv) comprises a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs:167-182. In certain embodiments, the humanized single chain variable fragment (scFv) comprises a polypeptide sequence having an amino acid sequence selected from the group consisting of SEQ ID NOs:167-182.

[00145] According to another particular aspect, the chimeric antigen receptor comprises one or more antigen binding domains.

[00146] According to another particular aspect, the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

[00147] In another general aspect, the invention relates to an isolated nucleic acid encoding a monoclonal antibody or antigen-binding fragment thereof and/or a bispecific antibody or antigen-binding fragment thereof of the invention. In another general aspect, the invention relates to an isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain thereof of the invention. It will be appreciated by those skilled in the art that the coding sequence of a protein can be changed (e.g., replaced, deleted, inserted, etc.) without changing the amino acid sequence of the protein. Accordingly, it will be understood by those skilled in the art that nucleic acid sequences encoding monoclonal antibodies or antigen-binding fragments thereof of the invention can be altered without changing the amino acid sequences of the proteins.

[00148] In another general aspect, the invention relates to a vector comprising an isolated nucleic acid encoding a monoclonal antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, and/or a CAR of the invention. Any vector known to those skilled in the art in view of the present disclosure can be used, such as a plasmid, a cosmid, a phage vector or a viral vector. In some embodiments, the vector is a recombinant expression vector such as a plasmid. The vector can include any element to establish a

conventional function of an expression vector, for example, a promoter, ribosome binding element, terminator, enhancer, selection marker, and origin of replication. The promoter can be a constitutive, inducible, or repressible promoter. A number of expression vectors capable of delivering nucleic acids to a cell are known in the art and can be used herein for production of an antibody or antigen-binding fragment thereof in the cell. Conventional cloning techniques or artificial gene synthesis can be used to generate a recombinant expression vector according to embodiments of the invention.

[00149] In another general aspect, the invention relates to a host cell comprising an isolated nucleic acid encoding a monoclonal antibody or antigen-binding fragment thereof and/or a bispecific antibody or antigen-binding fragment thereof of the invention. Any host cell known to those skilled in the art in view of the present disclosure can be used for recombinant expression of antibodies or antigen-binding fragments thereof of the invention. In some embodiments, the host cells are E. coli TG1 or BL21 cells (for expression of, e.g., an scFv or Fab antibody), CHO-DG44 or CHO-K1 cells or HEK293 cells (for expression of, e.g., a full-length IgG antibody). According to particular embodiments, the recombinant expression vector is transformed into host cells by conventional methods such as chemical transfection, heat shock, or electroporation, where it is stably integrated into the host cell genome such that the recombinant nucleic acid is effectively expressed.

[00150] In another general aspect, the invention relates to a method of producing a monoclonal antibody or antigen-binding fragment thereof and/or a bispecific antibody or antigen-binding fragment thereof of the invention, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof under conditions to produce a monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof of the invention, and recovering the antibody or antigen-binding fragment thereof from the cell or cell culture (e.g., from the supernatant). Expressed antibodies or antigen-binding fragments thereof can be harvested from the cells and purified according to conventional techniques known in the art and as described herein.

[00151] In another general aspect, the invention relates to a cell transduced with the vector comprising the isolated nucleic acids encoding the CARs of the invention. The term "transduced" or "transduction" refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A "transduced" cell is one which has been transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny. In certain embodiments, the cell is a CAR-T cell, preferably a human CAR-T cell, wherein the T cell is engineered to express the CAR of the invention to treat diseases such as cancer. In certain

embodiments, the cell is a CAR-NK cell, preferably a human CAR-NK cell, wherein the NK cell engineered to express the CAR of the invention is used to treat diseases such as cancer.

[00152] In another general aspect, the invention relates to a method of making a CAR-T cell by transducing a T cell with a vector comprising the isolated nucleic acids encoding the CARs of the invention.

[00153] In another general aspect, the invention relates to a method of producing the CAR-T cell thereof of the invention, comprising culturing T cells comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of the invention under conditions to produce the CAR-T cell, and recovering the CAR-T cell.

[00154] In another general aspect, the invention relates to a method of making a CAR-NK cell by transducing a NK cell with a vector comprising the isolated nucleic acids encoding the CARs of the invention.

[00155] In another general aspect, the invention relates to a method of producing a CAR-NK cell of the invention, comprising culturing NK cells comprising nucleic acids encoding the chimeric antigen receptor (CAR) thereof under conditions to produce the CAR-NK cell, and recovering the CAR-NK cell.

[00156] In another general aspect, the invention relates to a method of generating a population of RNA-engineered cells comprising a chimeric antigen receptor (CAR) of the invention. The methods comprise contacting a population of cells with isolated polynucleotides comprising a nucleic acid encoding a CAR of the invention, wherein the isolated polynucleotides are *in vitro* transcribed RNA or synthetic RNA.

[00157] Pharmaceutical Compositions

[00158] In another general aspect, the invention relates to a pharmaceutical composition, comprising an isolated monoclonal antibody or antigen-binding fragment thereof, a bispecific antibody or antigen-binding fragment thereof, an isolated polynucleotide, an isolated polypeptide, a host cell, and/or an engineered immune cell of the invention and a pharmaceutically acceptable carrier.

[00159] The term "pharmaceutical composition" as used herein means a product comprising an isolated polynucleotide of the invention, an isolated polypeptide of the invention, a host cell of the invention, an engineered immune cell of the invention, an anti-TIP-1 or anti-GPC3 monoclonal antibody or antigen-binding fragment thereof, and/or a bispecific antibody of the invention together with a pharmaceutically acceptable carrier. Polynucleotides, polypeptides, host cells, engineered immune cells of the invention, an anti-TIP-1 or anti-GPC3 monoclonal antibody or antigen-binding fragment thereof, and/or a bispecific antibody of the invention and

compositions comprising them are also useful in the manufacture of a medicament for therapeutic applications mentioned herein.

[00160] As used herein, the term "carrier" refers to any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, oil, lipid, lipid containing vesicle, microsphere, liposomal encapsulation, or other material well known in the art for use in pharmaceutical formulations. It will be understood that the characteristics of the carrier, excipient or diluent will depend on the route of administration for a particular application. As used herein, the term "pharmaceutically acceptable carrier" refers to a non-toxic material that does not interfere with the effectiveness of a composition according to the invention or the biological activity of a composition according to the invention. According to particular embodiments, in view of the present disclosure, any pharmaceutically acceptable carrier suitable for use in an antibody pharmaceutical composition can be used in the invention.

[00161] The formulation of pharmaceutically active ingredients with pharmaceutically acceptable carriers is known in the art, e.g., Remington: The Science and Practice of Pharmacy (e.g. 21st edition (2005), and any later editions). Non-limiting examples of additional ingredients include buffers, diluents, solvents, tonicity regulating agents, preservatives, stabilizers, and chelating agents. One or more pharmaceutically acceptable carrier(s) can be used in formulating the pharmaceutical compositions of the invention.

[00162] In one embodiment of the invention, the pharmaceutical composition is a liquid formulation. A preferred example of a liquid formulation is an aqueous formulation, i.e., a formulation comprising water. The liquid formulation can comprise a solution, a suspension, an emulsion, a microemulsion, a gel, and the like. An aqueous formulation typically comprises at least 50% w/w water, or at least 60%, 70%, 75%, 80%, 85%, 90%, or at least 95% w/w of water.

[00163] In one embodiment, the pharmaceutical composition can be formulated as an injectable which can be injected, for example, via an injection device (e.g., a syringe or an infusion pump). The injection can be delivered subcutaneously, intramuscularly, intraperitoneally, intravitreally, or intravenously, for example.

[00164] In another embodiment, the pharmaceutical composition is a solid formulation, e.g., a freeze-dried or spray-dried composition, which can be used as is, or whereto the physician or the patient adds solvents, and/or diluents prior to use. Solid dosage forms can include tablets, such as compressed tablets, and/or coated tablets, and capsules (e.g., hard or soft gelatin capsules). The pharmaceutical composition can also be in the form of sachets, dragees, powders, granules, lozenges, or powders for reconstitution, for example.

[00165] The dosage forms may be immediate release, in which case they can comprise a water-soluble or dispersible carrier, or they can be delayed release, sustained release, or modified

release, in which case they can comprise water-insoluble polymers that regulate the rate of dissolution of the dosage form in the gastrointestinal tract or under the skin.

[00166] In other embodiments, the pharmaceutical composition can be delivered intranasally, intrabuccally, or sublingually.

[00167] The pH in an aqueous formulation can be between pH 3 and pH 10. In one embodiment of the invention, the pH of the formulation is from about 7.0 to about 9.5. In another embodiment of the invention, the pH of the formulation is from about 3.0 to about 7.0.

[00168] In another embodiment of the invention, the pharmaceutical composition comprises a buffer. Non-limiting examples of buffers include: arginine, aspartic acid, bicine, citrate, disodium hydrogen phosphate, fumaric acid, glycine, glycylglycine, histidine, lysine, maleic acid, malic acid, sodium acetate, sodium carbonate, sodium dihydrogen phosphate, sodium phosphate, succinate, tartaric acid, tricine, and tris(hydroxymethyl)-aminomethane, and mixtures thereof. The buffer can be present individually or in the aggregate, in a concentration from about 0.01 mg/ml to about 50 mg/ml, for example from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific buffers constitute alternative embodiments of the invention.

[00169] In another embodiment of the invention, the pharmaceutical composition comprises a preservative. Non-limiting examples of preservatives include: benzethonium chloride, benzoic acid, benzyl alcohol, bronopol, butyl 4-hydroxybenzoate, chlorobutanol, chlorocresol, chlorohexidine, chlorphenesin, o-cresol, m-cresol, p-cresol, ethyl 4-hydroxybenzoate, imidurea, methyl 4-hydroxybenzoate, phenol, 2-phenoxyethanol, 2-phenylethanol, propyl 4-hydroxybenzoate, sodium dehydroacetate, thiomerosal, and mixtures thereof. The preservative can be present individually or in the aggregate, in a concentration from about 0.01 mg/ml to about 50 mg/ml, for example from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific preservatives constitute alternative embodiments of the invention.

[00170] In another embodiment of the invention, the pharmaceutical composition comprises an isotonic agent. Non-limiting examples of isotonic agents include a salt (such as sodium chloride), an amino acid (such as glycine, histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, and threonine), an alditol (such as glycerol, 1,2-propanediol propyleneglycol), 1,3-propanediol, and 1,3-butanediol), polyethyleneglycol (e.g. PEG400), and mixtures thereof. Another example of an isotonic agent includes a sugar. Non-limiting examples of sugars may be mono-, di-, or polysaccharides, or water-soluble glucans, including for example fructose, glucose, mannose, sorbose, xylose, maltose, lactose, sucrose, trehalose, dextran, pullulan, dextrin, cyclodextrin, alpha and beta-HPCD, soluble starch, hydroxyethyl starch, and sodium carboxymethylcellulose.

Another example of an isotonic agent is a sugar alcohol, wherein the term "sugar alcohol" is defined as a C(4-8) hydrocarbon having at least one -OH group. Non-limiting examples of sugar alcohols include mannitol, sorbitol, inositol, galactitol, dulcitol, xylitol, and arabitol. The isotonic agent can be present individually or in the aggregate, in a concentration from about 0.01 mg/ml to about 50 mg/ml, for example from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific isotonic agents constitute alternative embodiments of the invention.

[00171] In another embodiment of the invention, the pharmaceutical composition comprises a chelating agent. Non-limiting examples of chelating agents include citric acid, aspartic acid, salts of ethylenediaminetetraacetic acid (EDTA), and mixtures thereof. The chelating agent can be present individually or in the aggregate, in a concentration from about 0.01 mg/ml to about 50 mg/ml, for example from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific chelating agents constitute alternative embodiments of the invention.

[00172] In another embodiment of the invention, the pharmaceutical composition comprises a stabilizer. Non-limiting examples of stabilizers include one or more aggregation inhibitors, one or more oxidation inhibitors, one or more surfactants, and/or one or more protease inhibitors.

[00173] In another embodiment of the invention, the pharmaceutical composition comprises a stabilizer, wherein said stabilizer is carboxy-/hydroxycellulose and derivatives thereof (such as HPC, HPC-SL, HPC-L and HPMC), cyclodextrins, 2-methylthioethanol, polyethylene glycol (such as PEG 3350), polyvinyl alcohol (PVA), polyvinyl pyrrolidone, salts (such as sodium chloride), sulphur-containing substances such as monothioglycerol), or thioglycolic acid. The stabilizer can be present individually or in the aggregate, in a concentration from about 0.01 mg/ml to about 50 mg/ml, for example from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific stabilizers constitute alternative embodiments of the invention.

[00174] In further embodiments of the invention, the pharmaceutical composition comprises one or more surfactants, preferably a surfactant, at least one surfactant, or two different surfactants. The term "surfactant" refers to any molecules or ions that are comprised of a water-soluble (hydrophilic) part, and a fat-soluble (lipophilic) part. The surfactant can, for example, be selected from the group consisting of anionic surfactants, cationic surfactants, nonionic surfactants, and/or zwitterionic surfactants. The surfactant can be present individually or in the aggregate, in a concentration from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific surfactants constitute alternative embodiments of the invention.

[00175] In a further embodiment of the invention, the pharmaceutical composition comprises one or more protease inhibitors, such as, e.g., EDTA, and/or benzamidine hydrochloric acid (HCl). The protease inhibitor can be present individually or in the aggregate, in a concentration from about 0.1 mg/ml to about 20 mg/ml. Pharmaceutical compositions comprising each one of these specific protease inhibitors constitute alternative embodiments of the invention.

[00176] In another general aspect, the invention relates to a method of producing a pharmaceutical composition comprising a monoclonal antibody or antigen-binding fragment thereof and/or a bispecific antibody or antigen-binding fragment thereof of the invention, comprising combining a monoclonal antibody or antigen-binding fragment thereof and/or a bispecific antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

[00177] **Methods of use**

[00178] In another general aspect, the invention relates to a method of treating a cancer in a subject in need thereof, comprising administering to the subject the CAR-T cells and/or CAR-NK cells of the invention. The cancer can, for example, be selected from but not limited to, a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

[00179] In another general aspect, the invention relates to a method of targeting a TAA (e.g., TIP-1 or GPC3) on a cancer cell surface in a subject to achieve cell killing, the method comprising administering to the subject an isolated monoclonal antibody or antigen binding fragment thereof and/or bispecific antibody or antigen-binding fragment thereof that specifically binds the TAA or a pharmaceutical composition comprising the isolated monoclonal antibody or antigen binding fragment thereof and/or bispecific antibody or antigen-binding fragment thereof of the invention. Binding of the TAA monoclonal or bispecific antibody or antigen-binding fragment to the TAA can mediate complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and/or antibody-dependent cellular cytotoxicity (ADCC) or other effects that result in the death of the targeted cancer cell. The monoclonal or bispecific antibody or antigen binding fragment thereof can, for example, serve to recruit conjugated drugs, and/or can form a bispecific antibody with another monoclonal antibody to mediate the death of the targeted cancer cell.

[00180] The functional activity of antibodies and antigen-binding fragments thereof that bind a TAA (e.g., TIP-1 or GPC3) can be characterized by methods known in the art and as described herein. Methods for characterizing antibodies and antigen-binding fragments thereof that bind a TAA include, but are not limited to, affinity and specificity assays including Biacore, ELISA, and OctetRed analysis, and detection of the binding of antibodies and antigen-binding fragments to the TAA on cells (either cells transfected with the TAA or cells that naturally express the TAA) by FACS. According to particular embodiments, the methods for characterizing antibodies and antigen-binding fragments thereof that bind a TAA include those described below.

[00181] In another general aspect, the invention relates to a method of treating a cancer in a subject in need thereof, comprising administering to the subject an isolated monoclonal antibody or antigen-binding fragment thereof and/or bispecific antibody or antigen-binding fragment thereof that specifically binds a TAA (e.g., TIP-1 or GPC3) or a pharmaceutical composition of the invention. The cancer can, for example, be selected from but not limited to, a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

[00182] In another general aspect, the invention relates to a method of treating an inflammatory disease in a subject in need thereof, comprising administering to the subject an isolated monoclonal antibody or antigen-binding fragment thereof and/or bispecific antibody or antigen-binding fragment thereof that specifically binds a TAA (e.g., TIP-1 or GPC3) or a pharmaceutical composition of the invention.

[00183] According to embodiments of the invention, the CAR-T cell or CAR-NK cells comprise a therapeutically effective amount of the expressed CARs of the invention and the pharmaceutical composition comprises a therapeutically effective amount of an anti-TAA antibody or antigen-binding fragment thereof (e.g., anti-TIP-1 antibody or anti-GPC3 antibody). As used herein, the term "therapeutically effective amount" refers to an amount of an active ingredient or component that elicits the desired biological or medicinal response in a subject. A therapeutically effective amount can be determined empirically and in a routine manner, in relation to the stated purpose.

[00184] As used herein with reference to CARs, a therapeutically effective amount means an amount of the CAR molecule expressed in the transduced T cell or NK cell that modulates an immune response in a subject in need thereof. Also, as used herein with reference to CARs, a therapeutically effective amount means an amount of the CAR molecule expressed in the transduced T cell or NK cell that results in treatment of a disease, disorder, or condition; prevents or slows the progression of the disease, disorder, or condition; or reduces or completely alleviates symptoms associated with the disease, disorder, or condition.

[00185] As used herein with reference to CAR-T cell or CAR-NK cell, a therapeutically effective amount means an amount of the CAR-T cells or CAR-NK cells that modulates an immune response in a subject in need thereof. Also, as used herein with reference to CAR-T cell or CAR-NK cell, a therapeutically effective amount means an amount of the CAR-T cells or CAR-NK cells that results in treatment of a disease, disorder, or condition; prevents or slows the progression of the disease, disorder, or condition; or reduces or completely alleviates symptoms associated with the disease, disorder, or condition.

[00186] As used herein with reference to anti-TAA antibodies or antigen-binding fragments thereof, a therapeutically effective amount means an amount of the anti-TAA antibody or antigen-binding fragment thereof that modulates an immune response in a subject in need thereof. Also, as used herein with reference to anti-TAA antibodies or antigen-binding fragments thereof, a therapeutically effective amount means an amount of the anti-TAA antibody or antigen-binding fragment thereof that results in treatment of a disease, disorder, or condition; prevents or slows the progression of the disease, disorder, or condition; or reduces or completely alleviates symptoms associated with the disease, disorder, or condition.

[00187] According to particular embodiments, the disease, disorder or condition to be treated is cancer, preferably a cancer selected from the group consisting of a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors. According to other particular embodiments, the disease, disorder or condition to be treated is an inflammatory disease.

[00188] According to particular embodiments, a therapeutically effective amount refers to the amount of therapy which is sufficient to achieve one, two, three, four, or more of the following effects: (i) reduce or ameliorate the severity of the disease, disorder or condition to be treated or

a symptom associated therewith; (ii) reduce the duration of the disease, disorder or condition to be treated, or a symptom associated therewith; (iii) prevent the progression of the disease, disorder or condition to be treated, or a symptom associated therewith; (iv) cause regression of the disease, disorder or condition to be treated, or a symptom associated therewith; (v) prevent the development or onset of the disease, disorder or condition to be treated, or a symptom associated therewith; (vi) prevent the recurrence of the disease, disorder or condition to be treated, or a symptom associated therewith; (vii) reduce hospitalization of a subject having the disease, disorder or condition to be treated, or a symptom associated therewith; (viii) reduce hospitalization length of a subject having the disease, disorder or condition to be treated, or a symptom associated therewith; (ix) increase the survival of a subject with the disease, disorder or condition to be treated, or a symptom associated therewith; (xi) inhibit or reduce the disease, disorder or condition to be treated, or a symptom associated therewith in a subject; and/or (xii) enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

[00189] The therapeutically effective amount or dosage can vary according to various factors, such as the disease, disorder or condition to be treated, the means of administration, the target site, the physiological state of the subject (including, e.g., age, body weight, health), whether the subject is a human or an animal, other medications administered, and whether the treatment is prophylactic or therapeutic. Treatment dosages are optimally titrated to optimize safety and efficacy.

[00190] According to particular embodiments, the compositions described herein are formulated to be suitable for the intended route of administration to a subject. For example, the compositions described herein can be formulated to be suitable for intravenous, subcutaneous, or intramuscular administration.

[00191] The cells of the invention can be administered in any convenient manner known to those skilled in the art. For example, the cells of the invention can be administered to the subject by aerosol inhalation, injection, ingestion, transfusion, implantation, and/or transplantation. The compositions comprising the cells of the invention can be administered transarterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, intrapleurally, by intravenous (i.v.) injection, or intraperitoneally. In certain embodiments, the cells of the invention can be administered with or without lymphodepletion of the subject.

[00192] The pharmaceutical compositions comprising cells of the invention expressing CARs of the invention can be provided in sterile liquid preparations, typically isotonic aqueous solutions with cell suspensions, or optionally as emulsions, dispersions, or the like, which are typically buffered to a selected pH. The compositions can comprise carriers, for example, water,

saline, phosphate buffered saline, and the like, suitable for the integrity and viability of the cells, and for administration of a cell composition.

[00193] Sterile injectable solutions can be prepared by incorporating cells of the invention in a suitable amount of the appropriate solvent with various other ingredients, as desired. Such compositions can include a pharmaceutically acceptable carrier, diluent, or excipient such as sterile water, physiological saline, glucose, dextrose, or the like, that are suitable for use with a cell composition and for administration to a subject, such as a human. Suitable buffers for providing a cell composition are well known in the art. Any vehicle, diluent, or additive used is compatible with preserving the integrity and viability of the cells of the invention.

[00194] The cells of the invention can be administered in any physiologically acceptable vehicle. A cell population comprising cells of the invention can comprise a purified population of cells. Those skilled in the art can readily determine the cells in a cell population using various well-known methods. The ranges in purity in cell populations comprising genetically modified cells of the invention can be from about 50% to about 55%, from about 55% to about 60%, from about 60% to about 65%, from about 65% to about 70%, from about 70% to about 75%, from about 75% to about 80%, from about 80% to about 85%, from about 85% to about 90%, from about 90% to about 95%, or from about 95% to about 100%. Dosages can be readily adjusted by those skilled in the art, for example, a decrease in purity could require an increase in dosage.

[00195] The cells of the invention are generally administered as a dose based on cells per kilogram (cells/kg) of body weight of the subject to which the cells are administered. Generally, the cell doses are in the range of about 10^4 to about 10^{10} cells/kg of body weight, for example, about 10^5 to about 10^9, about 10^5 to about 10^8, about 10^5 to about 10^7, or about 10^5 to about 10^6, depending on the mode and location of administration. In general, in the case of systemic administration, a higher dose is used than in regional administration, where the immune cells of the invention are administered in the region of a tumor and/or cancer. Exemplary dose ranges include, but are not limited to, 1×10^4 to 1×10^8, 2×10^4 to 1×10^8, 3×10^4 to 1×10^8, 4×10^4 to 1×10^8, 5×10^4 to 6×10^8, 7×10^4 to 1×10^8, 8×10^4 to 1×10^8, 9×10^4 to 1×10^8, 1×10^5 to 1×10^8, 1×10^5 to 9×10^7, 1×10^5 to 8×10^7, 1×10^5 to 7×10^7, 1×10^5 to 6×10^7, 1×10^5 to 5×10^7, 1×10^5 to 4×10^7, 1×10^5 to 4×10^7, 1×10^5 to 3×10^7, 1×10^5 to 2×10^7, 1×10^5 to 1×10^7, 1×10^5 to 9×10^6, 1×10^5 to 8×10^6, 1×10^5 to 7×10^6, 1×10^5 to 6×10^6, 1×10^5 to 5×10^6, 1×10^5 to 4×10^6, 1×10^5 to 4×10^6, 1×10^5 to 3×10^6, 1×10^5 to 2×10^6, 1×10^5 to 1×10^6, 2×10^5 to 9×10^7, 2×10^5 to 8×10^7, 2×10^5 to 7×10^7, 2×10^5 to 6×10^7, 2×10^5 to 5×10^7, 2×10^5 to 4×10^7, 2×10^5 to 4×10^7, 2×10^5 to 3×10^7, 2×10^5 to 2×10^7, 2×10^5 to 1×10^7, 2×10^5 to 9×10^6, 2×10^5 to 8×10^6, 2×10^5 to 7×10^6, 2×10^5 to 6×10^6, 2×10^5 to 5×10^6, 2×10^5 to 4×10^6, 2×10^5 to 4×10^6, 2×10^5 to 3×10^6, 2×10^5 to 2×10^6, 2×10^5 to 1×10^6, 3×10^5 to 3×10^6 cells/kg,

and the like. Additionally, the dose can be adjusted to account for whether a single dose is being administered or whether multiple doses are being administered. The precise determination of what would be considered an effective dose can be based on factors individual to each subject.

