(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 October 2020 (15.10.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/210247 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61K 39/395* (2006.01)
C07K 16/30 (2006.01)

(21) International Application Number:
PCT/US2020/027092

(22) International Filing Date:
07 April 2020 (07.04.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/832,975	12 April 2019 (12.04.2019)	US
62/863,330	19 June 2019 (19.06.2019)	US
62/931,988	07 November 2019 (07.11.2019)	US

(71) Applicant: **PHANES THERAPEUTICS, INC.** [US/US]; 9215 Brown Deer Road, Suite B, San Diego, CA 92121 (US).

(72) Inventors: **WANG, Minghan**; 6104 Alida Row, San Diego, CA 92130 (US). **ZOU, Hui**; 3443 Binkley Avenue, Dallas, TX 75205 (US). **JIA, Haiqun**; 12972 Pipilo Court, San Diego, CA 92129 (US).

(74) Agent: **BARANIAK, Andrew, P.** et al.; Ice Miller LLP, 1735 Market Street, Suite 3450, Philadelphia, PA 19103-7509 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: HUMANIZED ANTI-FOLATE RECEPTOR 1 CHIMERIC ANTIGEN RECEPTORS AND USES THEREOF

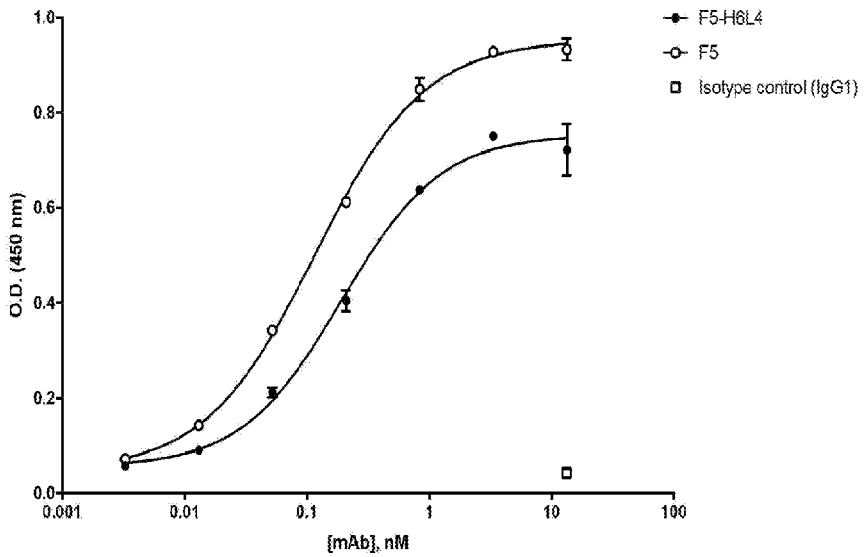


FIG. 1A

(57) Abstract: Chimeric antigen receptors (CARs) specific to FOLR1, vectors encoding the FOLR1 CAR, recombinant host cells comprising the FOLR1 CAR (CAR-Ts or CAR-NKs), and methods of using the CAR-Ts or CAR-NKs to treat a disease associated with the expression of FOLR1 thereof are described. Humanized anti-FOLR1 monoclonal antibodies and antigen-binding fragments thereof are also described.

WO 2020/210247 A1

[Continued on next page]