[00196] As used herein, the terms "treat," "treating," and "treatment" are all intended to refer to an amelioration or reversal of at least one measurable physical parameter related to a cancer and/or an inflammatory disease, disorder or condition, which is not necessarily discernible in the subject, but can be discernible in the subject. The terms "treat," "treating," and "treatment," can also refer to causing regression, preventing the progression, or at least slowing down the progression of the disease, disorder, or condition. In a particular embodiment, "treat," "treating," and "treatment" refer to an alleviation, prevention of the development or onset, or reduction in the duration of one or more symptoms associated with the disease, disorder, or condition, such as a tumor or more preferably a cancer. In a particular embodiment, "treat," "treating," and "treatment" refer to prevention of the recurrence of the disease, disorder, or condition. In a particular embodiment, "treat," "treating," and "treatment" refer to an increase in the survival of a subject having the disease, disorder, or condition. In a particular embodiment, "treat," "treating," and "treatment" refer to elimination of the disease, disorder, or condition in the subject.

[00197] According to particular embodiments, provided are compositions used in the treatment of a cancer and/or an inflammatory disease, disorder or condition. For cancer therapy, the provided compositions can be used in combination with another treatment including, but not limited to, a chemotherapy, an anti-CD20 mAb, an anti-TIM-3 mAb, an anti-LAG-3 mAb, an anti-EGFR mAb, an anti-HER-2 mAb, an anti-CD19 mAb, an anti-CD33 mAb, an anti-CD47 mAb, an anti-CD73 mAb, an anti-DLL-3 mAb, an anti-apelin mAb, an anti-FOLR1 mAb, an anti-CTLA-4 mAb, an anti-PD-L1 mAb, an anti-PD-1 mAb, an anti-Claudin 18.2 mAb, other immuno-oncology drugs, an antiangiogenic agent, a radiation therapy, an antibody-drug conjugate (ADC), a targeted therapy, or other anticancer drugs. Antibodies against a given TAA can be used to construct bispecific antibodies with partner mAbs against PD-1, PD-L1, LAG3, TIM-3, CTLA-4, EGFR, HER-2, CD19, CD20, CD33, CD73, CD47, CD3, apelin, DLL-3, TIP-1, GPC3, Claudin 18.2, folate receptor alpha (FOLR1), and/or a second TAA to treat cancers/tumors that express both TAAs. Two antibodies that recognize two different epitopes on the same TAA can also be used to construct a bispecific antibody to treat cancers/tumors that express the TAA.

[00198] According to particular embodiments, the methods of treating cancer in a subject in need thereof comprise administering to the subject the CAR-T cells and/or CAR-NK cells of the invention in combination with an agent that increases the efficacy of a cell expressing a CAR

molecule. Such agents include, but are not limited to, an antibody fragment that binds to CD73, CD39, PD1, PD-L1, PD-L2, CTLA4, TIM3 or LAG3, or an adenosine A2a receptor antagonist.

[00199] According to particular embodiments, the methods of treating cancer in a subject in need thereof comprise administering to the subject the CAR-T cells and/or CAR-NK cells of the invention in combination with an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR molecule. Such agents include, but are not limited to, a steroid, an inhibitor of TNFα, or an inhibitor of IL-6.

[00200] According to particular embodiments, the methods of treating cancer in a subject in need thereof comprise administering to the subject the CAR-T cells and/or CAR-NK cells of the invention in combination with an agent that treats the disease associated with GPC3. Such agents include, but are not limited to, an anti-GPC3 monoclonal antibody or bispecific antibody.

[00201] As used herein, the term "in combination," in the context of the administration of two or more therapies to a subject, refers to the use of more than one therapy. The use of the term "in combination" does not restrict the order in which therapies are administered to a subject. For example, a first therapy (e.g., a composition described herein) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 16 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 16 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy to a subject.

[00202] In another general aspect, the invention relates to a method of determining a level of a TAA (e.g., TIP-1 or GPC3) in a subject. The methods comprise (a) obtaining a sample from the subject; (b) contacting the sample with a monoclonal antibody or antigen-binding fragment thereof of the invention; and (c) determining a level of the TAA in the subject.

[00203] As used herein, "sample" refers to a biological sample isolated from a subject and can include, but is not limited to, whole blood, serum, plasma, blood cells, endothelial cells, tissue biopsies (e.g., a cancer tissue), lymphatic fluid, ascites fluid, interstitial fluid, bone marrow, cerebrospinal fluid, saliva, mucous, sputum, sweat, urine, or any other secretion, excretion, or other bodily fluids. A "blood sample" refers to whole blood or any fraction thereof, including blood cells, serum, and plasma.

[00204] In certain embodiments, the level of a TAA (e.g., TIP-1 or GPC3) in the subject can be determined utilizing assays selected from, but not limited to, a Western blot assay, immunohistochemistry (IHC) and an ELISA assay. Relative protein levels can be determined by utilizing Western blot analysis and IHC, and absolute protein levels can be determined by

utilizing an ELISA assay. When determining the relative levels of a TAA, the levels of the TAA can be determined between at least two samples, e.g., between samples from the same subject at different time points, between samples from different tissues in the same subject, and/or between samples from different subjects. Alternatively, when determining absolute levels of the TAA, such as by an ELISA assay, the absolute level of the TAA in the sample can be determined by creating a standard for the ELISA assay prior to testing the sample. A person skilled in the art would understand which analytical techniques to utilize to determine the level of a TAA in a sample from the subject utilizing the antibodies or antigen-binding fragments thereof of the invention.

[00205] Utilizing methods of determining a level of a TAA (e.g., TIP-1 or GPC3) in a sample from a subject can lead to the diagnosis of abnormal (elevated, reduced, or insufficient) TAA levels in a disease and making appropriate therapeutic decisions. Such a disease can be selected from, but not limited to, a cancer and an inflammatory disease. Additionally, by monitoring the levels of a TAA in a subject, the risk of developing a disease as indicated above can be determined based on the knowledge of the level of the TAA in a particular disease and/or during the progression of the particular disease.

EMBODIMENTS

[00206] The invention provides also the following non-limiting embodiments.

[00207] Embodiment 1 is an isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably specifically binds human GPC3.

[00208] Embodiment 2 is an isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a

light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably specifically binds human GPC3.

[00209] Embodiment 3 is an isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of

(1) SEQ ID NOs: 3, 4, 5, 6, 7, and 8, respectively.

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

[00210] Embodiment 4 is an isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 9, 10, 11, 12, 13, and 14, respectively.

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

[00211] Embodiment 5 is the isolated monoclonal antibody or antigen-binding fragment of any one of embodiments 1-4, comprising a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, 71, or 1, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, 72, or 2.

[00212] Embodiment 6 is the isolated monoclonal antibody or antigen-binding fragment of any one of embodiments 1-5, comprising

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72; or

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

[00213] Embodiment 7 is the isolated monoclonal antibody or antigen-binding fragment of any one of embodiments 1-6, wherein the antibody or antigen-binding fragment thereof is chimeric and/or human or humanized.

[00214] Embodiment 8 is the isolated monoclonal antibody or antigen-binding fragment of embodiment 7, wherein the humanized monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

[00215] Embodiment 9 is the isolated monoclonal antibody or antigen-binding fragment thereof of embodiment 8, wherein the humanized monoclonal antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;
(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

[00216] Embodiment 10 is the isolated monoclonal antibody or antigen-binding fragment of any one of embodiments 1-9, wherein the isolated antibody or antigen-binding fragment thereof is capable of inducing effector-mediated tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and/or complement-dependent cytotoxicity (CDC); and/or mediating the recruitment of conjugated drugs; and/or forming a bispecific antibody with another mAb or antigen-binding fragment thereof with cancer-killing effect.

[00217] Embodiment 11 is an isolated bispecific antibody or antigen-binding fragment thereof comprising the monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 1-10.

[00218] Embodiment 12 is an isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment of any one of embodiments 1-10.

[00219] Embodiment 13 is an isolated nucleic acid encoding the bispecific antibody or antigen-binding fragment thereof of embodiment 11.

[00220] Embodiment 14 is a vector comprising the isolated nucleic acid of embodiment 12 or 13.

[00221] Embodiment 15 is a host cell comprising the vector of embodiment 14.

[00222] Embodiment 16 is a pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment of any one of embodiments 1-10 or the bispecific antibody or antigen-binding fragment thereof of embodiment 11 and a pharmaceutically acceptable carrier.

[00223] Embodiment 17 is a method of targeting a TAA on a cancer cell surface, and/or treating a cancer, and/or treating an inflammatory disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of embodiment 16, optionally wherein the cancer is selected from the group consisting of a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic

melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a hon-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

[00224] Embodiment 18 is a method of producing the monoclonal antibody or antigen-binding fragment of any one of embodiments 1-10 or the bispecific antibody or antigen-binding fragment thereof of embodiment 11, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof and recovering the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof from the cell or culture.

[00225] Embodiment 19 is a method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 1-10 or the bispecific antibody or antigen-binding fragment thereof of embodiment 11, comprising combining the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

[00226] Embodiment 20 is a method of determining the level of a TAA in a subject, the method comprising:

a. obtaining a sample from the subject;
b. contacting the sample with the isolated monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 1-10; and
c. determining the level of a TAA in the subject.

[00227] Embodiment 21 is the method of embodiment 20, wherein the sample is a tissue sample or a blood sample, optionally wherein the tissue sample is a cancer tissue sample.

[00228] Embodiment 22 is an isolated polynucleotide comprising a nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises:

(a) an extracellular domain comprising at least one antigen binding domain that specifically binds GPC3;
(b) a hinge region;
(c) a transmembrane region; and
(d) an intracellular signaling domain.

[00229] Embodiment 23 is the isolated polynucleotide of embodiment 22, wherein the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

[00230] Embodiment 24 is the isolated polynucleotide of embodiment 22, wherein the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

[00231] Embodiment 25 is the isolated polynucleotide of any one of embodiments 22-24, wherein the antigen binding domain comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, or 71, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, or 72.

[00232] Embodiment 26 is the isolated polynucleotide of embodiment 25, wherein the antigen binding domain comprises:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;

b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107

c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;
f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58; or
g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72.

[00233] Embodiment 27 is the isolated polynucleotide of any one of embodiments 22-24, wherein the antigen binding domain is humanized and comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

[00234] Embodiment 28 is the isolated polynucleotide of embodiment 27, wherein the antigen binding domain is humanized and comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;
(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;

(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

[00235] Embodiment 29 is the isolated polynucleotide of any one of embodiments 22-28, wherein the antigen binding domain is a single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3.

[00236] Embodiment 30 is the isolated polynucleotide of embodiment 29, wherein the single chain variable fragment (scFv) is humanized.

[00237] Embodiment 31 is the isolated polynucleotide of embodiment 29 or 30, wherein the single chain variable fragment (scFv) comprises a polypeptide sequence at least 95% identical to any one of SEQ ID NOs: 167-182.

[00238] Embodiment 32 is the isolated polynucleotide of any one of embodiments 22-31, wherein the chimeric antigen receptor (CAR) comprises one or more antigen binding domains.

[00239] Embodiment 33 is the isolated polynucleotide of any one of embodiments 22-32, wherein the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

[00240] Embodiment 34 is a chimeric antigen receptor (CAR) encoded by the isolated polynucleotide of any one of embodiments 22-33.

[00241] Embodiment 35 is a vector comprising the isolated polynucleotide of any one of embodiments 22-33.

[00242] Embodiment 36 is a host cell comprising the vector of embodiment 35.

[00243] Embodiment 37 is the host cell of embodiment 36, wherein the host cell is a T cell, preferably a human T cell.

[00244] Embodiment 38 is the host cell of embodiment 36, wherein the host cell is a NK cell, preferably a human NK cell.

[00245] Embodiment 39 is a method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a T cell with the vector of embodiment 35.

[00246] Embodiment 40 is a method of producing a chimeric antigen receptor (CAR)-T cell, the method comprising culturing T cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of embodiments 22-33 under conditions to produce the CAR-T cell and recovering the CAR-T cell.

[00247] Embodiment 41 is a method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a NK cell with a vector of embodiment 35.

[00248] Embodiment 42 is a method of producing a chimeric antigen receptor (CAR)-NK cell, the method comprising culturing NK cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of embodiments 22-33 under conditions to produce the CAR-NK cell and recovering the CAR-NK cell.

[00249] Embodiment 43 is a method of generating a cell comprising a chimeric antigen receptor (CAR), the method comprising contacting a cell with the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of

embodiments 22-33, wherein the isolated polynucleotide is an *in vitro* transcribed RNA or synthetic RNA.

[00250] Embodiment 44 is a method of treating cancer in a subject in need thereof, comprising administering to the subject in need thereof the host cell of any one of embodiments 36-38, optionally wherein the cancer is selected from a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

[00251] Embodiment 45 is the method of embodiment 44, further comprising administering to the subject in need thereof an agent that increases the efficacy of a cell expressing a CAR.

[00252] Embodiment 46 is the method of embodiment 44, further comprising administering to the subject in need thereof an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR.

[00253] Embodiment 47 is the method of embodiment 44, further comprising administering to the subject in need thereof an agent that treats the disease associated with GPC3.

EXAMPLES

[00254] Example 1: Identification of anti-TAA monoclonal antibodies

[00255] Mice were immunized with antigens and hybridomas were produced and screened by ELISA and/or FACS. Positive clones were isolated and sequenced.

[00256] Sequences of heavy and light chain variable regions (VH and VL regions, respectively) for anti-TAA monoclonal antibodies are provided in Tables 1 and 2, and the CDR regions for the anti-TAA monoclonal antibodies are provided in Tables 3-6.

Table 1: Sequences of heavy chain variable regions for mAbs

Target	mAb clones	VH	SEQ ID NO:
TIP-1	T5	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSMHWVKQAPGK GLKWMGWIKTETGKPIYTDDFKGRFAFSLETSASTAYLQINNLK NEDTATYFCAPTGMDYWGQGTSVTVSS	1
GPC3	26A1	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPG QGLEWIGEIDPFDSYTYYNQKFKGKATLTVDKSSNTAYMQLSSL TSEDSAVYYCARRDGVYKWYFDVWGAGTTVTVSS	15

GPC3	30D11	QVQLQQSGAELVRPGASVKLSCKASGYTFTDYEMHWVKETPV HGLEWIGAIDPENGGIAFNQKFKDKATLSADKSSSTAYMELRSL TYEDSAVYYCTREEIYNDYDGVDYWGQGTTLTVSS	29
GPC3	36F8	QVQLQQSGPELVKPGASVKISCKASGYAFSNSWMNWVKQRPG KGLEWIGWIYPGDGDTNYNGKFKGKATLAADKSSSTAYMQLSS LTSEDSAVYFCARSGPITMGFTYWGQGTLVTVSA	43
GPC3	39E1	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPG QGLEWIGEIDPFDSYTYYNQKFKGKATLTVDKSSSTAYMQLSSL TSEDSAVYYCARHYGYDRWYFDVWGAGTTVTVSS	57
GPC3	43B9	QVQLQQSGPELLKPGASVKISCKASGYAFSDYWMNWVKQRPG EGLEWIGRIYPGDGDTNYSGKFKGKATLTADKSSSTAYMQLSSL TSEDSAVYFCARLSFGAWFAYWGQGTLVTVSA	71
GPC3	M3	QVQLQQSGAELVRPGASVKLSCKASGYTFTDYEMHWVKQTPV HGLEWIGAIDPETGDTAYNQKFKGKATLTADKSSSTAYMDLRS LTSEDSAVYYCTRYFSFAYWGQGTLVTVSA	85
GPC3	F7	EVKLEESGGGLVQPGGSMKLSCVASGFTFSNYWMNWVRQSPE KGLEWVAQIRLKSDNYATHYAESVKGRFTISRDDSKSSVYLQM NNLRAEDTGIYYCTVGGNYWGQGTSVTVSS	106

VH: heavy chain variable region

Table 2: Sequences of light chain variable regions for mAbs

Target	**mAb clones**	**VL**	**SEQ ID NO:**
TIP-1	T5	DVVMTQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWLLQRP GQSPKRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISRVEAEDLGV YYCWQGTHFPRTFGGGTKLEIK	2
GPC3	26A1	DIQMTQSPSSLSASLGGKVTITCKASQDINKSIAWYQHKPGKGPR LLIHYTSTLQPGIPSRFSGSGSGRDYSFSISNLEPEDIATYYCLQYD SLLYTFGGGTKLEIK	16
GPC3	30D11	DVVMTQTPLSLSVTIGQPASISCKSSQSLLYSDGKTYLNWLQQRP GQSPKRLMYQVSKLDPGIPDRFSGSGSETDFTLKISRVEAEDLGV YYCLQVTYYPYTFGGGTKLEIK	30
GPC3	36F8	DIQMTQTTSSLSASLGDRVTISCSASQGISNYLSWYQQKPDGTVK LLIYYTSNLHSGVPSRFSGSESGTDYSLTITNLEPEDIATYYCQQY SKFPWTFGGGTKLEIK	44
GPC3	39E1	DIQMTQSPSSLSASLGGKVTITCKASQDINKYIVWYQHKPGKGP RLLIHYTSTLQPGIPSRFSGSGSGRDYSFSISNLEPEDIATYYCQQY DNLLRTFGGGTKLEIK	58
GPC3	43B9	DIQMTQSPSSLSASLGGKVTITCKASRDINKYIGWYQHKPGKGP RLLIHYTSTLQPGTPSRFSGSGSGRDYSFSISNLEPEDIATYYCLQ YDNLYTFGGGTKLEIK	72
GPC3	M3	DVVMTQTPLSLPVSLGDQASISCRSSQSLRHSNGNTYLQWYLQK PGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGI YFCYQSKHVPYTFGGGTKLEIK	86
GPC3	F7	AIQMTQSPSSLSASLGERVSLTCRASQEISGNLGWLQQKPHGTIK RLIYAATTLDSGVPKRFSGSRSGSDYTLTISSLESEDFADYYCLQ YDSYPWTFGGGTKLEIK	107

VL: light chain variable region

Table 3: CDR regions 1-3 of heavy chain for mAbs

Target	**mAb clones**	**HC CDR1**	**NO**	**HC CDR2**	**NO**	**HC CDR3**	**NO**
TIP-1	T5	GYTFTDYS	3	IKTETGKP	4	APTGMDY	5
GPC3	26A1	GYTFTSYW	17	IDPFDSYT	18	ARRDGVYKWYFDV	19
GPC3	30D11	GYTFTDYE	31	IDPENGGI	32	TREEIYNDYDGVDY	33

GPC3	36F8	GYAFSNSW	45	IYPGDGDT	46	ARSGPITMGFTY	47
GPC3	39E1	GYTFTSYW	59	IDPFDSYT	60	ARHYGYDRWYFDV	61
GPC3	43B9	GYAFSDYW	73	IYPGDGDT	74	ARLSFGAWFAY	75
GPC3	M3	GYTFTDYE	87	IDPETGDT	88	TRYFSFAY	89
GPC3	F7	GFTFSNYW	108	IRLKSDNYAT	109	TVGGNY	110

HC: heavy chain; CDR: complementarity determining region; NO: SEQ ID NO

The HC CDRs for the anti-TAA mAbs were determined utilizing the IMGT method (Lefranc, M.-P. et al., Nucleic Acids Res. 1999; 27:209-212).

Table 4: CDR regions 1-3 of light chain for mAbs

Target	mAb clones	LC CDR1	NO	LC CDR2	NO	LC CDR3	NO
TIP-1	T5	QSLLDSDGKTY	6	LVS	7	WQGTHFPRT	8
GPC3	26A1	QDINKS	20	YTS	21	LQYDSLLYT	22
GPC3	30D11	QSLLYSDGKTY	34	QVS	35	LQVTYYPYT	36
GPC3	36F8	QGISNY	48	YTS	49	QQYSKFPWT	50
GPC3	39E1	QDINKY	62	YTS	63	QQYDNLLRT	64
GPC3	43B9	RDINKY	76	YTS	77	LQYDNLYT	78
GPC3	M3	QSLRHSNGNTY	90	KVS	91	YQSKHVPYT	92
GPC3	F7	QEISGN	111	AAT	112	LQYDSYPWT	113

LC: light chain; CDR: complementarity determining region; NO: SEQ ID NO

The LC CDRs for the anti-TAA mAbs were determined utilizing the IMGT method (Lefranc, M.-P. et al., Nucleic Acids Res. 1999; 27:209-212).

Table 5: CDR regions 1-3 of heavy chain for mAbs

Target	mAb clones	HC CDR1	NO	HC CDR2	NO	HC CDR3	NO
TIP-1	T5	DYSMH	9	WIKTETGKPIYTDDFKG	10	TGMDY	11
GPC3	26A1	SYWMH	23	EIDPFDSYTYYNQKFKG	24	RDGVYKWYFDV	25
GPC3	30D11	DYEMH	37	AIDPENGGIAFNQKFKD	38	EEIYNDYDGVDY	39
GPC3	36F8	NSWMN	51	WIYPGDGDTNYNGKFKG	52	SGPITMGFTY	53
GPC3	39E1	SYWMH	65	EIDPFDSYTYYNQKFKG	66	HYGYDRWYFDV	67
GPC3	43B9	DYWMN	79	RIYPGDGDTNYSGKFKG	80	LSFGAWFAY	81
GPC3	M3	DYEMH	93	AIDPETGDTAYNQKFKG	94	YFSFAY	95
GPC3	F7	NYWMN	114	QIRLKSDNYATHYAESVKG	115	GGNY	116

HC: heavy chain; CDR: complementarity determining region; NO: SEQ ID NO

The HC CDRs for the anti-TAA mAbs were determined utilizing the Kabat method (Elvin A. Kabat et al, Sequences of Proteins of Immunological Interest 5th ed. 1991).

Table 6: CDR regions 1-3 of light chain for mAbs

Target	mAb clones	LC CDR1	NO	LC CDR2	NO	LC CDR3	NO
TIP-1	T5	KSSQSLLDSDGKTYLN	12	LVSKLDS	13	WQGTHFPRT	14
GPC3	26A1	KASQDINKSIA	26	YTSTLQP	27	LQYDSLLYT	28
GPC3	30D11	KSSQSLLYSDGKTYLN	40	QVSKLDP	41	LQVTYYPYT	42
GPC3	36F8	SASQGISNYLS	54	YTSNLHS	55	QQYSKFPWT	56

GPC3	39E1	KASQDINKYIV	68	YTSTLQP	69	QQYDNLLRT	70
GPC3	43B9	KASRDINKYIG	82	YTSTLQP	83	LQYDNLYT	84
GPC3	M3	RSSQSLRHSNGNTYLQ	96	KVSNRFS	97	YQSKHVPYT	98
GPC3	F7	RASQEISGNLG	117	AATTLDS	118	LQYDSYPWT	119

LC: light chain; CDR: complementarity determining region; NO: SEQ ID NO

The LC CDRs for the anti-TAA mAbs were determined utilizing the Kabat method (Elvin A. Kabat et al, Sequences of Proteins of Immunological Interest 5th ed. 1991).