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

HUMANIZED ANTI-FOLATE RECEPTOR 1 CHIMERIC ANTIGEN RECEPTORS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/832,975, filed on April 12, 2019; U.S. Provisional Application No. 62/863,330, filed on June 19, 2019; and U.S. Provisional Application No. 62/931,988, filed on November 7, 2019. Each disclosure is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to anti-folate receptor 1 (FOLR1) chimeric antigen receptors (CARs), nucleic acids and expression vectors encoding the CARs, T cells engineered to express the CARs (CAR-T) and NK cells engineered to express the CARs (CAR-NK). Methods of making the CARs, methods of making the CAR-Ts/CAR-NKs, and methods of using the CAR-Ts/CAR-NKs to treat a disease associated with the expression of FOLR1, including cancer, 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 "065799.21WO1 Sequence Listing" and a creation date of March 26, 2020 and having a size of 140 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] The standard of care anti-cancer medicines provides significant benefits. Recently, the availability of immuno-oncology drugs such as anti-PD-1 mAbs, anti-PD-L1 mAbs and anti-CD3 bispecific T cell engagers has advanced the concept of leveraging and activating patients' immune system to fight various types of cancer. However, poor response, insufficient efficacy, and/or safety issues remain to be resolved. CAR-T (chimeric antigen receptor-T) cell therapies involve genetically engineering a patient's own immune cells, such as T cells, and redirecting them to a suitable cell surface antigen on cancer cells (Mayor et al., Immunotherapy. 2016; 8:491-494). This approach has demonstrated success in patients suffering from chemorefractory B cell malignancies and other cancers (Pettitt et al., Mol Ther. 2018; 26:342-353). T cells can be engineered to possess specificity to one or more cancer cell surface targets/antigens to recognize

and kill the cancer cell. The process includes transducing T cells with DNA or other genetic material encoding the chimeric antigen receptor (CAR), which comprises an extracellular antigen specific binding domain, such as one or more single chain variable fragments (scFv) of a monoclonal antibody (mAb), a hinge and transmembrane region, and an intracellular signaling domain (including one or more costimulatory domains and one or more activating domains) (Kochenderfer et al., Nat Rev Clin Oncol. 2013; 10:267–276). CAR-expressing immune cells, such as T cells and NK cells, can be used to treat various diseases, including liquid and solid tumors. Successful CAR-T cell therapies can specifically recognize and destroy targeted cells and maintain the ability to persist and proliferate over time.

[0005] Folate receptor 1 (FOLR1), also known as folate receptor α (FRα) or folate binding protein (FBP), is a glycosylphosphatidylinositol (GPI)-anchored membrane protein on cell surface that has high affinity for and transports the active form of folate, 5-methyltetrahydrofolate (5-MTF), and its derivatives into cells (Salazar and Ratnam, Cancer Metastasis Rev 2007; 26:141-52). FOLR1 has become an oncology target because it is overexpressed in certain solid tumors such as ovarian, lung and breast cancers (Toffoli et al., Int J Cancer 1997; 74:193-198 and Boogerd et al., Oncotarget 2016; 7:17442-17454), but its expression is at low levels in limited normal human tissues (Weitman, et al., Cancer Res 1992; 52:3396-3401). Consistent with this observation, phase 1 clinical trials conducted so far with FOLR1-targeting small and large molecules revealed good drug tolerability (Cheung et al., Oncotarget 2016; 7:52553–52574). Therefore, FOLR1 is an ideal target for CAR-T cell therapies to treat and cure FOLR1-positive cancers.

BRIEF SUMMARY OF THE INVENTION

[0006] In one 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 folate receptor 1 (FOLR1), a hinge region, a transmembrane region, and an intracellular signaling domain.

[0007] 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 folate receptor 1 (FOLR1); (b) a hinge region; (c) a transmembrane region; and (d) an intracellular signaling domain.

[0008] 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: 17, 18, 19, 41, 42 and 43, respectively;

(2) SEQ ID NOs: 20, 21, 22, 44, 45 and 46, respectively;

(3) SEQ ID NOs: 23, 24, 25, 47, 48 and 49, respectively;

(4) SEQ ID NOs: 26, 27, 28, 50, 51 and 52, respectively;

(5) SEQ ID NOs: 29, 30, 31, 53, 54 and 55, respectively;

(6) SEQ ID NOs: 32, 33, 34, 56, 57 and 58, respectively;