[00257] Example 2: Production and purification of mAbs from culture media of transfected cells

[00258] To obtain recombinant anti-TAA chimeric mAbs, the expression vectors containing the mouse variable regions (VH and VL) fused to the constant regions of human IgG1 heavy chain and kappa light chain, respectively, were transiently transfected into ExpiCHO-S or Expi293F cells. The recombinant antibodies produced in the suspension of the ExpiCHO-S or Expi293F cells were purified using Protein A affinity chromatography.

[00259] Example 3: ELISA binding analysis of purified chimeric mAbs

[00260] Purified chimeric mAbs were tested in an ELISA assay for their ability to bind to immobilized TIP-1. Recombinant human TIP-1 in PBS buffer was coated on a 96-well plate at room temperature for 1 hour. The plate is blocked by 5% BSA in TBST for 1 hour at room temperature. In each well of an individual plate, mAbs at various concentrations were incubated for 1 hour at room temperature. The plate was washed and the binding to TIP-1 was detected by anti-human IgG conjugated to horseradish peroxidase (hIgG-HRP) (ThermoFisher Scientific, Cat#: H10007) with incubation for 1 hour at room temperature. Then after washing, the ELISA was developed using One-step Detection Solution (ThermoFisher Scientific, Cat#: 34028) and measured as the absorbance at 450 nm. The anti-GPC3 chimeric antibodies were tested in a similar assay except that a nickel coated plate (ThermoFisher, Cat#: 15442) was used. The results are shown in FIG. 1 and FIGs. 2A-2B.

[00261] Example 4: FACS binding analysis of purified mAbs

[00262] HEK293 cells expressing the full-length human GPC3 were transferred to a 96-well plate. Around 50,000 cells were incubated with purified chimeric anti-GPC3 mAbs (variable regions of mouse mAbs fused to the constant regions of human IgG1 heavy chain and kappa light chain, respectively) at various concentrations for 15 minutes at 4°C. In some instances, 100,000 cells per well were used. Cells were then centrifuged for 5 minutes and washed once with FACS buffer (HBSS supplemented with 5% BSA and 0.05% sodium azide). The cells were

then incubated with Alexa Fluor 488-conjugated anti-human IgG secondary antibody (ThermoFisher, Cat#: H10120) and incubated on ice for another 15 minutes. Cells were then washed with FACS buffer once and resuspended in FACS buffer. Cells were then run through the Attune NxT and the data were analyzed by the Attune NxT software. The results are shown in FIGs. 2C-2E. HEK293 cells with no GPC3 expression were used as negative control (FIG. 2F-2G).

[00263] Example 5: Humanization of anti-GPC3 mAbs

[00264] The mouse anti-GPC3 mAbs were humanized to reduce the potential of immunogenicity when used in human patients. The sequences of the variable regions of the heavy and light chains (VH and VL) were compared with the human antibody sequences in the Protein Data Bank (PDB) database and homology models were built. The CDRs in both the heavy and light chains of the mouse mAbs were grafted into human frameworks that have the highest possibility of maintaining the proper structure likely required for antigen binding. Backmutations from human residues to mouse residue or other mutations were designed when necessary. The sequences of the humanized VH and VL regions are shown in Table 7. The humanized VH and VL regions were fused to the constant regions of human IgG1 heavy chain and kappa light chain, respectively. The binding of the humanized mAbs to GPC3 was assessed using FACS assay (FIGs. 3A-3O). M3-H1L1 refers to the humanized mAb constructed with M3-H1 heavy chain and M3-L1 light chain shown in Table 7; other humanized clones follow the same naming rule.

Table 7: Sequences of heavy chain and light chain variable regions of humanized anti-GPC3 mAbs

VH/VL	SEQUENCE	NO
M3-H1	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGQGLEWIG AIDPETGDTAYNQKFKGRATLTADKSTSTAYMELSSLRSEDTAVYYCTRY FSFAYWGQGTLVTVSS	99
M3-H2	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGDTAYNQKFKGRATLTADTSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	100
M3-H3	EVVLVESGGGLVQPGGSLRLSCAASGYTFTDYEMSWVRQAPGKGLEWIG AIDPETGDTYYADSVKGRATLSADKSKNTAYLQMNSLRAEDTAVYYCTR YFSFAYWGQGTLVTVSS	101
M3-H4	EVQLVESGAEVKKPGESLKISCKASGYTFTDYEIGWVRQMPGKGLEWIGII DPETGDTRYSPSFQGQATLSADKSISTAYLQWSSLKASDTAMYYCTRYFSF AYWGQGTMVTVSS	102
M3-L1	DVQMTQSPSSVSASVGDRVTITCRSSQSLRHSNGNTYLQWYQQKPGKAPK LLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCYQSKHVPYTF GQGTKVEIK	103

M3-L2	EVVMTQSPATLSLSPGERATLSCRSSQSLRHSNGNTYLQWYQQKPGQAPR LLIYKVSNRFSGVPARFSGSGSGTDFTLTISSLEPEDFAVYFCYQSKHVPYT FGGGTKVEIK	104
M3-L3	EVVMTQSPATLSLSPGERATLSCRSSQSLRHSNGNTYLQWYQQKPGQAPR LLIYKVSNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYFCYQSKHVPYTF GQGTKVEIK	105
26A1-H1	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWI GEIDPFDSYTYYNQKFKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCAR RDGVYKWYFDVWGQGTLVTVSS	120
26A1-H2	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGKGLEWI GEIDPFDSYTYYNQKFKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCAR RDGVYKWYFDVWGQGTLVTVSS	121
26A1-H3	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMHWVRQAPGKGLEWIG EIDPFDSYTYYNQKFKGRATLSVDKSKNTAYLQMNSLRAEDTAVYYCAR RDGVYKWYFDVWGQGTLVTVSS	122
26A1-H4	EVQLVESGGGLVQPGGSLRLSCKASGYTFTSYWMHWVRQAPGKGLEWIG EIDPFDSYTYYNQKFKGRATLSVDKSKNTAYLQMNSLRAEDTAVYYCAR RDGVYKWYFDVWGQGTLVTVSS	123
26A1-L1	DIQMTQSPSSVSASVGDRVTITCKASQDINKSIAWYQHKPGKAPKLLIHYT STLQPGVPSRFSGSGSGRDYTLTISSLQPEDFATYYCLQYDSLLYTFGQGTK VEIK	124
26A1-L2	DIQMTQSPSSLSASVGDRVTITCKASQDINKSIAWYQHKPGKAPKLLIHYTS TLQPGVPSRFSGSGSGRDFTLTISSLQPEDFATYYCLQYDSLLYTFGQGTKV EIK	125
30D11-H1	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVREAPGQGLEWIG AIDPENGGIAFNQKFKDRATLTADKSTSTAYMELSSLRSEDTAVYYCTREE IYNDYDGVDYWGQGTLVTVSS	126
30D11-H2	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEMHWVREAPGQGLEWI GAIDPENGGIAFNQKFKDRATLTADKSTSTAYMELSSLRSEDTAVYYCTRE EIYNDYDGVDYWGQGTLVTVSS	127
30D11-H3	EVQLLESGGGLVQPGGSLRLSCAASGYTFTDYEMHWVREAPGKGLEWIG AIDPENGGIAFNQKFKDRATLSADKSKNTAYLQMNSLRAEDTAVYYCTRE EIYNDYDGVDYWGQGTMVTVSS	128
30D11-H4	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEFHWVREAPGQGLEWIG IIDPENGGISYAQKFGDRAILTADKSTSTAYMELSSLRSEDTAVYYCTREEI YNDYDGVDYWGQGTLVTVSS	129
30D11-H5	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEMHWVREAPGQGLEWI GIIDPENGGISYAQKFGDRAILTADKSTSTAYMELSSLRSEDTAVYYCTREE IYNDYDGVDYWGQGTLVTVSS	130
30D11-H6	EQQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEISWVREAPGQGLEWIGS IDPENGGINYAQKFQGRATLTADKSTSTAYMELSSLRSEDTAVYYCTREEI YNDYDGVDYWGQGTLVTVSS	131
30D11-H7	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMSWVREAPGQGLEWIG AIDPENGGIAFAQKFQGRATLTADKSTSTAYMELSSLRSEDTAVYYCTREE IYNDYDGVDYWGQGTLVTVSS	132
30D11-L1	DVVMTQSPDSLAVSLGERATINCKSSQSLLYSDGKTYLNWLQQKPGQPPK RLMYQVSKLDPGVPDRFSGSGSETDFTLTISSLQAEDVAVYYCLQVTYYP YTFGQGTRLEIK	133
30D11-L2	DVQMTQSPSTLSASVGDRVTITCRSSQSLLYSDGKTYLNWLQQKPGKAPK RLMYQVSKLDPGVPSRFSGSGSETEFTLTISSLQPDDFATYYCLQVTYYPY TFGQGTKVEIK	134
30D11-L3	EVVMTQSPSSLSASVGDRVTITCRSSQSLLYSDGKTYLNWLEQKPGKAPK RLMYQVSSLQSGVPSRFSGSGSETEFTLTISSLQPEDFATYYCLQVTYYPYT FGQGTRLEIK	135
30D11-L4	DIQMTQSPSSLSASVGDRVTITCRSSQSLLYSDGKTYLNWLEQKPGKAPKR LMYQVSKLQSGVPSRFSGSGSETEFTLTISSLQPEDFATYYCLQVTYYPYTF GQGTRLEIK	136
30D11-L5	DVQMTQSPSSVSASVGDRVTITCRSSQSLLYSDGKTYLNWLQQKPGKAPK RLMYQVSSLQSGVPSRFSGSGSETDFTLTISSLQPEDFATYYCLQVTYYPYT FGQGTKVEIK	137

30D11-L6	DVQMTQSPSSVSASVGDRVTITCRSSQSLLYSDGKTYLNWLQQKPGKAPK RLMYQVSKLQSGVPSRFSGSGSETDFTLTISSLQPEDFATYYCLQVTYYPY TFGQGTKVEIK	138
36F8-H1	QVQLVQSGAEVKKPGASVKVSCKASGYAFSNSWMHWVRQAPGQGLEWI GWIYPGDGDTNYAQKFQGRATLTADKSISTAYMELSRLRSDDTAVYFCAR SGPITMGFTYWGQGTLVTVSS	139
36F8-H2	QVQLVQSGAEVKKPGASVKVSCKASGYAFSNSWMNWVRQAPGQGLEWI GWIYPGDGDTNYAQKFQGRATLTADKSISTAYMELSRLRSDDTAVYFCAR SGPITMGFTYWGQGTLVTVSS	140
36F8-L1	EIVMTQSPATLSLSPGERATLSCRASQGISNYLSWYQQKPGQAVRLLIYYT SNRATGIPARFSGSESGTDYTLTISSLEPEDFAVYYCQQYSKFPWTFGQGTK LEIK	141
36F8-L2	EIVMTQSPATLSLSPGERATLSCRASQGISNYLSWYQQKPGQAVRLLIYYT SNLHTGIPARFSGSESGTDYTLTISSLEPEDFAVYYCQQYSKFPWTFGQGTK LEIK	142
39E1-H1	QVQLEESGPGLVKPSETLSLTCSASGYTFTSYWMHWVRQPPGKGLEWIGE IDPFDSYTYYNQKFKGRATLSVDKSKNEASLRLTSVTAADTAVYYCARHY GYDRWYFDVWGQGTLVTVSS	143
39E1-H2	QVQLEESGPGLVKPSETLSLTCTASGYTFTSYWMHWVRQPPGKGLEWIGE IDPFDSYTYYNQKFKGRATISVDKSKNEASLRLTSVTAADTAVYYCARHY GYDRWYFDVWGQGTLVTVSS	144
39E1-H3	QVQLEESGPGLVKPSETLSLTCTASGYTFTSYWMHWVRQPPGKGLEWIGE IDPFDSYTYYNPKFKGRATISVDKSKNEASLRLTSVTAADTAVYYCARHY GYDRWYFDVWGQGTLVTVSS	145
39E1-H4	QVVLVQSGAEVKKPGSSVKVSCKASGYTFTSYWISWVRQAPGQGLEWIG GIDPFDSYTNYAQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARH YGYDRWYFDVWGQGTLVTVSS	146
39E1-H5	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWI GEIDPFDSYTYYAQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCAR HYGYDRWYFDVWGQGTLVTVSS	147
39E1-H6	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWI GEIDPFDSYTYYNQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCAR HYGYDRWYFDVWGQGTLVTVSS	148
39E1-H7	EVQLVQSGAEVKKPGESLKISCKASGYTFTSYWMHWVRQMPGKGLEWIG EIDPFDSYTYYAPSFQGQATLSVDKSISTAYLQWSSLKASDTAMYYCARH YGYDRWYFDVWGQGTLVTVSS	149
39E1-L1	DIVMTQSPSSLSASIGDRVTITCKASQDINKYIVWYQHKPGKAPKLLIHYTS TLQPGVPSRFSGSGSGREYTLTIRSLQPEDFATYYCQQYDNLLRTFGQGTK VEIK	150
39E1-L2	DIQMTQSPSSLSASVGDRVTITCRASQDINKYLVWYQHKPGKAPKLLIHYT SSLQSGVPSRFSGSGSGRDYTLTISSLQPEDFATYYCQQYDNLLRTFGQGT KVEIK	151
39E1-L3	DIQMTQSPSSLSASVGDRVTITCKASQDINKYIVWYQHKPGKAPKLLIHYT STLQSGVPSRFSGSGSGRDYTLTISSLQPEDFATYYCQQYDNLLRTFGQGT KVEIK	152
43B9-H1	EVQLVQSGAEVKKPGATVKISCKASGYAFSDYWMYWVRQAPGKGLEWI GLIYPGDGDTMYAEKFRGRATLTADKSTDTAYLELSSLRSEDTAVYFCAR LSFGAWFAYWGQGTLVSVSS	153
43B9-H2	EVQLVQSGAEVKKPGATVKISCKASGYAFSDYWMNWVRQAPGKGLEWI GRIYPGDGDTNYAEKFRGRVTITADTSTDTAYLELSSLRSEDTAVYYCARL SFGAWFAYWGQGTTVTVSS	154
43B9-H3	EVQLVESGGGLVQPGGSLRLSCAASGYAFSDYWMNWVRQAPGKGLEWI GRIYPGDGDTNYSGKFKGRATLSADKSKNTAYLQMNSLRAEDTAVYFCA RLSFGAWFAYWGQGTLVTVSS	155
43B9-H4	EVQLVESGGGLVQPGGSLRLSCKASGYAFSDYWMNWVRQAPGKGLEWI GRIYPGDGDTNYSGKFKGRATLSADKSKNTAYLQMNSLRAEDTAVYFCA RLSFGAWFAYWGQGTLVTVSS	156
43B9-L1	DIQMTQSPSSVSASVGDRVTITCRASRDINKYLGWYQHKPGKAPKLLIHYT STLQSGVPSRFSGSGSGRDYSLTINSLQPEDFATYYCLQYDNLYTFGGGTK VEIK	157

43B9-L2	DIQMTQSPSSLSASVGDRVTITCRASRDINKYLGWYQQKPGKAPKLLIHYT STLQSGVPSRFSGSGSGRDFSLTINSLQPEDFATYYCLQYDNLYTFGGGTK VEIK	158
43B9-L3	DIQMTQSPSSLSASVGDRVTITCKASRDINKYIGWYQHKPGKAPKLLIHYT STLQPGVPSRFSGSGSGRDYTLTISSLQPEDFATYYCLQYDNLYTFGQGTK VEIK	159
F7-H1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYAESVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYYC TVGGNYWGQGTLVTVSS	160
F7-H2	EVQLVESGGGLVQPGGSLRLSCVASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYAESVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYYC TVGGNYWGQGTLVTVSS	161
F7-H3	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATYYAESLEGRFTISRDDSKNSVYLQMNSLKTEDTAVYYC TVGGNYWGQGTLVTVSS	162
F7-H4	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYAESLEGRFTISRDDSKNSVYLQMNSLKTEDTAVYYC TVGGNYWGQGTLVTVSS	163
F7-L1	DIQMTQSPSSLSASVGDRVTITCRASQEISGNLGWLQQKPGKAIKRLIYAAT TLDSGVPSRFSGSRSGSDYTLTISSLQPEDFATYYCLQYDSYPWTFGQGTK VEIK	164
F7-L2	DIQMTQSPSSLSASVGDRVTITCQASQEISGNLGWLQQKPGKAIKRLIYAA TNLADGVPSRFSGSRSGSDYTLTISSLQPEDFATYYCLQYDSYPWTFGQGT KLEIK	165
F7-L3	DIQMTQSPSSLSASVGDRVTITCRASQEISGNLGWLQQKPGKAIKRLIYAAT TLADGVPSRFSGSRSGSDYTLTISSLQPEDFATYYCLQYDSYPWTFGQGTK LEIK	166
M3-H5	QVQLVQSGSGVKKPGASVRVSCWASGYTFTDYEMHWVRQAPGQGLEWI GAIDPETGDTAYNQKFKGRASLTADKDLFTAHMDIRGLTQGDTATYYCTR YFSFAYWGRGTLIVVSS	183
M3-H6	QVQLVQSGAEMKKPGASVKVSCKASGYTFTDYEINWVRQAPGQGLEWIG WMDPETGDTGYPQKFQGRATLTANKSISTAYMELSSLRSEDTAVYYCTRY FSFAYWGQGTTVTVSS	184
M3-H7	QVQLVQSGVEVKKPGASVKVSCKASGYTFTDYEMHWVRQAPGQGLEWI GAIDPETGDTAYNQKFKGRATLTADKSTTTAYMELKSLQFDDTAVYYCT RYFSFAYWGQGTTVTVSS	185
M3-H8	QVQLVQSGVEVKKPGASVKVSCKASGYTFTDYEMHWVKQAPGQGLEWI GAIDPETGDTAYNQKFKGKATLTADKSTTTAYMELKSLQFDDTAVYYCT RYFSFAYWGQGTTVTVSS	186
M3-H9	QVQLVQSGVEVKKPGASVKVSCKASGYTFTDYEMHWVRQAPGQGLEWI GAIDPETGATAYNQKFKGRATLTADKSTTTAYMELKSLQFDDTAVYYCT RYFSFAYWGQGTTVTVSS	187
M3-H10	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGQGLEWIG AIDPETGATAYNQKFKGRATLTADKSTSTAYMELSSLRSEDTAVYYCTRY FSFAYWGQGTLVTVSS	188
M3-H11	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGDTAYNQKFKGRATLTADKSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	189
M3-H12	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGDTAYNQKFKGKATLTADKSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	190
M3-H13	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGATAYNQKFKGKATLTADKSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	191
M3-H14	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGDTAYNQKFKGKATLTADTSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	192
M3-H15	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGATAYNQKFKGKATLTADTSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	193

M3-H16	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGHGLEWI GAIDPETGDTAYNQKFKGKATLTADKSTTTAYMELSSLQFDDTAVYYCTR YFSFAYWGQGTLVTVSS	194
M3-H18	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVKQAPGHGLEWI GAIDPETGDTAYNQKFKGKATLTADTSTSTAYMELSSLRSEDTAVYYCTR YFSFAYWGQGTLVTVSS	195
M3-H19	QVTLRESGPALVKPTQTLTLTCTASGYTFTDYEMHWVRQPPGKALEWIGA IDPETGDTAYNQKFKGRATLSADKSKNQAVLTMTNMDPVDTATYYCTRY FSFAYWGQGSLVTVSS	196
M3-H20	QVTLRESGPALVKPTQTLTLTCKASGYTFTDYEMHWVKQPPGKALEWIG AIDPETGDTAYNQKFKGKATLSADKSKNQAVLTMTNMDPVDTATYYCTR YFSFAYWGQGSLVTVSS	197
M3-L4	EVVMTQSPGTLSLSPGETASLSCRSSQSLRHSNGNTYLQWYQQKPGQPPK LLIYKVSNRFSGIPDRFSGSGFGTQFTLTITRMEPEDFARYFCYQSKHVPYT FGQGTRLEIR	198
M3-L5	EVVMTQSPATLSLSPGERATISCRSSQSLRHSNGNTYLQWYQQKPGQAPR LLIYKVSNRFSGVPARFSGSGSGTDFTLTISSLEPEDFAVYFCYQSKHVPYT FGGGTKVEIK	199
M3-L6	EIVLTQSPATLSLSPGERATISCRSSQSLRHSNGNTYLQWYQQKPGQAPRLL IYKVSNRFSGVPARFSGSGSGTDFTLTISSLEPEDFAVYFCYQSKHVPYTFG GGTKVEIK	200
M3-L7	DVVMTQSPDSLSVSLGERATINCRSSQSLRHSNGNTYLQWYQQKPGQPPK LLIYKVSNRFSGVPDRFSGSGSGTDFTLTISSLQAEDVAVYFCYQSKHVPYT FGGGTKVEIK	201
F7-H5	QVQLVESGGGVVQPGKSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYADSVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYY CTVGGNYWGQGTLVTVSS	202
F7-H6	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQATGKGLEWV AQIRLKSDNYATHYPDSVKGRFTISREDAKNSVYLQMNSLRAGDTAVYYC TVGGNYWGQGTTVTVSS	203
F7-H9	EVQLVESGGGLVQPGRSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYAESVKGRFTISRDDAKNSVYLDMNSLRAEDTAVYY CTVGGNYWGQGTLVTVSS	204
F7-H10	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYADSVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYY CTVGGNYWGQGTLVTVSS	205

NO: SEQ ID NO.

[00265] Example 6: Construction of anti-GPC3 mAbs scFv molecules

[00266] The humanized sequences of the anti-GPC3 mAbs were used to construct scFv molecules which were fused to the human IgG1 Fc region. The sequences of the designed scFv molecules are listed in Table 8. The fusion molecules were expressed in CHO cells and purified and tested for binding to GPC3 using FACS assay (FIG.s 4A-4E).