(7) SEQ ID NOs: 35, 36, 37, 59, 60 and 61, respectively; or

(8) SEQ ID NOs: 38, 39, 40, 62, 63 and 64, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

[0009] 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: 65, 66, 67, 89, 90 and 91, respectively;

(2) SEQ ID NOs: 68, 69, 70, 92, 93 and 94, respectively;

(3) SEQ ID NOs: 71, 72, 73, 95, 96 and 97, respectively;

(4) SEQ ID NOs: 74, 75, 76, 98, 99 and 100, respectively;

(5) SEQ ID NOs: 77, 78, 79, 101, 102 and 103, respectively;

(6) SEQ ID NOs: 80, 81, 82, 104, 105 and 106, respectively;

(7) SEQ ID NOs: 83, 84, 85, 107, 108 and 109, respectively; or

(8) SEQ ID NOs: 86, 87, 88, 110, 111 and 112, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

[0010] 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: 1, 3, 5, 7, 9, 11, 13, or 15, 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: 2, 4, 6, 8, 10, 12, 14, or 16.

[0011] In certain embodiments, the antigen binding domain comprises:

(1) 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;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of SEQ ID NO:14; or

(8) 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.

[0012] 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: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, 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: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

[0013] 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:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

[0014] In certain embodiments, the antigen binding domain is a single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1.

[0015] In certain embodiments, the antigen binding domain is a humanized single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1. 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: 159-170.

[0016] In certain embodiments, the chimeric antigen receptor (CAR) comprises one or more antigen binding domains.

[0017] In certain embodiments, the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

[0018] Also provided are chimeric antigen receptors (CARs) encoded by the isolated polynucleotides of the invention.

[0019] Also provided are vectors comprising the isolated polynucleotides comprising nucleic acids encoding the CARs of the invention.

[0020] Also provided are host cells comprising the vectors of the invention.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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 FOLR1.

[0029] Also provided are humanized anti-FOLR1 monoclonal antibodies or antigen-binding fragments thereof, wherein the antibodies or antigen-binding fragments thereof comprise a heavy chain variable region having a polypeptide sequence at least 95% identical to any one of SEQ ID NO: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

[0030] In certain embodiments, the humanized anti-FOLR1 monoclonal antibodies or antigen-binding fragments thereof comprise:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

[0031] In certain embodiments, the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof is capable of binding FOLR1, inducing effector-mediated tumor cell lysis, mediating the recruitment of conjugated drugs, and/or forming a bispecific antibody with another monoclonal antibody or antigen-binding fragment with a cancer-killing effect.

[0032] Also provided are isolated nucleic acids encoding the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[0033] Also provided are vectors comprising the isolated nucleic acid encoding the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[0034] Also provided are host cells comprising the vector comprising the isolated nucleic acid encoding the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[0035] Also provided is a pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention and a pharmaceutically acceptable carrier.

[0036] Also provided are methods of targeting FOLR1 on a cancer cell surface in a subject in need thereof, comprising administering to the subject in need thereof a pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[0037] Also provided are methods of treating cancer in a subject in need thereof, comprising administering to the subject the pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof 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.

[0038] Also provided are methods of producing the humanized anti-FOLR1 monoclonal 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 under conditions to produce the monoclonal antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or culture.

[0039] Also provided are method of producing a pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] 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.

[0041] FIGs. 1A-1L show the binding of humanized mAbs to immobilized recombinant human FOLR1 protein by ELISA.

[0042] FIGs. 2A-2E show the binding of humanized mAbs to SK-OV-3 cells. The experiment was carried out by FACS analysis.

[0043] FIGs. 3A-3G show the binding of humanized scFvs to immobilized recombinant human FOLR1 protein by ELISA.

[0044] FIGs. 4A-4G show the binding of humanized scFvs to SK-OV-3 cells. The experiment was carried out by FACS analysis.

DETAILED DESCRIPTION OF THE INVENTION

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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).

[0051] 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."