Table 8: Sequences of Single Chain Fragment Variable (ScFv) of humanized anti-GPC3 mAbs

VH/VL	SEQUENCE	NO
M3-H1L1/VH-(G4S)4-VL	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGQGLEWIG AIDPETGDTAYNQKFKGRATLTADKSTSTAYMELSSLRSEDTAVYYCTRY FSFAYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDVQMTQSPSSVSA SVGDRVTITCRSSQSLRHSNGNTYLQWYQQKPGKAPKLLIYKVSNRFSGVP SRFSGSGSGTDFTLTISSLQPEDFATYFCYQSKHVPYTFGQGTKVEIK	167
M3-H1L1/VH-(G4S)3-VL	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYEMHWVRQAPGQGLEWIG AIDPETGDTAYNQKFKGRATLTADKSTSTAYMELSSLRSEDTAVYYCTRY	168

	FSFAYWGQGTLVTVSSGGGGSGGGGSGGGGSDVQMTQSPSSVSASVGDR VTITCRSSQSLRHSNGNTYLQWYQQKPGKAPKLLIYKVSNRFSGVPSRFSG SGSGTDFTLTISSLQPEDFATYFCYQSKHVPYTFGQGTKVEIK	
M3-H1L1/VL -(G4S)4-VH	DVQMTQSPSSVSASVGDRVTITCRSSQSLRHSNGNTYLQWYQQKPGKAPK LLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCYQSKHVPYTF GQGTKVEIKGGGGSGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGSSVKV SCKASGYTFTDYEMHWVRQAPGQGLEWIGAIDPETGDTAYNQKFKGRAT LTADKSTSTAYMELSSLRSEDTAVYYCTRYFSFAYWGQGTLVTVSS	169
M3-H1L1/VL -(G4S)3-VH	DVQMTQSPSSVSASVGDRVTITCRSSQSLRHSNGNTYLQWYQQKPGKAPK LLIYKVSNRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCYQSKHVPYTF GQGTKVEIKGGGGSGGGGSGGGGSEVQLVQSGAEVKKPGSSVKVSCKAS GYTFTDYEMHWVRQAPGQGLEWIGAIDPETGDTAYNQKFKGRATLTADK STSTAYMELSSLRSEDTAVYYCTRYFSFAYWGQGTLVTVSS	170
26A1-H3L2 / VH-(G4S)4-VL	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMHWVRQAPGKGLEWIG EIDPFDSYTYYNQKFKGRATLSVDKSKNTAYLQMNSLRAEDTAVYYCARR DGVYKWYFDVWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQS PSSLSASVGDRVTITCKASQDINKSIAWYQHKPGKAPKLLIHYTSTLQPGVP SRFSGSGSGRDFTLTISSLQPEDFATYYCLQYDSLLYTFGQGTKVEIK	171
26A1-H3L2/ VH-(G4S)3-VL	EVQLVESGGGLVQPGGSLRLSCAASGYTFTSYWMHWVRQAPGKGLEWIG EIDPFDSYTYYNQKFKGRATLSVDKSKNTAYLQMNSLRAEDTAVYYCARR DGVYKWYFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCKASQDINKSIAWYQHKPGKAPKLLIHYTSTLQPGVPSRFSGS GSGRDFTLTISSLQPEDFATYYCLQYDSLLYTFGQGTKVEIK	172
43B9-H1L2/ VH-(G4S)4-VL	EVQLVQSGAEVKKPGATVKISCKASGYAFSDYWMYWVRQAPGKGLEWI GLIYPGDGDTMYAEKFRGRATLTADKSTDTAYLELSSLRSEDTAVYFCAR LSFGAWFAYWGQGTLVSVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPS SLSASVGDRVTITCRASRDINKYLGWYQQKPGKAPKLLIHYTSTLQSGVPS RFSGSGSGRDFSLTINSLQPEDFATYYCLQYDNLYTFGGGTKVEIK	173
43B9-H1L2/ VH-(G4S)3-VL	EVQLVQSGAEVKKPGATVKISCKASGYAFSDYWMYWVRQAPGKGLEWI GLIYPGDGDTMYAEKFRGRATLTADKSTDTAYLELSSLRSEDTAVYFCAR LSFGAWFAYWGQGTLVSVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASV GDRVTITCRASRDINKYLGWYQQKPGKAPKLLIHYTSTLQSGVPSRFSGSG SGRDFSLTINSLQPEDFATYYCLQYDNLYTFGGGTKVEIK	174
36F8-H2L1/ VH-(G4S)4-VL	QVQLVQSGAEVKKPGASVKVSCKASGYAFSNSWMNWVRQAPGQGLEWI GWIYPGDGDTNYAQKFQGRATLTADKSISTAYMELSRLRSDDTAVYFCAR SGPITMGFTYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSEIVMTQSPA TLSLSPGERATLSCRASQGISNYLSWYQQKPGQAVRLLIYYTSNRATGIPAR FSGSESGTDYTLTISSLEPEDFAVYYCQQYSKFPWTFGQGTKLEIK	175
36F8-H2L1/ VH-(G4S)3-VL	QVQLVQSGAEVKKPGASVKVSCKASGYAFSNSWMNWVRQAPGQGLEWI GWIYPGDGDTNYAQKFQGRATLTADKSISTAYMELSRLRSDDTAVYFCAR SGPITMGFTYWGQGTLVTVSSGGGGSGGGGSGGGGSEIVMTQSPATLSLSP GERATLSCRASQGISNYLSWYQQKPGQAVRLLIYYTSNRATGIPARFSGSES GTDYTLTISSLEPEDFAVYYCQQYSKFPWTFGQGTKLEIK	176
39E1-H6L3/ VH-(G4S)4-VL	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWI GEIDPFDSYTYYNQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCAR HYGYDRWYFDVWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQ SPSSLSASVGDRVTITCKASQDINKYIVWYQHKPGKAPKLLIHYTSTLQSGV PSRFSGSGSGRDYTLTISSLQPEDFATYYCQQYDNLLRTFGQGTKVEIK	177
39E1-H6L3/ VH-(G4S)3-VL	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWI GEIDPFDSYTYYNQKFQGRATLTVDKSTSTAYMELSSLRSEDTAVYYCAR HYGYDRWYFDVWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLS ASVGDRVTITCKASQDINKYIVWYQHKPGKAPKLLIHYTSTLQSGVPSRFS GSGSGRDYTLTISSLQPEDFATYYCQQYDNLLRTFGQGTKVEIK	178
F7-H1L1/ VH-(G4S)4-VL	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYAESVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYYC TVGGNYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLS ASVGDRVTITCRASQEISGNLGWLQQKPGKAIKRLIYAATTLDSGVPSRFSG SRSGSDYTLTISSLQPEDFATYYCLQYDSYPWTFGQGTKVEIK	179
F7-H1L1/ VH-(G4S)3-VL	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMNWVRQAPGKGLEWV AQIRLKSDNYATHYAESVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYYC TVGGNYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGD	180

	RVTITCRASQEISGNLGWLQQKPGKAIKRLIYAATTLDSGVPSRFSGSRSGS DYTLTISSLQPEDFATYYCLQYDSYPWTFGQGTKVEIK	
26A1-H1L1/ VH-(G4S)4-VL	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWIG EIDPFDSYTYYNQKFKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARR DGVYKWYFDVWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQS PSSVSASVGDRVTITCKASQDINKSIAWYQHKPGKAPKLLIHYTSTLQPGVP SRFSGSGSGRDYTLTISSLQPEDFATYYCLQYDSLLYTFGQGTKVEIK	181
26A1-H1L1/ VH-(G4S)3-VL	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWIG EIDPFDSYTYYNQKFKGRATLTVDKSTSTAYMELSSLRSEDTAVYYCARR DGVYKWYFDVWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSA SVGDRVTITCKASQDINKSIAWYQHKPGKAPKLLIHYTSTLQPGVPSRFSGS GSGRDYTLTISSLQPEDFATYYCLQYDSLLYTFGQGTKVEIK	182

NO: SEQ ID NO.

[00267] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the present description.

CLAIMS

It is claimed:

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably human GPC3.

2. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively;

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively; or

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds GPC3, preferably human GPC3.

3. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 3, 4, 5, 6, 7, and 8, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

4. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 9, 10, 11, 12, 13, and 14, respectively;

wherein the antibody or antigen-binding fragment thereof specifically binds TIP-1, preferably human TIP-1.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-4, comprising a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, 71, or 1, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, 72, or 2.

6. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-5, comprising:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;
b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;
c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;
d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;
e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;
f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58;
g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72; or
h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:1, and a light chain variable region having the polypeptide sequence of SEQ ID NO:2.

7. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof is chimeric and/or human or humanized.

8. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 7, wherein the humanized monoclonal antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to any one of SEQ ID NOs: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

9. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 8, wherein the humanized monoclonal antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;

(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;

(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;

(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;

(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or

(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

10. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen-binding fragment thereof is capable of inducing effector-mediated tumor cell lysis through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and/or complement-dependent cytotoxicity (CDC), and/or mediating the recruitment of conjugated drugs, and/or forming a bispecific antibody with another mAb or antigen-binding fragment thereof with cancer-killing effect.

11. A bispecific antibody or antigen-binding fragment thereof comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10.

12. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10.

13. An isolated nucleic acid encoding the bispecific antibody or antigen-binding fragment thereof of claim 11.

14. A vector comprising the isolated nucleic acid of claim 12 or 13.

15. A host cell comprising the vector of claim 14.

16. A pharmaceutical composition, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10 or the bispecific antibody or antigen-binding fragment thereof of claim 11 and a pharmaceutically acceptable carrier.

17. A method of targeting a TAA on a cancer cell surface, and/or treating a cancer, and/or treating an inflammatory disease in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 16, optionally wherein the cancer is selected from the group consisting of a lung cancer, a gastric cancer, an esophageal cancer, a bile duct cancer, a cholangiocarcinoma, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a hon-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

18. A method of producing the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10 or the bispecific antibody or antigen-binding fragment thereof of claim 11, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof and recovering the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof from the cell or culture.

19. A method of producing a pharmaceutical composition comprising the monoclonal antibody or antigen-binding fragment of any one of claims 1-10 or the bispecific antibody or antigen-binding fragment thereof of claim 11, comprising combining the monoclonal antibody or antigen-binding fragment thereof or bispecific antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

20. A method of determining the level of a TAA in a subject, the method comprising:

a. obtaining a sample from the subject;

b. contacting the sample with an isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-10; and

c. determining the level of a TAA in the subject.

21. The method of claim 20, wherein the sample is a tissue sample or a blood sample, optionally wherein the tissue sample is a cancer tissue sample.

22. An isolated polynucleotide comprising a nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises:

(a) an extracellular domain comprising at least one antigen binding domain that specifically binds GPC3;

(b) a hinge region;

(c) a transmembrane region; and

(d) an intracellular signaling domain.

23. The isolated polynucleotide of claim 22, wherein the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 87, 88, 89, 90, 91 and 92, respectively;

(2) SEQ ID NOs: 108, 109, 110, 111, 112 and 113, respectively;

(3) SEQ ID NOs: 17, 18, 19, 20, 21, and 22, respectively;

(4) SEQ ID NOs: 31, 32, 33, 34, 35, and 36, respectively;

(5) SEQ ID NOs: 45, 46, 47, 48, 49, and 50, respectively;

(6) SEQ ID NOs: 59, 60, 61, 62, 63, and 64, respectively; or

(7) SEQ ID NOs: 73, 74, 75, 76, 77, and 78, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

24. The isolated polynucleotide of claim 22, wherein the antigen binding domain comprises a heavy chain complementarity determining region 1 (HCDR1), HCDR2, HCDR3, a light chain complementarity determining region 1 (LCDR1), LCDR2, and LCDR3, having the polypeptide sequences of:

(1) SEQ ID NOs: 93, 94, 95, 96, 97 and 98, respectively;

(2) SEQ ID NOs: 114, 115, 116, 117, 118 and 119, respectively;

(3) SEQ ID NOs: 23, 24, 25, 26, 27, and 28, respectively;

(4) SEQ ID NOs: 37, 38, 39, 40, 41, and 42, respectively;

(5) SEQ ID NOs: 51, 52, 53, 54, 55, and 56, respectively; or

(6) SEQ ID NOs: 65, 66, 67, 68, 69, and 70, respectively;

(7) SEQ ID NOs: 79, 80, 81, 82, 83, and 84, respectively;

wherein the antigen binding domain specifically binds GPC3, preferably human GPC3.

25. The isolated polynucleotide of any one of claims 22-24, wherein the antigen binding domain comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 85, 106, 15, 29, 43, 57, or 71, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 86, 107, 16, 30, 44, 58, or 72.

26. The isolated polynucleotide of claim 25, wherein the antigen binding domain comprises:

a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:85, and a light chain variable region having the polypeptide sequence of SEQ ID NO:86;

b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:106, and a light chain variable region having the polypeptide sequence of SEQ ID NO:107;

c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:15, and a light chain variable region having the polypeptide sequence of SEQ ID NO:16;

d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:29, and a light chain variable region having the polypeptide sequence of SEQ ID NO:30;

e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:43, and a light chain variable region having the polypeptide sequence of SEQ ID NO:44;

f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:57, and a light chain variable region having the polypeptide sequence of SEQ ID NO:58; or

g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO:71, and a light chain variable region having the polypeptide sequence of SEQ ID NO:72.

27. The isolated polynucleotide of any one of claims 22-24, wherein the antigen binding domain is humanized and comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 99-102, 120-123, 126-132, 139-140, 143-149, 153-156, 160-163, 183-197, or 202-205, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 103-105, 124-125, 133-138, 141-142, 150-152, 157-159, 164-166, or 198-201.

28. The isolated polynucleotide of claim 27, wherein the antigen binding domain is humanized and comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:99, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:100, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:103;
(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:101, and a light chain variable region having the polypeptide sequence of SEQ ID NO:104;
(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:102, and a light chain variable region having the polypeptide sequence of SEQ ID NO:105;
(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:120, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:121, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(12) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(13) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:122, and a light chain variable region having the polypeptide sequence of SEQ ID NO:125;
(14) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:123, and a light chain variable region having the polypeptide sequence of SEQ ID NO:124;
(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:139, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;
(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:140, and a light chain variable region having the polypeptide sequence of SEQ ID NO:142;
(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:153, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:157;
(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:154, and a light chain variable region having the polypeptide sequence of SEQ ID NO:158;
(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 143, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 144, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 145, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 150;
(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 147, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 148, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 151;
(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 149, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 152;
(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 160, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 161, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 162, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 163, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 205, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 202, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 203, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 204, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 164;
(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 100, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(41) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(42) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 183, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 198;
(43) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(44) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(45) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(46) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(47) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 188, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 103;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(56) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(57) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(58) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(59) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 189, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 190, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 191, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 192, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(64) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 193, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(65) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 186, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(66) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(67) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(68) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 195, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(69) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 194, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(70) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 185, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;

(71) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 104;
(72) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 200;
(73) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 187, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 199;
(74) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 196, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201; or
(75) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 197, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 201.

29. The isolated polynucleotide of any one of claims 22-28, wherein the antigen binding domain is a single chain variable fragment (scFv) that specifically binds GPC3, preferably human GPC3.

30. The isolated polynucleotide of claim 29, wherein the single chain variable fragment (scFv) is humanized.

31. The isolated polynucleotide of claim 29 or 30, wherein the single chain variable fragment (scFv) comprises a polypeptide sequence at least 95% identical to any one of SEQ ID NOs: 167-182.

32. The isolated polynucleotide of any one of claims 22-31, wherein the chimeric antigen receptor (CAR) comprises one or more antigen binding domains.

33. The isolated polynucleotide of any one of claims 22-32, wherein the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

34. A chimeric antigen receptor (CAR) encoded by the isolated polynucleotide of any one of claims 22-33.

35. A vector comprising the isolated polynucleotide of any one of claims 22-33.

36. A host cell comprising the vector of claim 35.

37. The host cell of claim 36, wherein the host cell is a T cell, preferably a human T cell.

38. The host cell of claim 36, wherein the host cell is a NK cell, preferably a human NK cell.

39. A method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a T cell with the vector of claim 35.

40. A method of producing a chimeric antigen receptor (CAR)-T cell, the method comprising culturing T cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of claims 22-33 under conditions to produce the CAR-T cell and recovering the CAR-T cell.

41. A method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a NK cell with a vector of claim 35.

42. A method of producing a chimeric antigen receptor (CAR)-NK cell, the method comprising culturing NK cells comprising the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of claims 22-33 under conditions to produce the CAR-NK cell and recovering the CAR-NK cell.

43. A method of generating a cell comprising a chimeric antigen receptor (CAR), the method comprising contacting a cell with the isolated polynucleotide comprising a nucleic acid encoding a chimeric antigen receptor (CAR) of any one of claims 22-33, wherein the isolated polynucleotide is an *in vitro* transcribed RNA or synthetic RNA.

44. A method of treating cancer in a subject in need thereof, comprising administering to the subject in need thereof the host cell of any one of claims 36-38, optionally wherein the cancer is selected from a lung cancer, a gastric cancer, a colon cancer, a hepatocellular carcinoma, a renal cell carcinoma, a bladder urothelial carcinoma, a metastatic melanoma, a breast cancer, an ovarian cancer, a cervical cancer, a head and neck cancer, a pancreatic cancer, a glioma, a glioblastoma, and other solid tumors, and a non-Hodgkin's lymphoma (NHL), an acute lymphocytic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a chronic myelogenous leukemia (CML), a multiple myeloma (MM), an acute myeloid leukemia (AML), and other liquid tumors.

45. The method of claim 44, further comprising administering to the subject in need thereof an agent that increases the efficacy of a cell expressing a CAR.

46. The method of claim 44, further comprising administering to the subject in need thereof an agent that ameliorates one or more side effects associated with administration of a cell expressing a CAR.

47. The method of claim 44, further comprising administering to the subject in need thereof an agent that treats the disease associated with GPC3.

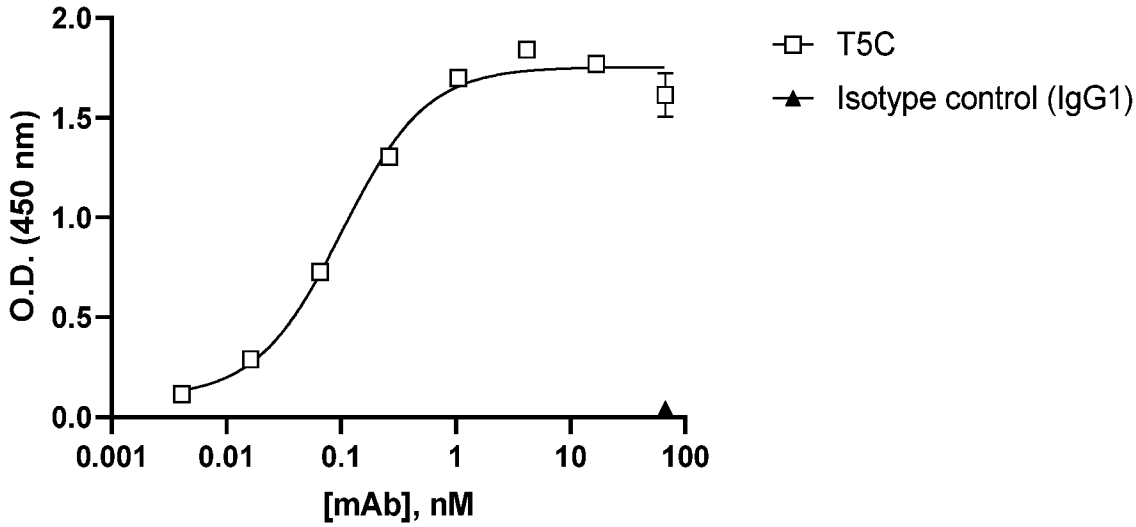

2.0
1.5
1.0
0.5
0.0
O.D. (450 nm)
0.001
0.01
0.1
1
10
100
[mAb], nM
T5C
Isotype control (IgG1)

FIG. 1

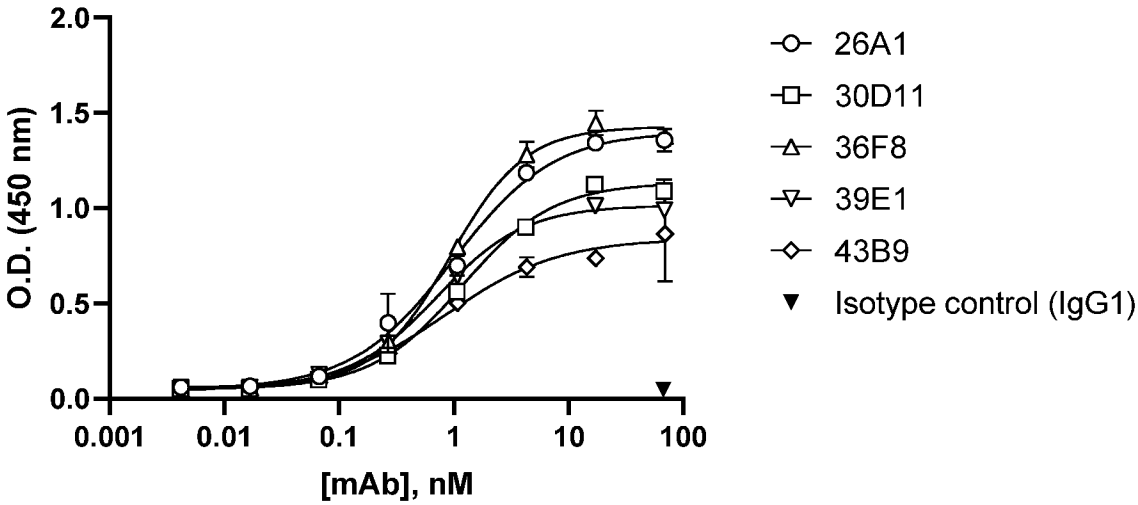

2.0
1.5
1.0
0.5
0.0
O.D. (450 nm)
0.001
0.01
0.1
1
10
100
[mAb], nM
26A1
30D11
36F8
39E1
43B9
Isotype control (IgG1)

FIG. 2A

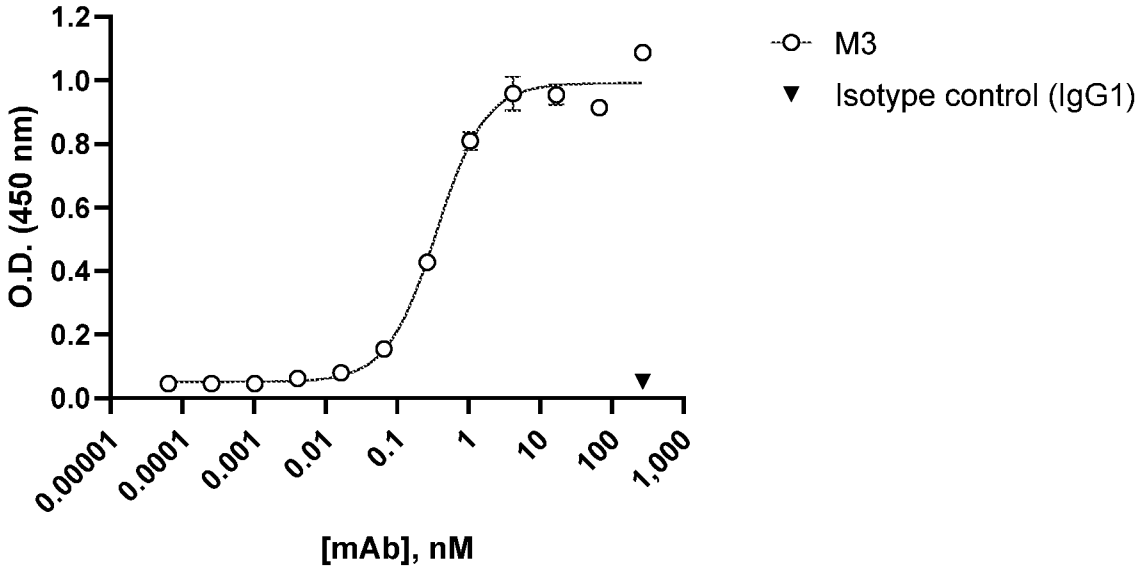

1.2
1.0
0.8
0.6
0.4
0.2
0.0
O.D. (450 nm)
0.00001
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3
Isotype control (IgG1)