[0052] 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.

[0053] 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.

[0054] 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.

[0055] The words "right," "left," "lower," and "upper" designate directions in the drawings to which reference is made.

[0056] 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.

[0057] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences (e.g., chimeric antigen receptors (CARs) comprising antigen binding domains specific for FOLR1 and polynucleotides that encode them, FOLR1 polypeptides and FOLR1 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.

[0058] 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.

[0059] 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)).

[0060] 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.

[0061] 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).

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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 or transduced with a nucleic acid molecule of the invention. In another embodiment, a "host cell" is a progeny or

potential progeny of such a transfected or transduced 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.

[0068] 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 CAR 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.

[0069] As used herein, the term "immune cell" or "immune effector cell" refers to a cell that is involved in an immune response, e.g., in the promotion of an immune effector response. Examples of immune cells include T cells, B cells, natural killer (NK) cells, mast cells, and myeloid-derived phagocytes. According to particular embodiments, the engineered immune cells are T cells, and are referred to as CAR-T cells because they are engineered to express CARs of the invention.

[0070] As used herein, the term "engineered immune cell" refers to an immune cell, also referred to as an immune effector cell, that has been genetically modified by the addition of extra genetic material in the form of DNA or RNA to the total genetic material of the cell. According to embodiments herein, the engineered immune cells have been genetically modified to express a CAR construct according to the invention.

Chimeric Antigen Receptor (CAR)

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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

[0077] 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

[0078] 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

[0079] 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

[0080] 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

[0081] 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).

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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).

[0086] 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.

[0087] 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.

Antibodies and Antigen binding domains

[0088] 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.

[0089] 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 FOLR1 is substantially free of antibodies that do not bind to FOLR1). In addition, an isolated antibody is substantially free of other cellular material and/or chemicals.

[0090] As used herein, the term "monoclonal antibody" or "mAb" 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.

[0091] 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 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).

[0092] 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 5 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.

[0093] 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.

[0094] 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 antigen binding domain are retained, but its antigenicity in the human body is reduced.

[0095] 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.

[0096] As used herein, the term "multispecific 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.*, the different proteins (or different subunits of a multimeric protein). In an embodiment, a multispecific antibody comprises a third, fourth, or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody is a bispecific antibody molecule, a trispecific antibody molecule, or a tetraspecific antibody molecule.

[0097] As used herein, the term "bispecifc antibody" refers to a multispecific 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.*, the 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 FOLR1 and the second epitope is located on PD-1, PD-L1, TIM-3, LAG-3, CD73, apelin, CTLA-4, EGFR, HER-2, CD3, CD19, CD20, CD33, CD47, TIP-1, CLDN18.2, DLL3, and/or other tumor associated immune suppressors or surface antigens.

[0098] As used herein, the term "FOLR1" refers to folate receptor 1 (FOLR1), also known as folate receptor α (FRα) or folate binding protein (FBP), which is a glycosylphosphatidylinositol (GPI)-anchored membrane protein on a cell surface that has high affinity for and transports the active form of folate, 5-methyltetrahydrofolate (5-MTF), and its derivatives into cells (Salazar and Ratnam, Cancer Metastasis Rev 2007; 26:141-52). FOLR1 has become an oncology target because it is overexpressed in certain solid tumors such as ovarian, lung and breast cancers

(Toffoli et al., Int J Cancer 1997; 74:193-198 and Boogerd et al., Oncotarget 2016; 7:17442-17454), but its expression is at low levels in limited normal human tissues (Weitman, et al., Cancer Res 1992; 52:3396-3401). Consistent with this observation, phase 1 clinical trials conducted so far with FOLR1-targeted small and large molecules revealed good drug tolerability (Cheung et al., Oncotarget 2016; 7:52553–52574). Therefore, FOLR1 is an ideal target for CAR-T cell therapies to treat and cure FOLR1-positive cancers. An exemplary amino acid sequence of a human FOLR1 is represented by GenBank Accession No. NP_057937 (SEQ ID NO:135).