FIG. 2B

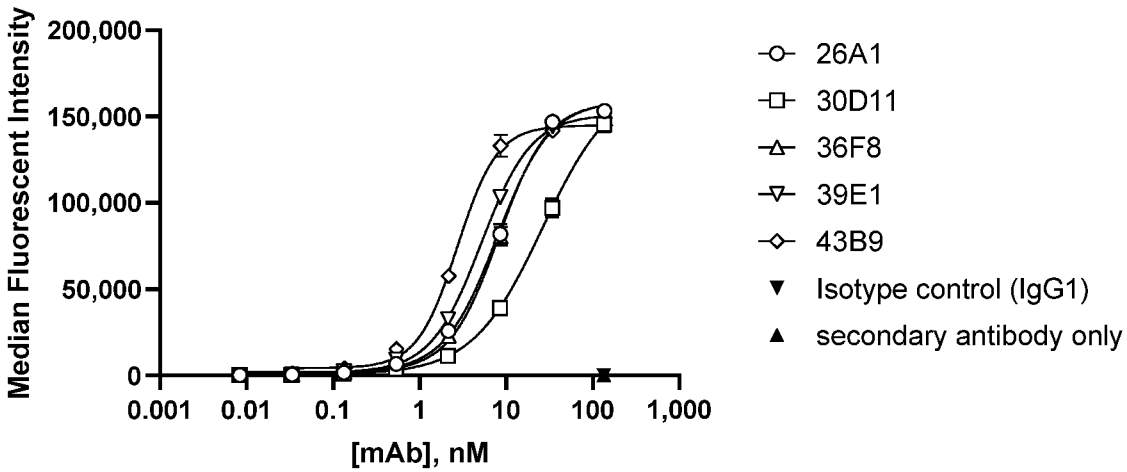

200,000
150,000
100,000
50,000
0
Median Fluorescent Intensity
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
26A1
30D11
36F8
39E1
43B9
Isotype control (IgG1)
secondary antibody only

FIG. 2C

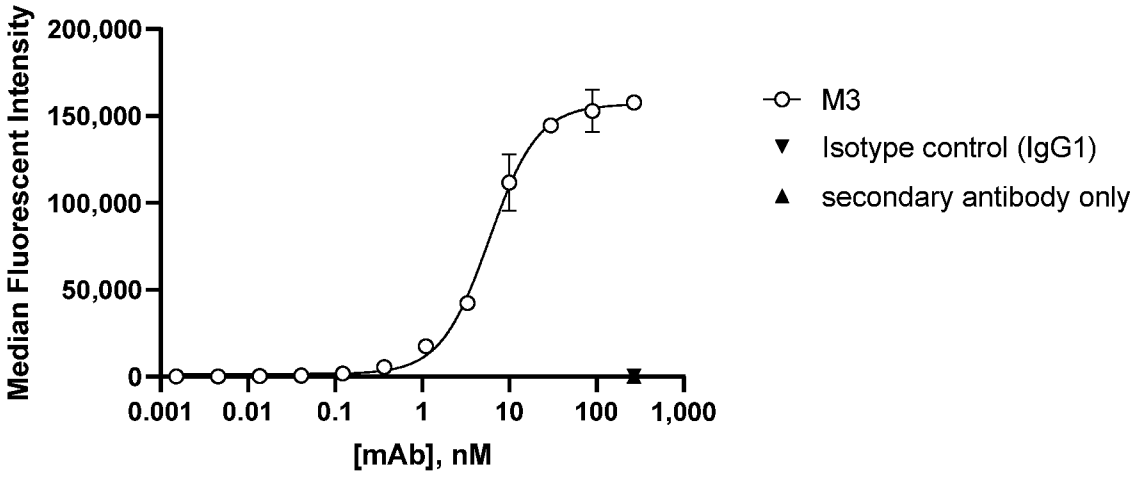
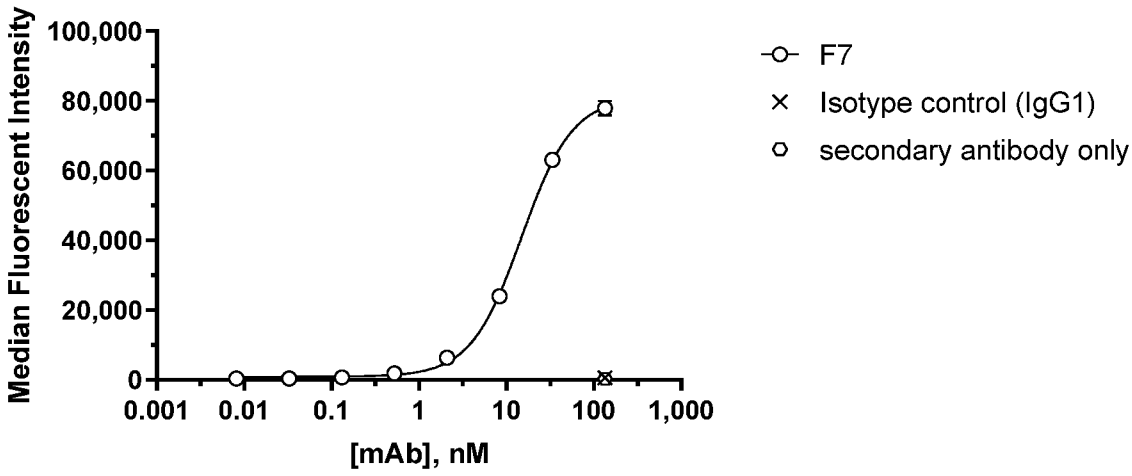

Median Fluorescent Intensity
200,000
150,000
100,000
50,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3
Isotype control (IgG1)
secondary antibody only

FIG. 2D


Median Fluorescent Intensity
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80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F7
Isotype control (IgG1)
secondary antibody only

FIG. 2E

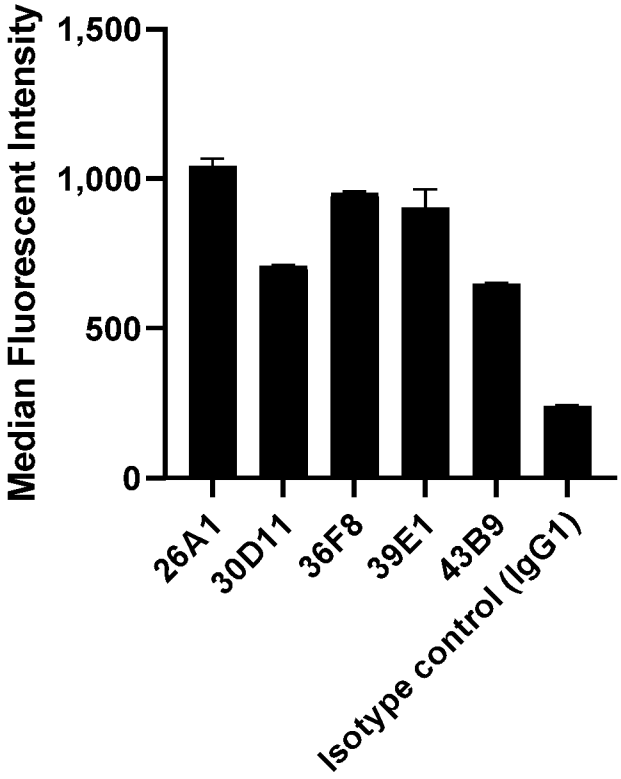

Median Fluorescent Intensity
1,500
1,000
500
0
26A1
30D11
36F8
39E1
43B9
Isotype control (IgG1)

FIG. 2F

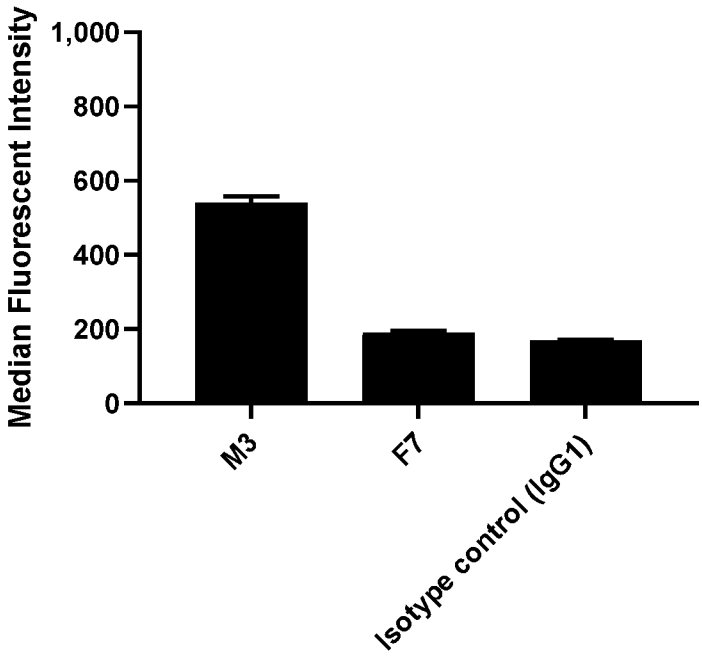
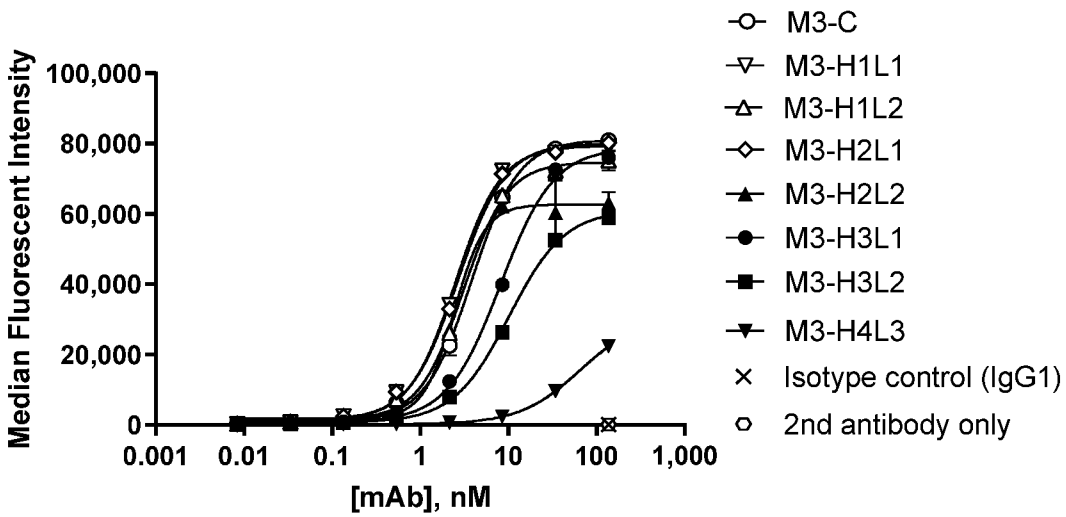

Median Fluorescent Intensity
1,000
800
600
400
200
0
M3
F7
Isotype control (IgG1)

FIG. 2G


Median Fluorescent Intensity
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80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H1L1
M3-H1L2
M3-H2L1
M3-H2L2
M3-H3L1
M3-H3L2
M3-H4L3
Isotype control (IgG1)
2nd antibody only

FIG. 3A

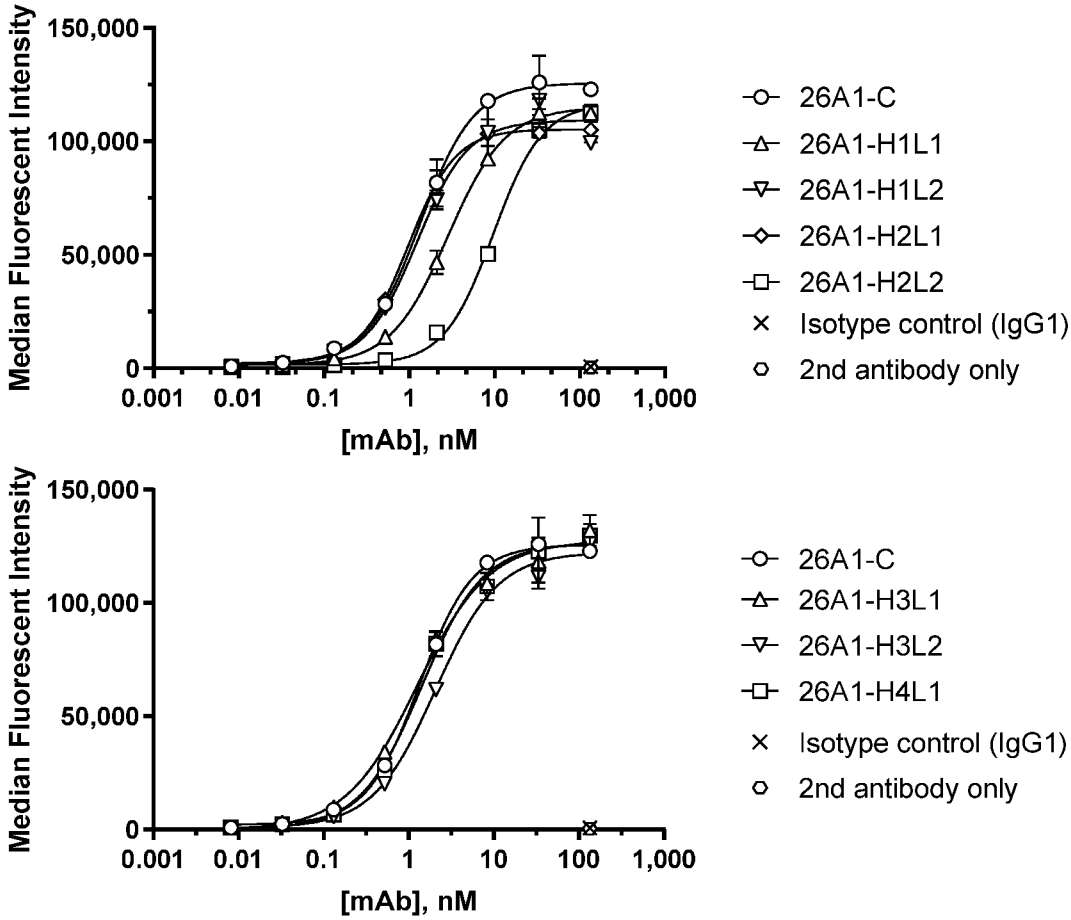

Median Fluorescent Intensity
150,000
100,000
50,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
26A1-C
26A1-H1L1
26A1-H1L2
26A1-H2L1
26A1-H2L2
Isotype control (IgG1)
2nd antibody only
Median Fluorescent Intensity
150,000
100,000
50,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
26A1-C
26A1-H3L1
26A1-H3L2
26A1-H4L1
Isotype control (IgG1)
2nd antibody only

FIG. 3B

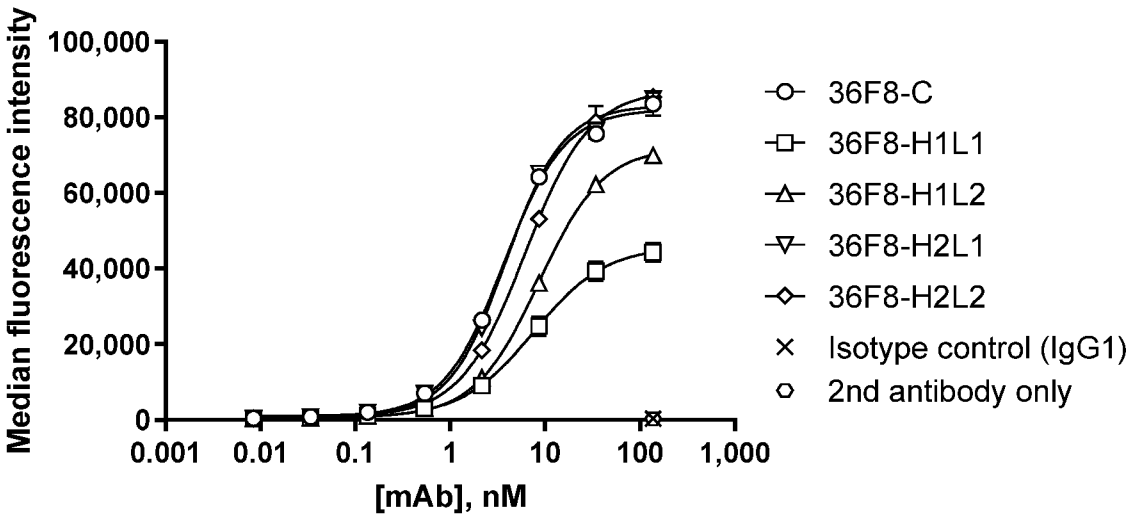

Median fluorescence intensity
100,000
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
36F8-C
36F8-H1L1
36F8-H1L2
36F8-H2L1
36F8-H2L2
Isotype control (IgG1)
2nd antibody only

FIG. 3C

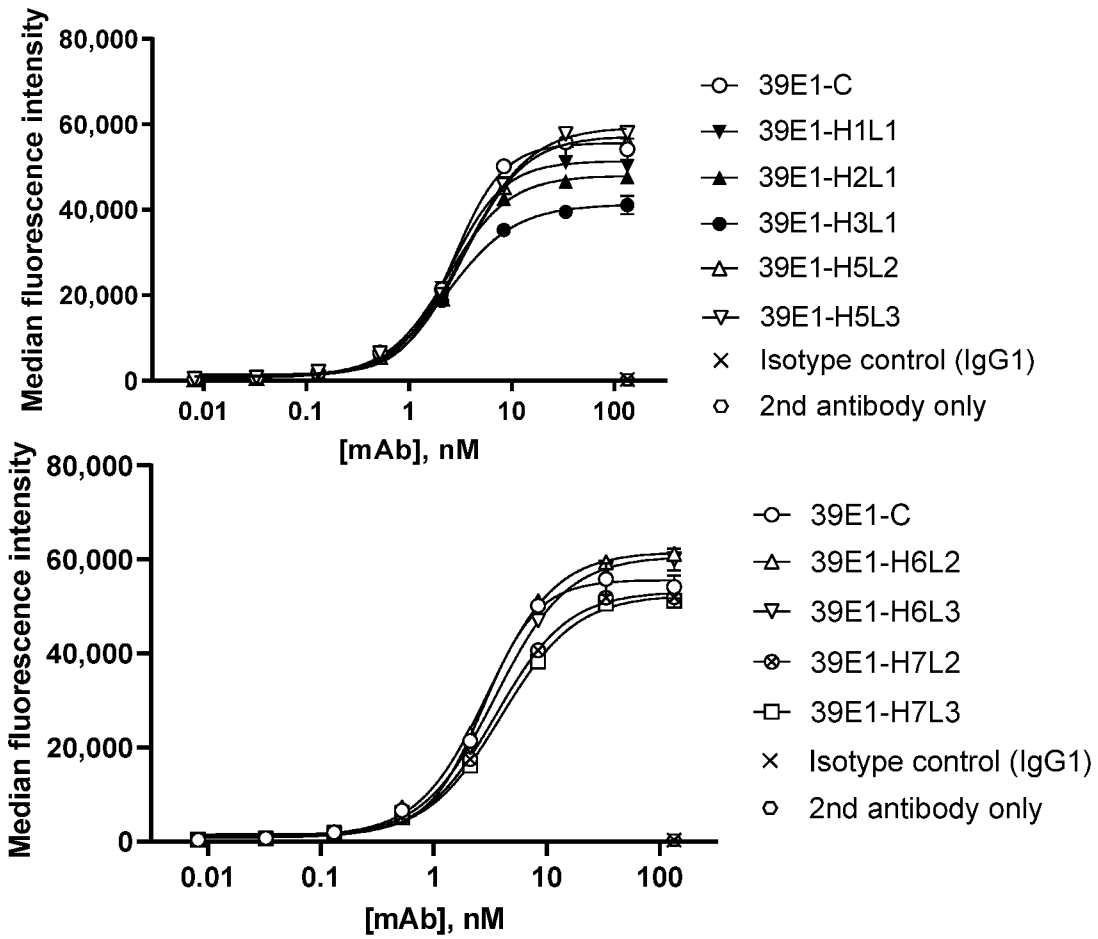
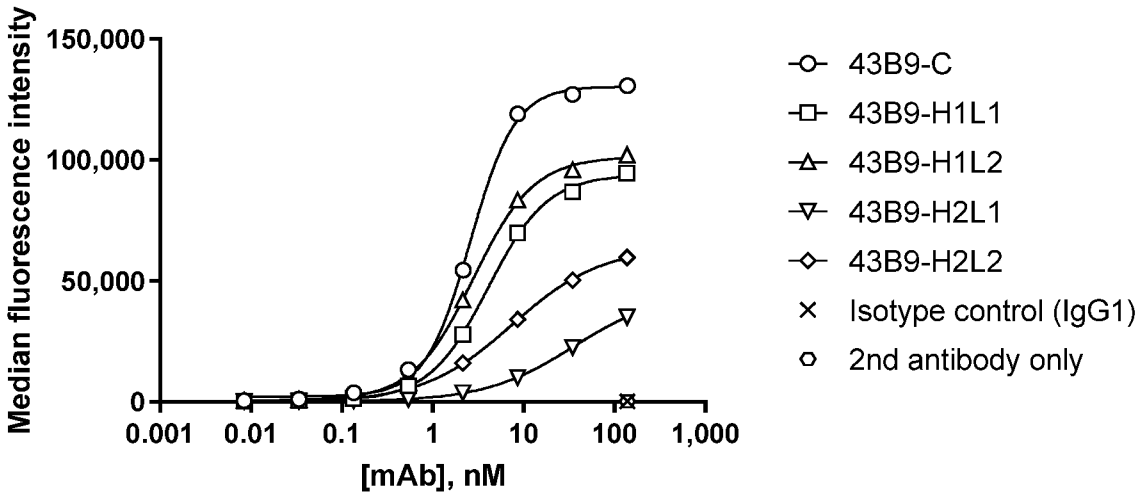

Median fluorescence intensity
80,000
60,000
40,000
20,000
0
0.01
0.1
1
10
100
[mAb], nM
39E1-C
39E1-H1L1
39E1-H2L1
39E1-H3L1
39E1-H5L2
39E1-H5L3
Isotype control (IgG1)
2nd antibody only
Median fluorescence intensity
80,000
60,000
40,000
20,000
0
0.01
0.1
1
10
100
[mAb], nM
39E1-C
39E1-H6L2
39E1-H6L3
39E1-H7L2
39E1-H7L3
Isotype control (IgG1)
2nd antibody only

FIG. 3D


Median fluorescence intensity
150,000
100,000
50,000
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0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
43B9-C
43B9-H1L1
43B9-H1L2
43B9-H2L1
43B9-H2L2
Isotype control (IgG1)
2nd antibody only

FIG. 3E

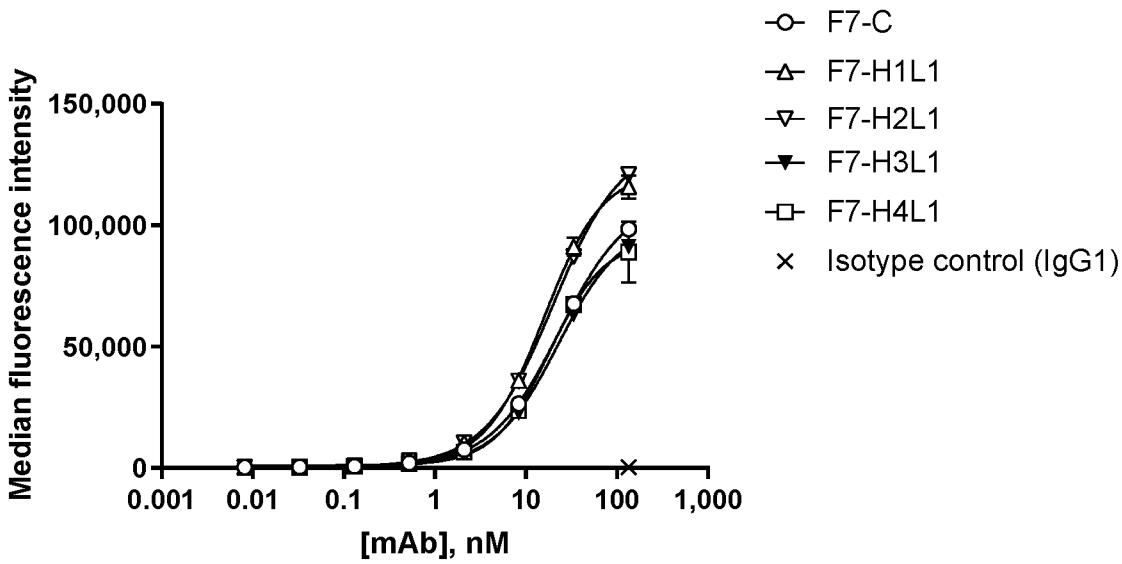
Median fluorescence intensity
150,000
100,000
50,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F7-C
F7-H1L1
F7-H2L1
F7-H3L1
F7-H4L1
Isotype control (IgG1)

FIG. 3F

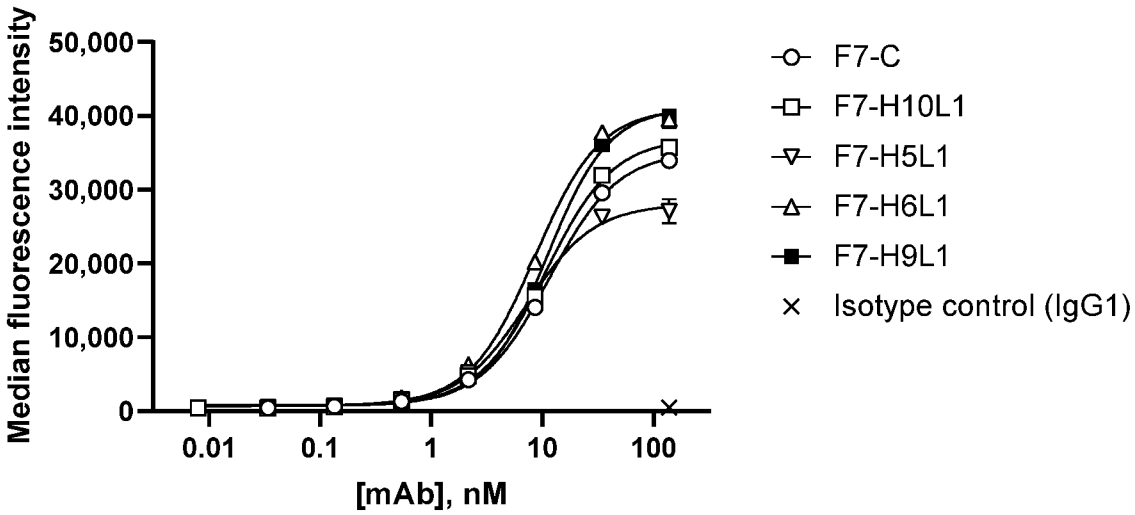
Median fluorescence intensity
50,000
40,000
30,000
20,000
10,000
0
0.01
0.1
1
10
100
[mAb], nM
F7-C
F7-H10L1
F7-H5L1
F7-H6L1
F7-H9L1
Isotype control (IgG1)

FIG. 3G

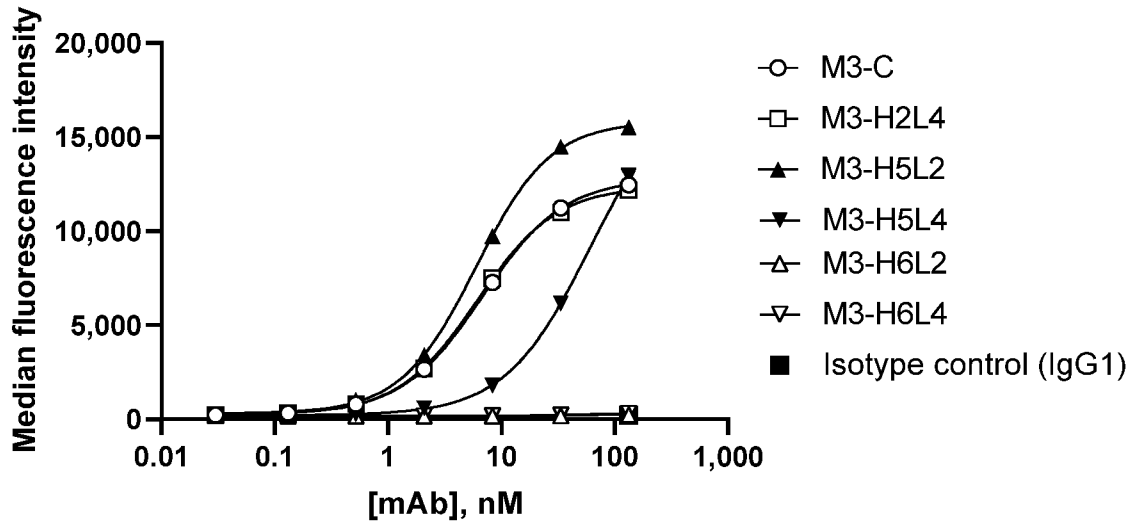
Median fluorescence intensity
20,000
15,000
10,000
5,000
0
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H2L4
M3-H5L2
M3-H5L4
M3-H6L2
M3-H6L4
Isotype control (IgG1)

FIG. 3H

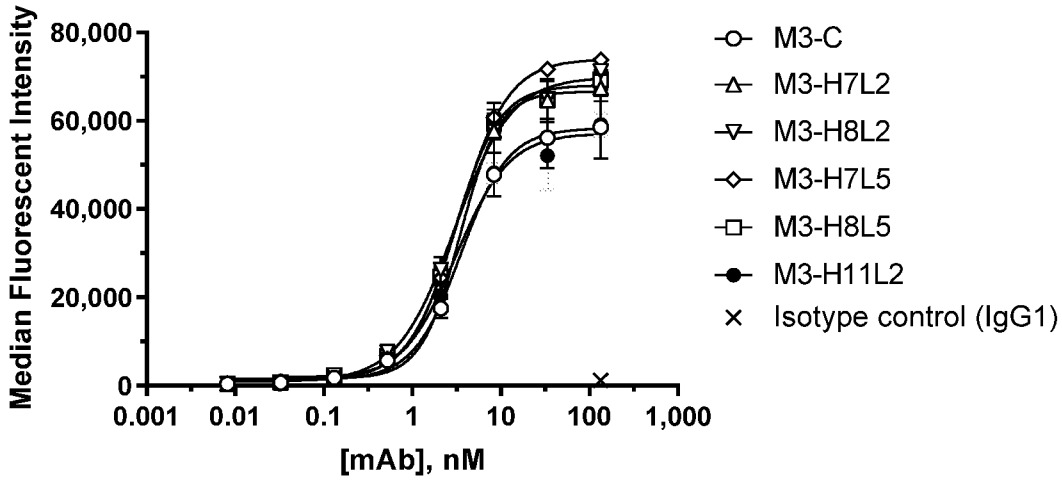
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H7L2
M3-H8L2
M3-H7L5
M3-H8L5
M3-H11L2
Isotype control (IgG1)

FIG. 3I

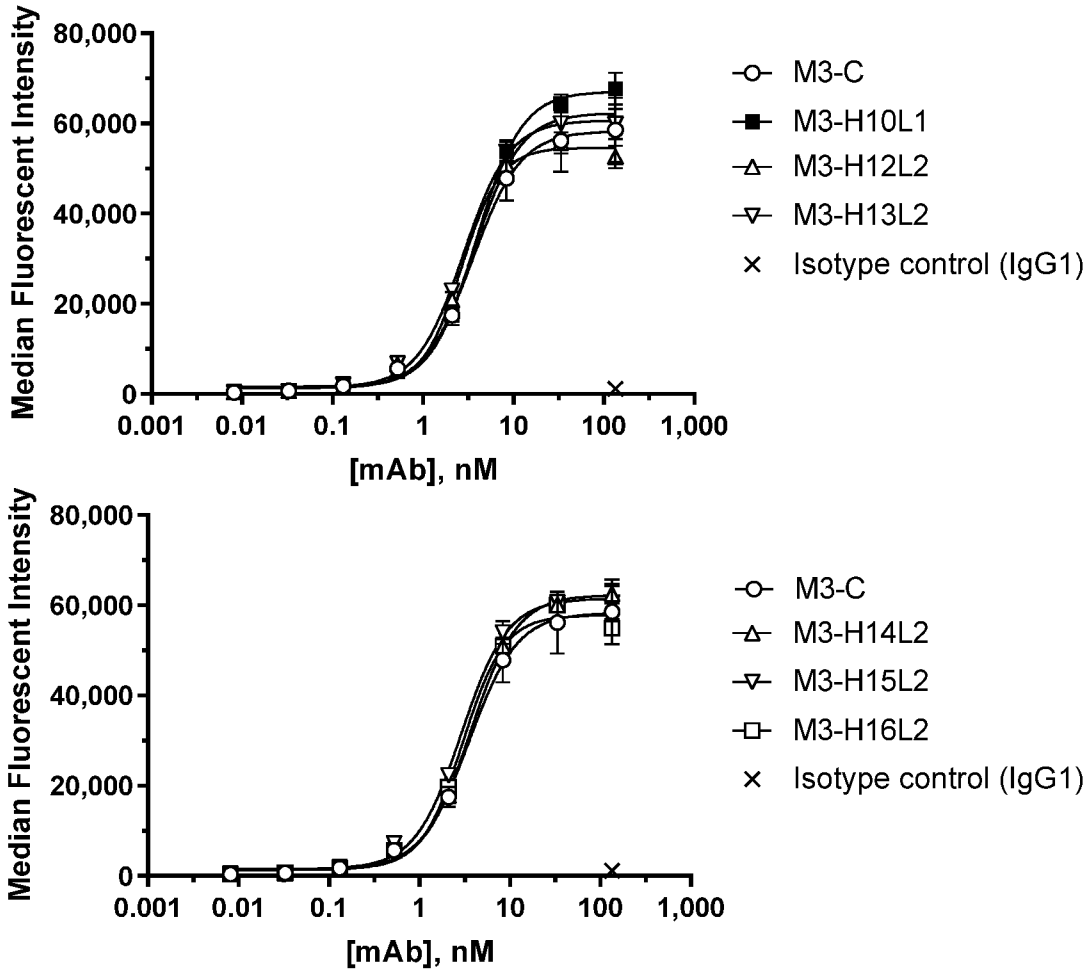
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H10L1
M3-H12L2
M3-H13L2
Isotype control (IgG1)
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H14L2
M3-H15L2
M3-H16L2
Isotype control (IgG1)

FIG. 3J

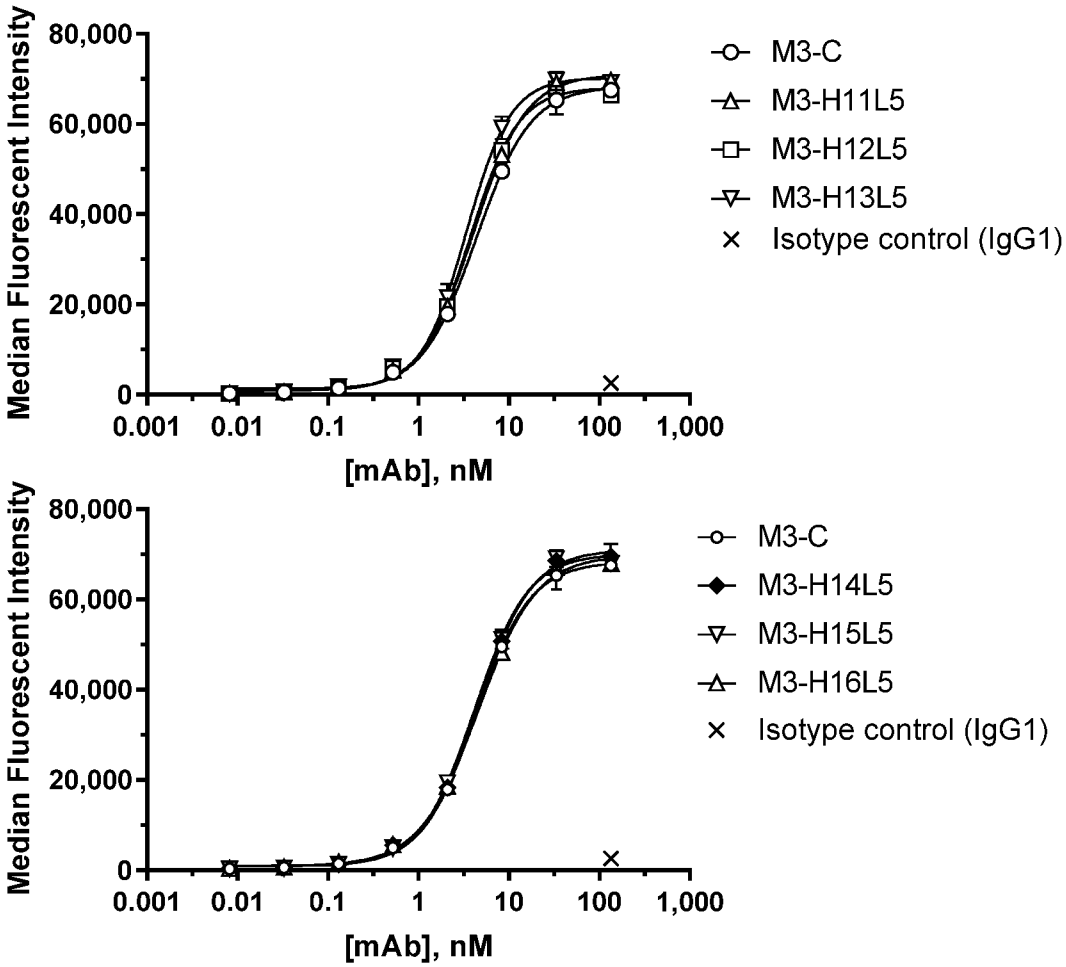
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H11L5
M3-H12L5
M3-H13L5
Isotype control (IgG1)
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H14L5
M3-H15L5
M3-H16L5
Isotype control (IgG1)

FIG. 3K

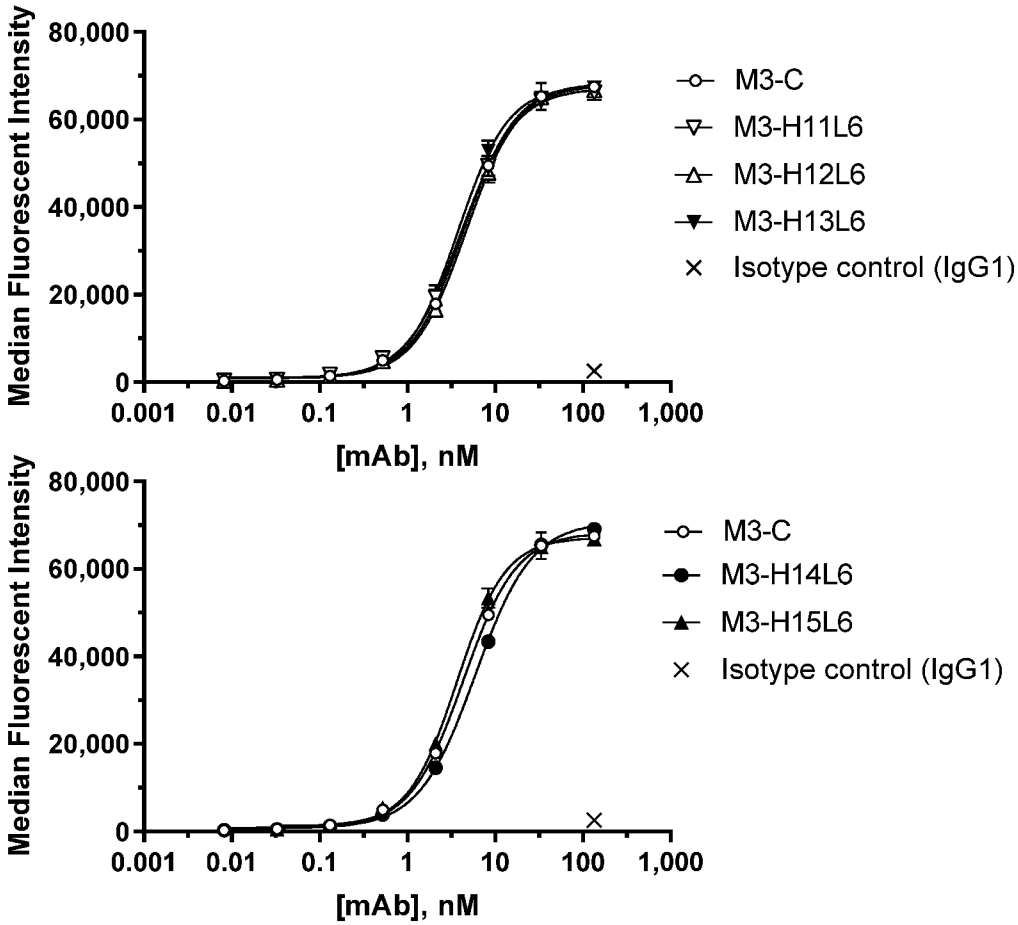
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H11L6
M3-H12L6
M3-H13L6
Isotype control (IgG1)
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H14L6
M3-H15L6
Isotype control (IgG1)

FIG. 3L

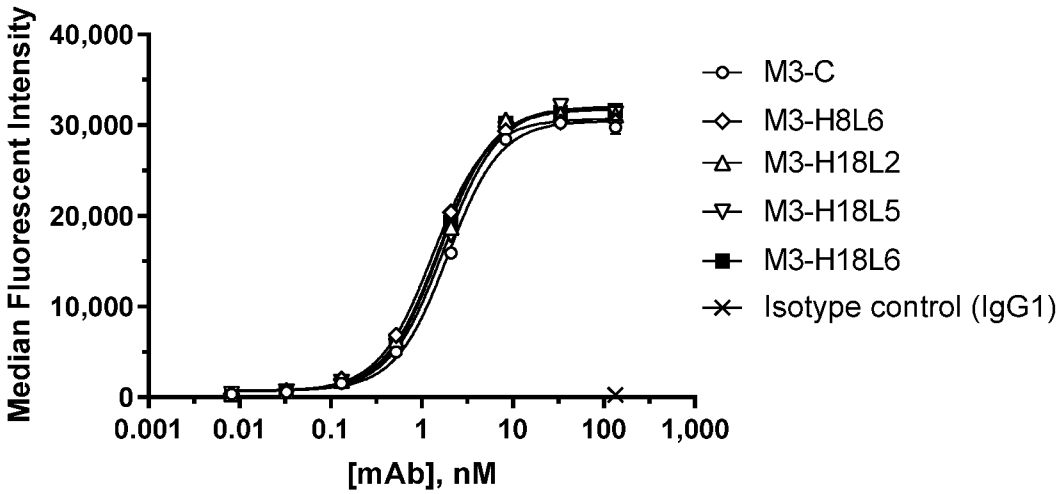
Median Fluorescent Intensity
40,000
30,000
20,000
10,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H8L6
M3-H18L2
M3-H18L5
M3-H18L6
Isotype control (IgG1)

FIG. 3M

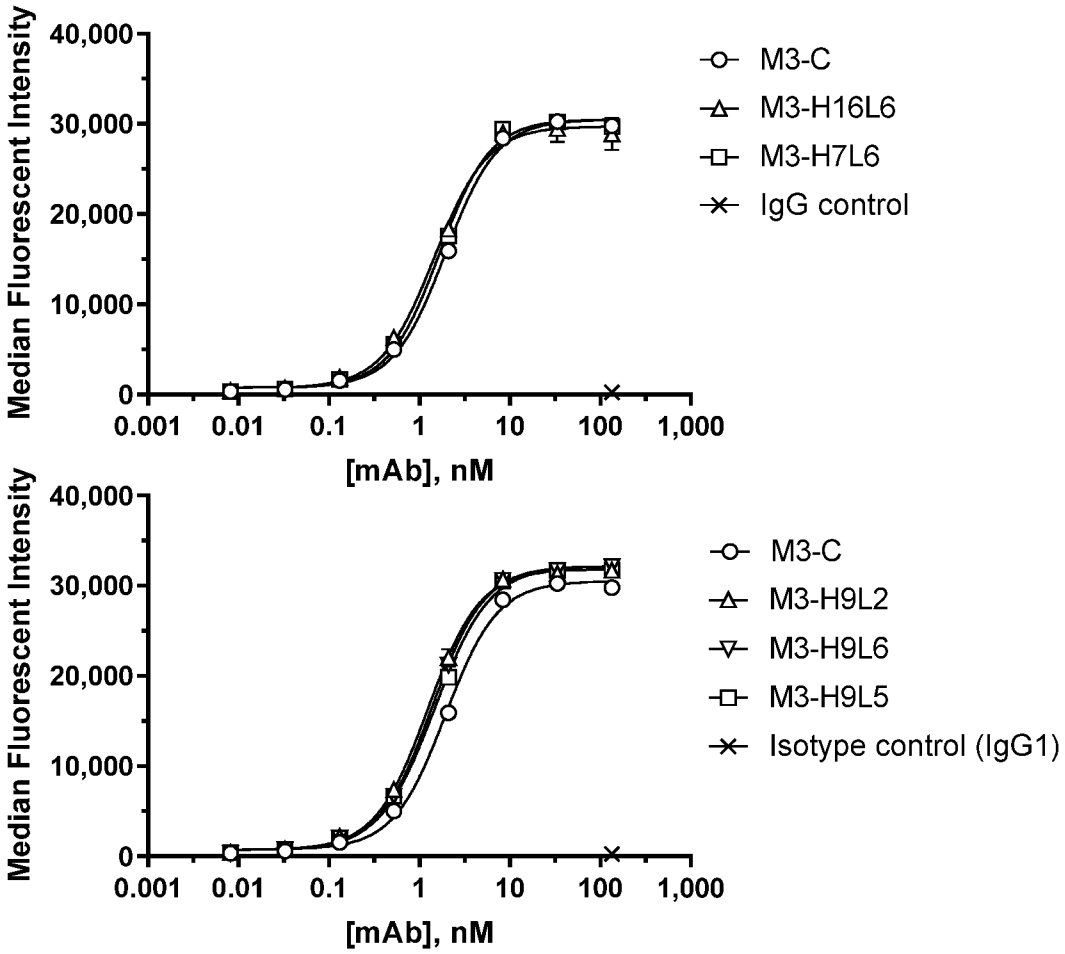
Median Fluorescent Intensity
40,000
30,000
20,000
10,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H16L6
M3-H7L6
IgG control
Median Fluorescent Intensity
40,000
30,000
20,000
10,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H9L2
M3-H9L6
M3-H9L5
Isotype control (IgG1)

FIG. 3N

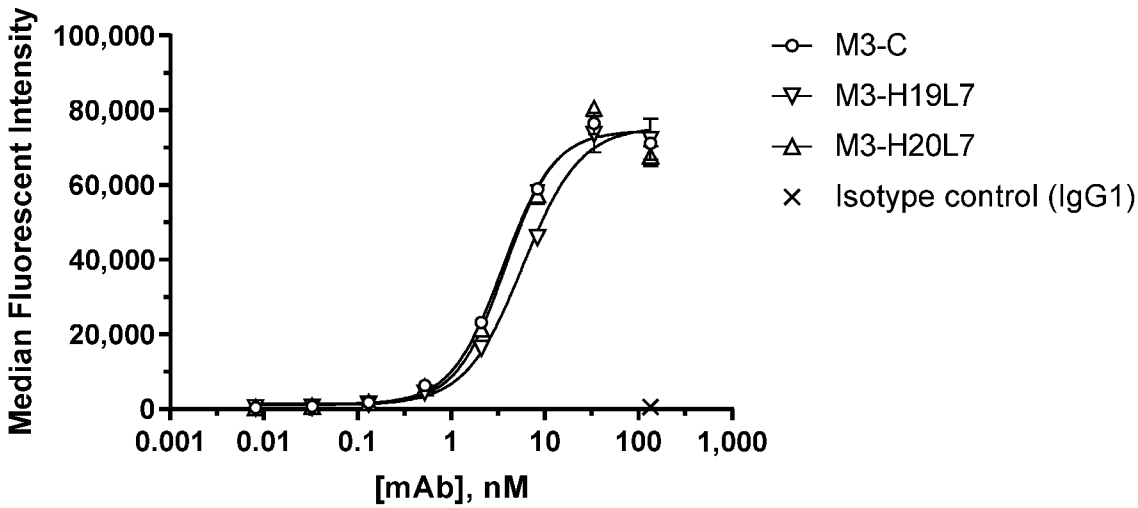
Median Fluorescent Intensity
100,000
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-C
M3-H19L7
M3-H20L7
Isotype control (IgG1)

FIG. 3O

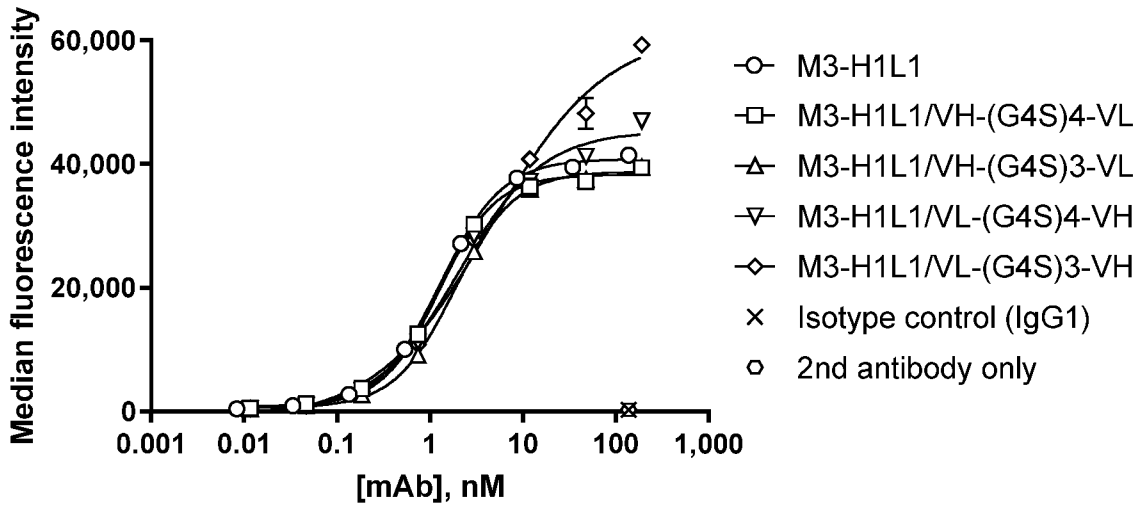
Median fluorescence intensity
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
M3-H1L1
M3-H1L1/VH-(G4S)4-VL
M3-H1L1/VH-(G4S)3-VL
M3-H1L1/VL-(G4S)4-VH
M3-H1L1/VL-(G4S)3-VH
Isotype control (IgG1)
2nd antibody only

FIG. 4A

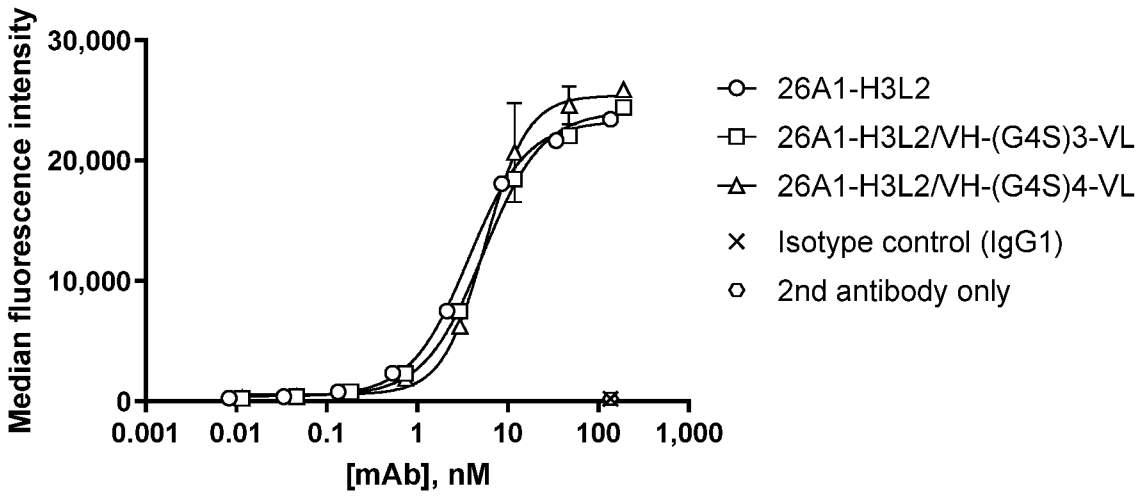
Median fluorescence intensity
30,000
20,000
10,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
26A1-H3L2
26A1-H3L2/VH-(G4S)3-VL
26A1-H3L2/VH-(G4S)4-VL
Isotype control (IgG1)
2nd antibody only

FIG. 4B

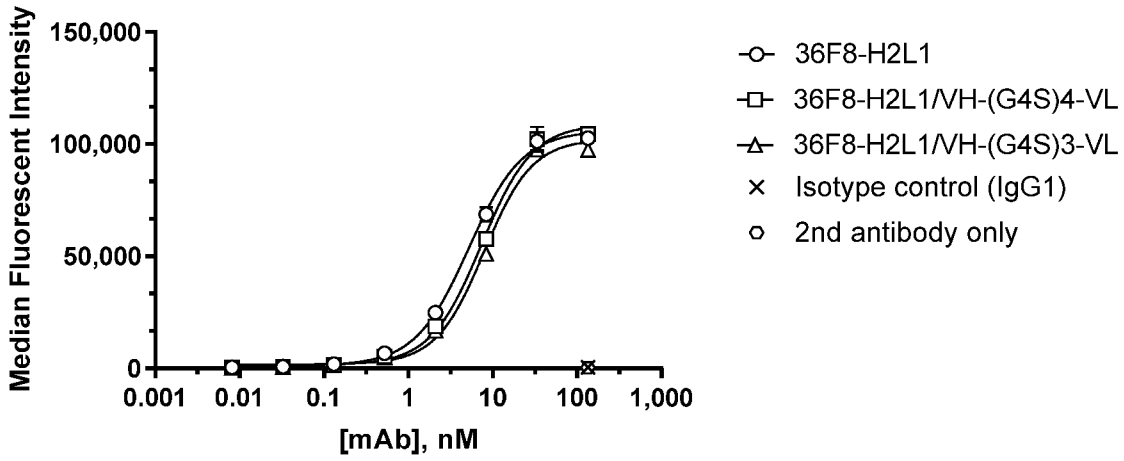
Median Fluorescent Intensity
150,000
100,000
50,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
36F8-H2L1
36F8-H2L1/VH-(G4S)4-VL
36F8-H2L1/VH-(G4S)3-VL
Isotype control (IgG1)
2nd antibody only

FIG. 4C

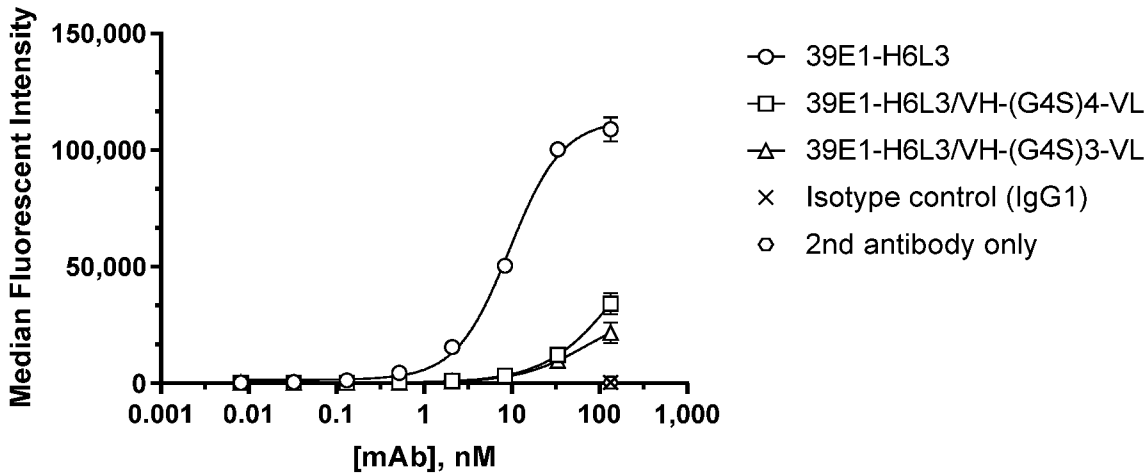
Median Fluorescent Intensity
150,000
100,000
50,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
39E1-H6L3
39E1-H6L3/VH-(G4S)4-VL
39E1-H6L3/VH-(G4S)3-VL
Isotype control (IgG1)
2nd antibody only

FIG. 4D

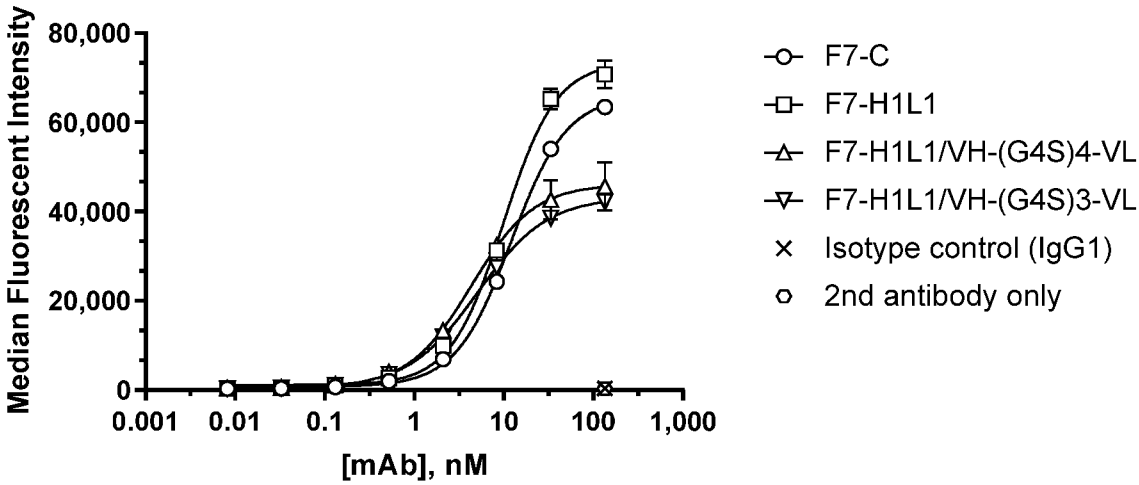
Median Fluorescent Intensity
80,000
60,000
40,000
20,000
0
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F7-C
F7-H1L1
F7-H1L1/VH-(G4S)4-VL
F7-H1L1/VH-(G4S)3-VL
Isotype control (IgG1)
2nd antibody only

FIG. 4E

SEQUENCE LISTING

<110> Phanes Therapeutics, Inc.

<120> Anti-Tumor Associated Antigen Antibodies and Uses Thereof

<130> 065799.34WO1

<150> US 63/021,215
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<170> PatentIn version 3.5

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

Ser Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met
35 40 45

Gly Trp Ile Lys Thr Glu Thr Gly Lys Pro Ile Tyr Thr Asp Asp Phe
50 55 60

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

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

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

Ser Ser

<210> 2
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1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

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

<210> 3
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Gly Tyr Thr Phe Thr Asp Tyr Ser
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Ile Lys Thr Glu Thr Gly Lys Pro
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<211> 7
<212> PRT
<213> Artificial Sequence

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<400> 5

Ala Pro Thr Gly Met Asp Tyr
1   5

<210> 6
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> T5 LCDR1

<400> 6

Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr
1   5   10

<210> 7
<211> 3

<212> PRT
<213> Artificial Sequence

<220>
<223> T5 LCDR2

<400> 7

Leu Val Ser
1

<210> 8
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<213> Artificial Sequence

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<400> 8

Trp Gln Gly Thr His Phe Pro Arg Thr
1   5

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<213> Artificial Sequence

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<223> T5 HCDR1

<400> 9

Asp Tyr Ser Met His
1   5

<210> 10
<211> 17
<212> PRT
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<400> 10

Trp Ile Lys Thr Glu Thr Gly Lys Pro Ile Tyr Thr Asp Asp Phe Lys
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Gly

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<400> 11

Thr Gly Met Asp Tyr
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<210> 12
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Leu Val Ser Lys Leu Asp Ser
1 5

<210> 14
<211> 9
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<223> T5 LCDR3

<400> 14

Trp Gln Gly Thr His Phe Pro Arg Thr
1 5

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<213> Artificial Sequence

<220>
<223> 26A1 VH

<400> 15

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

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

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Ala
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 16
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> 26A1 VL

<400> 16

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1               5                  10                  15


Gly Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Ser
            20                  25                  30


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


His Tyr Thr Ser Thr Leu Gln Pro Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Leu Leu Tyr
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
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<210> 17
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<212> PRT
<213> Artificial Sequence

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<223> 26A1 HCDR1

<400> 17

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Gly Tyr Thr Phe Thr Ser Tyr Trp
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<210> 18
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<223> 26A1 HCDR2

<400> 18

Ile Asp Pro Phe Asp Ser Tyr Thr
1 5

<210> 19
<211> 13
<212> PRT
<213> Artificial Sequence

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<223> 26A1 HCDR3

<400> 19

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val
1 5 10

<210> 20
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<223> 26A1 LCDR1

<400> 20

Gln Asp Ile Asn Lys Ser
1 5

<210> 21
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<220>
<223> 26A1 LCDR2

<400> 21

Tyr Thr Ser
1

<210> 22
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> 26A1 LCDR3

<400> 22

Leu Gln Tyr Asp Ser Leu Leu Tyr Thr
1   5

<210> 23
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 HCDR1

<400> 23

Ser Tyr Trp Met His
1   5

<210> 24
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 HCDR2

<400> 24

Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe Lys
1   5   10   15

Gly

<210> 25
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 HCDR3

<400> 25

Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val
1   5   10

<210> 26
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 LCDR1

<400> 26

Lys Ala Ser Gln Asp Ile Asn Lys Ser Ile Ala
1 5 10

<210> 27
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 LCDR2

<400> 27

Tyr Thr Ser Thr Leu Gln Pro
1 5

<210> 28
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 LCDR3

<400> 28

Leu Gln Tyr Asp Ser Leu Leu Tyr Thr
1 5

<210> 29
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VH

<400> 29

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

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

Glu Met His Trp Val Lys Glu Thr Pro Val His Gly Leu Glu Trp Ile
        35   40   45

Gly Ala Ile Asp Pro Glu Asn Gly Gly Ile Ala Phe Asn Gln Lys Phe
    50   55   60

Lys Asp Lys Ala Thr Leu Ser Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Arg Ser Leu Thr Tyr Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Thr Leu Thr Val Ser Ser
        115   120

<210> 30
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL

<400> 30

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20   25   30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Arg Pro Gly Gln Ser
        35   40   45

Pro Lys Arg Leu Met Tyr Gln Val Ser Lys Leu Asp Pro Gly Ile Pro
    50   55   60

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

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

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

<210> 31
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 HCDR1

<400> 31

Gly Tyr Thr Phe Thr Asp Tyr Glu
1 5

<210> 32
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 HCDR2

<400> 32

Ile Asp Pro Glu Asn Gly Gly Ile
1 5

<210> 33
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 HCDR3

<400> 33

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr
1 5 10

<210> 34
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 LCDR1

<400> 34

Gln Ser Leu Leu Tyr Ser Asp Gly Lys Thr Tyr
1   5   10

<210> 35
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 LCDR2

<400> 35

Gln Val Ser
1

<210> 36
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 LCDR3

<400> 36

Leu Gln Val Thr Tyr Tyr Pro Tyr Thr
1   5

<210> 37
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 HCDR1

<400> 37

Asp Tyr Glu Met His
1 5

<210> 38
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 HCDR2

<400> 38

Ala Ile Asp Pro Glu Asn Gly Gly Ile Ala Phe Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> 39
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 HCDR3

<400> 39

Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr
1 5 10

<210> 40
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 LCDR1

<400> 40

Lys Ser Ser Gln Ser Leu Leu Tyr Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> 41
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 LCDR2

<400> 41

Gln Val Ser Lys Leu Asp Pro
1   5

<210> 42
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 LCDR3

<400> 42

Leu Gln Val Thr Tyr Tyr Pro Tyr Thr
1   5

<210> 43
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 VH

<400> 43

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

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

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Trp Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50   55   60

Lys Gly Lys Ala Thr Leu Ala Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80

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Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ala
        115


<210>  44
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  36F8 VL

<400>  44

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


Asp Arg Val Thr Ile Ser Cys Ser Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30


Leu Ser Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45


Tyr Tyr Thr Ser Asn Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Glu Ser Gly Thr Asp Tyr Ser Leu Thr Ile Thr Asn Leu Glu Pro
65                  70                  75                  80


Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Phe Pro Trp
                85                  90                  95


Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  45
<211>  8
<212>  PRT
<213>  Artificial Sequence
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<220>
<223> 36F8 HCDR1

<400> 45

Gly Tyr Ala Phe Ser Asn Ser Trp
1   5

<210> 46
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 HCDR2

<400> 46

Ile Tyr Pro Gly Asp Gly Asp Thr
1   5

<210> 47
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 HCDR3

<400> 47

Ala Arg Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr
1   5   10

<210> 48
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 LCDR1

<400> 48

Gln Gly Ile Ser Asn Tyr
1   5

<210> 49
<211> 3

<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 LCDR2

<400> 49

Tyr Thr Ser
1

<210> 50
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 LCDR3

<400> 50

Gln Gln Tyr Ser Lys Phe Pro Trp Thr
1   5

<210> 51
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 HCDR1

<400> 51

Asn Ser Trp Met Asn
1   5

<210> 52
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 HCDR2

<400> 52

Trp Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys
1   5   10   15

Gly

<210> 53
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 HCDR3

<400> 53

Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr
1   5   10

<210> 54
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 LCDR1

<400> 54

Ser Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ser
1   5   10

<210> 55
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 LCDR2

<400> 55

Tyr Thr Ser Asn Leu His Ser
1   5

<210> 56
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 LCDR3

<400> 56

Gln Gln Tyr Ser Lys Phe Pro Trp Thr
1 5

<210> 57
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VH

<400> 57

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

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

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Ala
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 58
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> 39E1 VL

<400> 58

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

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

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

His Tyr Thr Ser Thr Leu Gln Pro Gly Ile Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65   70   75   80

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 59
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 HCDR1

<400> 59

Gly Tyr Thr Phe Thr Ser Tyr Trp
1   5

<210> 60
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 HCDR2

<400> 60

Ile Asp Pro Phe Asp Ser Tyr Thr
1 5

<210> 61
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 HCDR3

<400> 61

Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val
1 5 10

<210> 62
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 LCDR1

<400> 62

Gln Asp Ile Asn Lys Tyr
1 5

<210> 63
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 LCDR2

<400> 63

Tyr Thr Ser
1

<210> 64
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> 39E1 LCDR3

<400> 64

Gln Gln Tyr Asp Asn Leu Leu Arg Thr
1   5

<210> 65
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 HCDR1

<400> 65

Ser Tyr Trp Met His
1   5

<210> 66
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 HCDR2

<400> 66

Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe Lys
1   5   10   15

Gly

<210> 67
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 HCDR3

<400> 67

His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val
1   5   10

<210> 68
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 LCDR1

<400> 68

Lys Ala Ser Gln Asp Ile Asn Lys Tyr Ile Val
1   5   10

<210> 69
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 LCDR2

<400> 69

Tyr Thr Ser Thr Leu Gln Pro
1   5

<210> 70
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 LCDR3

<400> 70

Gln Gln Tyr Asp Asn Leu Leu Arg Thr
1   5

<210> 71
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 VH

<400> 71

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

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

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Glu Gly Leu Glu Trp Ile
        35                  40                  45

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

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ala
        115


<210>  72
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  43B9 VL

<400>  72

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

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

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

His Tyr Thr Ser Thr Leu Gln Pro Gly Thr Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Asn Leu Glu Pro
65 70 75 80

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

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 73
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 HCDR1

<400> 73

Gly Tyr Ala Phe Ser Asp Tyr Trp
1 5

<210> 74
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 HCDR2

<400> 74

Ile Tyr Pro Gly Asp Gly Asp Thr
1 5

<210> 75
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 HCDR3

<400> 75

Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr
1 5 10

<210> 76
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 LCDR1

<400> 76

Arg Asp Ile Asn Lys Tyr
1 5

<210> 77
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 LCDR2

<400> 77

Tyr Thr Ser
1

<210> 78
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 LCDR3

<400> 78

Leu Gln Tyr Asp Asn Leu Tyr Thr
1 5

<210> 79
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 HCDR1

<400> 79

Asp Tyr Trp Met Asn
1 5

<210> 80
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 HCDR2

<400> 80

Arg Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ser Gly Lys Phe Lys
1 5 10 15

Gly

<210> 81
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 HCDR3

<400> 81

Leu Ser Phe Gly Ala Trp Phe Ala Tyr
1 5

<210> 82
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 LCDR1

<400> 82

Lys Ala Ser Arg Asp Ile Asn Lys Tyr Ile Gly
1 5 10

<210> 83
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 LCDR2

<400> 83

Tyr Thr Ser Thr Leu Gln Pro
1   5

<210> 84
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 LCDR3

<400> 84

Leu Gln Tyr Asp Asn Leu Tyr Thr
1   5

<210> 85
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 VH

<400> 85

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1   5   10   15

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

Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
        35   40   45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50   55   60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65   70   75   80

Met Asp Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ala
        115

<210> 86
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 VL

<400> 86

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

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20   25   30

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35   40   45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60

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

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Phe Cys Tyr Gln Ser
                85   90   95

Lys His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105   110

<210> 87
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 HCDR1

<400> 87

Gly Tyr Thr Phe Thr Asp Tyr Glu
1   5

<210> 88
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 HCDR2

<400> 88

Ile Asp Pro Glu Thr Gly Asp Thr
1   5

<210> 89
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 HCDR3

<400> 89

Thr Arg Tyr Phe Ser Phe Ala Tyr
1   5

<210> 90
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 LCDR1

<400> 90

Gln Ser Leu Arg His Ser Asn Gly Asn Thr Tyr
1   5   10

<210> 91
<211> 3

<212> PRT
<213> Artificial Sequence

<220>
<223> M3 LCDR2

<400> 91

Lys Val Ser
1

<210> 92
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 LCDR3

<400> 92

Tyr Gln Ser Lys His Val Pro Tyr Thr
1   5

<210> 93
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 HCDR1

<400> 93

Asp Tyr Glu Met His
1   5

<210> 94
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 HCDR2

<400> 94

Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe Lys
1   5   10   15

Gly

<210> 95
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 HCDR3

<400> 95

Tyr Phe Ser Phe Ala Tyr
1 5

<210> 96
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 LCDR1

<400> 96

Arg Ser Ser Gln Ser Leu Arg His Ser Asn Gly Asn Thr Tyr Leu Gln
1 5 10 15

<210> 97
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 LCDR2

<400> 97

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 98
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 LCDR3

<400> 98

Tyr Gln Ser Lys His Val Pro Tyr Thr
1 5

<210> 99
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 VH H1

<400> 99

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 100
<211> 115
<212> PRT
<213> Artificial Sequence

<220>

<223> M3 VH H2

<400> 100

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35   40   45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50   55   60

Lys Gly Arg Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 101
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 VH H3

<400> 101

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30

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

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

Lys Gly Arg Ala Thr Leu Ser Ala Asp Lys Ser Lys Asn Thr Ala Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 102
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 VH H4

<400> 102

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

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

Glu Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

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

Gln Gly Gln Ala Thr Leu Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

```
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Met Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  103
<211>  112
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3 VL L1

<400>  103

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


Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20                  25                  30


Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Lys Ala
        35                  40                  45


Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


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


Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Tyr Gln Ser
                85                  90                  95


Lys His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


<210>  104
<211>  112
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> M3 VL L2

<400> 104

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

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

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
        35   40   45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60

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

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

Lys His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

<210> 105
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> M3 VL L3

<400> 105

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

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

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
        35   40   45

```
Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Ala Thr Gly Ile Pro
    50                  55                  60

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

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

Lys His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 106
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VH

<400> 106

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

Ser Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65                  70                  75                  80

Val Tyr Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Gly Ile Tyr
                85                  90                  95

Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Ser Val Thr
            100                 105                 110
```

Val Ser Ser
        115

<210> 107
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VL

<400> 107

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

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

Leu Gly Trp Leu Gln Gln Lys Pro His Gly Thr Ile Lys Arg Leu Ile
        35   40   45

Tyr Ala Ala Thr Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
    50   55   60

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

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 108
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR1

<400> 108

Gly Phe Thr Phe Ser Asn Tyr Trp
1 5

<210> 109
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR2

<400> 109

Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr
1 5 10

<210> 110
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR3

<400> 110

Thr Val Gly Gly Asn Tyr
1 5

<210> 111
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR1

<400> 111

Gln Glu Ile Ser Gly Asn
1 5

<210> 112
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR2

<400> 112

Ala Ala Thr
1

<210> 113
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR3

<400> 113

Leu Gln Tyr Asp Ser Tyr Pro Trp Thr
1 5

<210> 114
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR1

<400> 114

Asn Tyr Trp Met Asn
1 5

<210> 115
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR2

<400> 115

Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu Ser
1 5 10 15

Val Lys Gly

<210> 116
<211> 4

<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR3

<400> 116

Gly Gly Asn Tyr
1

<210> 117
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR1

<400> 117

Arg Ala Ser Gln Glu Ile Ser Gly Asn Leu Gly
1   5   10

<210> 118
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR2

<400> 118

Ala Ala Thr Thr Leu Asp Ser
1   5

<210> 119
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR3

<400> 119

Leu Gln Tyr Asp Ser Tyr Pro Trp Thr
1   5

<210> 120
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 VH H1

<400> 120

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

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50   55   60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 121
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 VH H2

<400> 121

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

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  122
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  26A1 VH H3

<400>  122

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Gly Arg Ala Thr Leu Ser Val Asp Lys Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  123
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  26A1 VH H4

<400>  123

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


Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Arg Ala Thr Leu Ser Val Asp Lys Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110
```

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 124
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 VL L1

<400> 124

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Ser
            20   25   30

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

His Tyr Thr Ser Thr Leu Gln Pro Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Leu Leu Tyr
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 125
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1 VL L2

<400> 125

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


Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Ser
            20                  25                  30


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


His Tyr Thr Ser Thr Leu Gln Pro Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Leu Leu Tyr
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  126
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  30D11 VH H1

<400>  126

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


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


Glu Met His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Asn Gly Gly Ile Ala Phe Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  127
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  30D11 VH H2

<400>  127

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


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


Glu Met His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Asn Gly Gly Ile Ala Phe Asn Gln Lys Phe
    50                  55                  60


Lys Asp Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 128
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VH H3

<400> 128

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30

Glu Met His Trp Val Arg Glu Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Ala Ile Asp Pro Glu Asn Gly Gly Ile Ala Phe Asn Gln Lys Phe
    50   55   60

Lys Asp Arg Ala Thr Leu Ser Ala Asp Lys Ser Lys Asn Thr Ala Tyr
65   70   75   80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Met Val Thr Val Ser Ser
        115   120

<210> 129
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VH H4

<400> 129

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

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

Glu Phe His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ile Ile Asp Pro Glu Asn Gly Gly Ile Ser Tyr Ala Gln Lys Phe
50 55 60

Gly Asp Arg Ala Ile Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 130
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VH H5

<400> 130

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

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

Glu Met His Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

```
Gly Ile Ile Asp Pro Glu Asn Gly Gly Ile Ser Tyr Ala Gln Lys Phe
    50                  55                  60

Gly Asp Arg Ala Ile Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 131
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VH H6

<400> 131

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

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

Glu Ile Ser Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ser Ile Asp Pro Glu Asn Gly Gly Ile Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 132
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VH H7

<400> 132

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

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

Glu Met Ser Trp Val Arg Glu Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Asn Gly Gly Ile Ala Phe Ala Gln Lys Phe
50 55 60

Gln Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Glu Glu Ile Tyr Asn Asp Tyr Asp Gly Val Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 133
<211> 112

<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL L1

<400> 133

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20   25   30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gln Pro
        35   40   45

Pro Lys Arg Leu Met Tyr Gln Val Ser Lys Leu Asp Pro Gly Val Pro
    50   55   60

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

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

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

<210> 134
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL L2

<400> 134

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
            20   25   30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Lys Ala
        35   40   45

Pro Lys Arg Leu Met Tyr Gln Val Ser Lys Leu Asp Pro Gly Val Pro
    50   55   60

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

Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Val
                85   90   95

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

<210> 135
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL L3

<400> 135

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
            20   25   30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Glu Gln Lys Pro Gly Lys Ala
        35   40   45

Pro Lys Arg Leu Met Tyr Gln Val Ser Ser Leu Gln Ser Gly Val Pro
    50   55   60

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

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

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

<210> 136
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL L4

<400> 136

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Glu Gln Lys Pro Gly Lys Ala
35 40 45

Pro Lys Arg Leu Met Tyr Gln Val Ser Lys Leu Gln Ser Gly Val Pro
50 55 60

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

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

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

<210> 137
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL L5

<400> 137

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

```
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Lys Ala
        35                  40                  45

Pro Lys Arg Leu Met Tyr Gln Val Ser Ser Leu Gln Ser Gly Val Pro
    50                  55                  60

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

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

Thr Tyr Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 138
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 30D11 VL L6

<400> 138

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Lys Ala
        35                  40                  45

Pro Lys Arg Leu Met Tyr Gln Val Ser Lys Leu Gln Ser Gly Val Pro
    50                  55                  60

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

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

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

<210> 139
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 VH H1

<400> 139

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Asn Ser
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 140
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 VH H2

<400> 140

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Asn Ser
            20   25   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

Gly Trp Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
                85   90   95

Ala Arg Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr Trp Gly Gln Gly
            100   105   110

Thr Leu Val Thr Val Ser Ser
        115

<210> 141
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 VL L1

<400> 141

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

```
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30

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

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

Ser Glu Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

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

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 142
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8 VL L2

<400> 142

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
            20                  25                  30

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

Tyr Tyr Thr Ser Asn Leu His Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Glu Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
```

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


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  143
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  39E1 VH H1

<400>  143

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


Thr Leu Ser Leu Thr Cys Ser Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Arg Ala Thr Leu Ser Val Asp Lys Ser Lys Asn Glu Ala Ser
65                  70                  75                  80


Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  144
<211>  120
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> 39E1 VH H2

<400> 144

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

Thr Leu Ser Leu Thr Cys Thr Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

Trp Met His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35   40   45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50   55   60

Lys Gly Arg Ala Thr Ile Ser Val Asp Lys Ser Lys Asn Glu Ala Ser
65   70   75   80

Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100   105   110

Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 145
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VH H3

<400> 145

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

Thr Leu Ser Leu Thr Cys Thr Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20   25   30

```
Trp Met His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Pro Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Ile Ser Val Asp Lys Ser Lys Asn Glu Ala Ser
65                  70                  75                  80

Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 146
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VH H4

<400> 146

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

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

Trp Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Gly Ile Asp Pro Phe Asp Ser Tyr Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  147
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  39E1 VH H5

<400>  147

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


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


Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 148
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VH H6

<400> 148

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

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
50 55 60

Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 149
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VH H7

<400> 149

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


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


Trp Met His Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


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


Gln Gly Gln Ala Thr Leu Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  150
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  39E1 VL L1

<400>  150

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


Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Tyr
            20                  25                  30


Ile Val Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
```

```
His Tyr Thr Ser Thr Leu Gln Pro Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Arg Glu Tyr Thr Leu Thr Ile Arg Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 151
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VL L2

<400> 151

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Asn Lys Tyr
            20                  25                  30

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

His Tyr Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 152
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1 VL L3

<400> 152

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Tyr
20 25 30

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

His Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 153
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 VH H1

<400> 153

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

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

```
Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Leu Ile Tyr Pro Gly Asp Gly Asp Thr Met Tyr Ala Glu Lys Phe
    50                  55                  60

Arg Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Ser Val Ser Ser
        115
```

<210> 154
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 VH H2

<400> 154

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

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

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

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

Arg Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Thr Val Thr Val Ser Ser
        115


<210>  155
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  43B9 VH H3

<400>  155

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ala Phe Ser Asp Tyr
            20                  25                  30


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


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


Lys Gly Arg Ala Thr Leu Ser Ala Asp Lys Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115
```

<210> 156
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 VH H4

<400> 156

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

Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Asp Tyr
20 25 30

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

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

Lys Gly Arg Ala Thr Leu Ser Ala Asp Lys Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 157
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 VL L1

<400> 157

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


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Asp Ile Asn Lys Tyr
            20                  25                  30


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


His Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Arg Asp Tyr Ser Leu Thr Ile Asn Ser Leu Gln Pro
65                  70                  75                  80


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


Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  158
<211>  106
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  43B9 VL L2

<400>  158

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


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg Asp Ile Asn Lys Tyr
            20                  25                  30


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


His Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

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

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

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 159
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9 VL L3

<400> 159

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Arg Asp Ile Asn Lys Tyr
20 25 30

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

His Tyr Thr Ser Thr Leu Gln Pro Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 160
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VH H1

<400> 160

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50   55   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65   70   75   80

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85   90   95

Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 161
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VH H2

<400> 161

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

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

```
Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80


Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  162
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F7 VH H3

<400>  162

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr Tyr Tyr Ala Glu
    50                  55                  60


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

```
Val Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  163
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F7 VH H4

<400>  163

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50                  55                  60


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


Val Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 164
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VL L1

<400> 164

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Asn
            20   25   30

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

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

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 165
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VL L2

<400> 165

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

```
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Glu Ile Ser Gly Asn
            20                  25                  30

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

Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 166
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 VL L3

<400> 166

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Asn
            20                  25                  30

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

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

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Tyr Pro Trp
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  167
<211>  247
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3-H1L1/VH-(G4S)4-VL

<400>  167

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


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


Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Asp Val Gln Met Thr Gln Ser Pro Ser
    130                 135                 140
```

```
Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser
145                 150                 155                 160


Ser Gln Ser Leu Arg His Ser Asn Gly Asn Thr Tyr Leu Gln Trp Tyr
                165                 170                 175


Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser
            180                 185                 190


Asn Arg Phe Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220


Thr Tyr Phe Cys Tyr Gln Ser Lys His Val Pro Tyr Thr Phe Gly Gln
225                 230                 235                 240


Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 168
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H1L1/VH-(G4S)3-VL

<400> 168

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


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


Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Asp Val Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser
    130                 135                 140

Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Arg
145                 150                 155                 160

His Ser Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Lys Ala Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Tyr
    210                 215                 220

Gln Ser Lys His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys
```

<210> 169
<211> 247
<212> PRT
<213> Artificial Sequence

<220>

<223> M3-H1L1/VL-(G4S)4-VH

<400> 169

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


Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20                  25                  30


Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Lys Ala
        35                  40                  45


Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


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


Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Tyr Gln Ser
                85                  90                  95


Lys His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
    130                 135                 140


Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
145                 150                 155                 160


Phe Thr Asp Tyr Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly
                165                 170                 175


Leu Glu Trp Ile Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr
            180                 185                 190


Asn Gln Lys Phe Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr
        195                 200                 205
```

```
Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
    210                 215                 220


Val Tyr Tyr Cys Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly
225                 230                 235                 240


Thr Leu Val Thr Val Ser Ser
                245


<210>  170
<211>  242
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3-H1L1/VL-(G4S)3-VH

<400>  170

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


Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20                  25                  30


Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Lys Ala
        35                  40                  45


Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


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


Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Tyr Gln Ser
                85                  90                  95


Lys His Val Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
        115                 120                 125
```

```
Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser
    130                 135                 140

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Glu
145                 150                 155                 160

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly
                165                 170                 175

Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe Lys
            180                 185                 190

Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr Met
        195                 200                 205

Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr
    210                 215                 220

Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser
```

<210> 171
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1-H3L2/VH-(G4S)4-VL

<400> 171

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Ser Val Asp Lys Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
    130                 135                 140

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160

Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Ser Ile Ala Trp Tyr
                165                 170                 175

Gln His Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser
            180                 185                 190

Thr Leu Gln Pro Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Arg Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220

Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Leu Leu Tyr Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 172
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1-H3L2/VH-(G4S)3-VL

<400> 172

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Arg Ala Thr Leu Ser Val Asp Lys Ser Lys Asn Thr Ala Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140


Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala
145                 150                 155                 160


Ser Gln Asp Ile Asn Lys Ser Ile Ala Trp Tyr Gln His Lys Pro Gly
                165                 170                 175
```

```
Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser Thr Leu Gln Pro Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu
    210                 215                 220

Gln Tyr Asp Ser Leu Leu Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys
```

<210> 173
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9-H1L2/VH-(G4S)4-VL

<400> 173

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

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

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Leu Ile Tyr Pro Gly Asp Gly Asp Thr Met Tyr Ala Glu Lys Phe
    50                  55                  60

Arg Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95
```

```
Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Ser Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln
    130                 135                 140

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
145                 150                 155                 160

Cys Arg Ala Ser Arg Asp Ile Asn Lys Tyr Leu Gly Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser Thr Leu
            180                 185                 190

Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp
        195                 200                 205

Phe Ser Leu Thr Ile Asn Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
    210                 215                 220

Tyr Cys Leu Gln Tyr Asp Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Val Glu Ile Lys
```

<210> 174
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> 43B9-H1L2/VH-(G4S)3-VL

<400> 174

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

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

Trp Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Leu Ile Tyr Pro Gly Asp Gly Asp Thr Met Tyr Ala Glu Lys Phe
    50                  55                  60

Arg Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Asp Thr Ala Tyr
65                  70                  75                  80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Arg Leu Ser Phe Gly Ala Trp Phe Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Ser Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
    130                 135                 140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Arg
145                 150                 155                 160

Asp Ile Asn Lys Tyr Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala
                165                 170                 175

Pro Lys Leu Leu Ile His Tyr Thr Ser Thr Leu Gln Ser Gly Val Pro
            180                 185                 190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Phe Ser Leu Thr Ile
        195                 200                 205

Asn Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr
    210                 215                 220

Asp Asn Leu Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225                 230                 235
```

<210> 175
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8-H2L1/VH-(G4S)4-VL

<400> 175

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


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Asn Ser
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Trp Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95


Ala Arg Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr
    130                 135                 140


Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu
145                 150                 155                 160


Ser Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ser Trp Tyr Gln
                165                 170                 175
```

```
Gln Lys Pro Gly Gln Ala Val Arg Leu Leu Ile Tyr Tyr Thr Ser Asn
            180                 185                 190

Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Glu Ser Gly Thr
        195                 200                 205

Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val
    210                 215                 220

Tyr Tyr Cys Gln Gln Tyr Ser Lys Phe Pro Trp Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Leu Glu Ile Lys
                245
```

<210> 176
<211> 241
<212> PRT
<213> Artificial Sequence

<220>
<223> 36F8-H2L1/VH-(G4S)3-VL

<400> 176

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Asn Ser
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Trp Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95
```

```
Ala Arg Ser Gly Pro Ile Thr Met Gly Phe Thr Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Glu Ile Val Met Thr Gln Ser Pro Ala Thr
    130                 135                 140

Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser
145                 150                 155                 160

Gln Gly Ile Ser Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Val Arg Leu Leu Ile Tyr Tyr Thr Ser Asn Arg Ala Thr Gly Ile
            180                 185                 190

Pro Ala Arg Phe Ser Gly Ser Glu Ser Gly Thr Asp Tyr Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
    210                 215                 220

Tyr Ser Lys Phe Pro Trp Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
225                 230                 235                 240

Lys
```

<210> 177
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> 39E1-H6L3/VH-(G4S)4-VL

<400> 177

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

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
    130                 135                 140

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160

Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Tyr Ile Val Trp Tyr
                165                 170                 175

Gln His Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser
            180                 185                 190

Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220
```

```
Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Leu Arg Thr Phe Gly Gln
225                 230                 235                 240


Gly Thr Lys Val Glu Ile Lys
                245


<210>  178
<211>  242
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  39E1-H6L3/VH-(G4S)3-VL

<400>  178

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


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


Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60


Gln Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg His Tyr Gly Tyr Asp Arg Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140
```

```
Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala
145                 150                 155                 160


Ser Gln Asp Ile Asn Lys Tyr Ile Val Trp Tyr Gln His Lys Pro Gly
                165                 170                 175


Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser Thr Leu Gln Ser Gly
            180                 185                 190


Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Tyr Thr Leu
        195                 200                 205


Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220


Gln Tyr Asp Asn Leu Leu Arg Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240


Ile Lys



<210>  179
<211>  242
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F7-H1L1/VH-(G4S)4-VL

<400>  179

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50                  55                  60
```

```
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Glu Ile Ser Gly Asn Leu Gly Trp Leu Gln Gln Lys Pro Gly
                165                 170                 175

Lys Ala Ile Lys Arg Leu Ile Tyr Ala Ala Thr Thr Leu Asp Ser Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu
    210                 215                 220

Gln Tyr Asp Ser Tyr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys
```

<210> 180
<211> 237
<212> PRT
<213> Artificial Sequence

<220>

<223> F7-H1L1/VH-(G4S)3-VL

<400> 180

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80


Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125


Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
    130                 135                 140


Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser
145                 150                 155                 160


Gly Asn Leu Gly Trp Leu Gln Gln Lys Pro Gly Lys Ala Ile Lys Arg
                165                 170                 175


Leu Ile Tyr Ala Ala Thr Thr Leu Asp Ser Gly Val Pro Ser Arg Phe
            180                 185                 190


Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu
        195                 200                 205
```

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Tyr
210 215 220

Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225 230 235

<210> 181
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1-H1L1/VH-(G4S)4-VL

<400> 181

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

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

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
130 135 140

```
Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160


Ile Thr Cys Lys Ala Ser Gln Asp Ile Asn Lys Ser Ile Ala Trp Tyr
                165                 170                 175


Gln His Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser
            180                 185                 190


Thr Leu Gln Pro Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205


Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220


Thr Tyr Tyr Cys Leu Gln Tyr Asp Ser Leu Leu Tyr Thr Phe Gly Gln
225                 230                 235                 240


Gly Thr Lys Val Glu Ile Lys
                245
```

<210> 182
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> 26A1-H1L1/VH-(G4S)3-VL

<400> 182

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


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


Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asp Pro Phe Asp Ser Tyr Thr Tyr Tyr Asn Gln Lys Phe
    50                  55                  60
```

```
Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Asp Gly Val Tyr Lys Trp Tyr Phe Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala
145                 150                 155                 160

Ser Gln Asp Ile Asn Lys Ser Ile Ala Trp Tyr Gln His Lys Pro Gly
                165                 170                 175

Lys Ala Pro Lys Leu Leu Ile His Tyr Thr Ser Thr Leu Gln Pro Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Arg Asp Tyr Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu
    210                 215                 220

Gln Tyr Asp Ser Leu Leu Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys
```

<210> 183
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H5

<400> 183

Gln Val Gln Leu Val Gln Ser Gly Ser Gly Val Lys Lys Pro Gly Ala
1   5   10   15

Ser Val Arg Val Ser Cys Trp Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20   25   30

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35   40   45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50   55   60

Lys Gly Arg Ala Ser Leu Thr Ala Asp Lys Asp Leu Phe Thr Ala His
65   70   75   80

Met Asp Ile Arg Gly Leu Thr Gln Gly Asp Thr Ala Thr Tyr Tyr Cys
                85   90   95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Arg Gly Thr Leu Ile Val
            100   105   110

Val Ser Ser
        115

<210> 184
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H6

<400> 184

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

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

```
Glu Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Trp Met Asp Pro Glu Thr Gly Asp Thr Gly Tyr Pro Gln Lys Phe
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Ala Asn Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110

Val Ser Ser
        115


<210>  185
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3-H7

<400>  185

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Thr Thr Ala Tyr
65                  70                  75                  80
```

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 186
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H8

<400> 186

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

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

Glu Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 187
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H9

<400> 187

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr
100 105 110

Val Ser Ser
115

<210> 188
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H10

<400> 188

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


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


Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  189
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3-H11

<400>  189

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


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


Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45
```

```
Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```

<210> 190
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H12

<400> 190

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 191
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H13

<400> 191

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 192
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H14

<400> 192

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35   40   45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50   55   60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65   70   75   80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 193
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H15

<400> 193

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

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

```
Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ala Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```

<210> 194
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H16

<400> 194

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

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

Glu Met His Trp Val Arg Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Thr Thr Thr Ala Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  195
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3-H18

<400>  195

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


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


Glu Met His Trp Val Lys Gln Ala Pro Gly His Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Thr Leu Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115
```

<210> 196
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H19

<400> 196

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Val Arg Gln Pro Pro Gly Lys Ala Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Leu Ser Ala Asp Lys Ser Lys Asn Gln Ala Val
65 70 75 80

Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
85 90 95

Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Ser Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 197
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-H20

<400> 197

```
Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15


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


Glu Met His Trp Val Lys Gln Pro Pro Gly Lys Ala Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Thr Leu Ser Ala Asp Lys Ser Lys Asn Gln Ala Val
65                  70                  75                  80


Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Thr Arg Tyr Phe Ser Phe Ala Tyr Trp Gly Gln Gly Ser Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  198
<211>  112
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  M3-L4

<400>  198

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


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


Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro
        35                  40                  45
```

```
Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Ile Pro
    50                  55                  60

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

Thr Arg Met Glu Pro Glu Asp Phe Ala Arg Tyr Phe Cys Tyr Gln Ser
                85                  90                  95

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

<210> 199
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-L5

<400> 199

```
Glu Val Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Ile Ser Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
        35                  40                  45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

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

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

Lys His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
```

<210> 200
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-L6

<400> 200

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

Glu Arg Ala Thr Ile Ser Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20   25   30

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Ala
        35   40   45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60

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

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

Lys His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

<210> 201
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> M3-L7

<400> 201

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

Glu Arg Ala Thr Ile Asn Cys Arg Ser Ser Gln Ser Leu Arg His Ser
            20   25   30

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro
        35   40   45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50   55   60

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

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

Lys His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100   105   110

<210> 202
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-H5

<400> 202

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Asp
    50   55   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65   70   75   80

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85   90   95

```
Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  203
<211>  115
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F7-H6

<400>  203

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


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Pro Asp
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Glu Asp Ala Lys Asn Ser
65                  70                  75                  80


Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Thr Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  204
<211>  115
```

<212> PRT
<213> Artificial Sequence

<220>
<223> F7-H9

<400> 204

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20   25   30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Glu
    50   55   60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ala Lys Asn Ser
65   70   75   80

Val Tyr Leu Asp Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85   90   95

Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 205
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-H10

<400> 205

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

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Gln Ile Arg Leu Lys Ser Asp Asn Tyr Ala Thr His Tyr Ala Asp
    50                  55                  60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Val Gly Gly Asn Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115
```