[0099] As used herein, an antibody and/or antigen binding domain that "specifically binds to FOLR1" refers to an antibody and/or antigen binding domain that binds to a FOLR1, preferably a human FOLR1, 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 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 domain 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.

[00100] 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.

[00101] According to a particular aspect, the invention relates to chimeric antigen receptors (CAR)s comprising an antigen binding domain, 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: 17, 18, 19, 41, 42 and 43, respectively;

(2) SEQ ID NOs: 20, 21, 22, 44, 45 and 46, respectively;

(3) SEQ ID NOs: 23, 24, 25, 47, 48 and 49, respectively;

(4) SEQ ID NOs: 26, 27, 28, 50, 51 and 52, respectively;

(5) SEQ ID NOs: 29, 30, 31, 53, 54 and 55, respectively;

(6) SEQ ID NOs: 32, 33, 34, 56, 57 and 58, respectively;

(7) SEQ ID NOs: 35, 36, 37, 59, 60 and 61, respectively; or

(8) SEQ ID NOs: 38, 39, 40, 62, 63 and 64, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

[00102] According to another particular aspect, the invention relates to chimeric antigen receptors (CARs) comprising an antigen binding domain, 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: 65, 66, 67, 89, 90 and 91, respectively;

(2) SEQ ID NOs: 68, 69, 70, 92, 93 and 94, respectively;

(3) SEQ ID NOs: 71, 72, 73, 95, 96 and 97, respectively;

(4) SEQ ID NOs: 74, 75, 76, 98, 99 and 100, respectively;

(5) SEQ ID NOs: 77, 78, 79, 101, 102 and 103, respectively;

(6) SEQ ID NOs: 80, 81, 82, 104, 105 and 106, respectively;

(7) SEQ ID NOs: 83, 84, 85, 107, 108 and 109, respectively; or

(8) SEQ ID NOs: 86, 87, 88, 110, 111 and 112, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

[00103] According to another particular aspect, the invention relates to an antigen binding domain comprising 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: 1, 3, 5, 7, 9, 11, 13, or 15, 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: 2, 4, 6, 8, 10, 12, 14, or 16.

[00104] According to another particular aspect, the invention relates to an antigen binding domain, comprising:

(1) 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;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of SEQ ID NO:14; or

(8) 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.

[00105] 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: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, 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: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

[00106] 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:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

[00107] According to another particular aspect, the antigen binding domain is a single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1.

[00108] In certain embodiments, the encoded antigen binding domain is a humanized single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1. In certain embodiments, the antigen binding domain is a humanized single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1. 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:159-170. 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:159-170.

[00109] According to another particular aspect, the chimeric antigen receptor comprises one or more antigen binding domains.

[00110] According to another particular aspect, the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

[00111] In another general aspect, the invention relates to an isolated polynucleotide comprising a nucleic acid encoding 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 antigen binding domains thereof of the invention can be altered without changing the amino acid sequences of the proteins.

[00112] In another general aspect, the invention relates to a vector comprising the isolated polynucleotide comprising the nucleic acid encoding the CAR, wherein the CAR comprises an antigen binding domain thereof 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 antigen binding domain 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.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] In another general aspect, the invention relates to a humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to any one of SEQ ID NO: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

[00120] According to another particular aspect, the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;
(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;
(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;
(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;
(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;
(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;
(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;
(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;
(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;
(56) 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:195;
(57) 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:196;
(58) 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:197;
(59) 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;
(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;
(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;
(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or
(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

[00121] According to another particular aspect, the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof is capable of binding FOLR1, inducing effector-mediated tumor cell lysis, mediating the recruitment of conjugated drugs, and/or forming a bispecific antibody with another monoclonal antibody or antigen-binding fragment with a cancer-killing effect.

[00122] In another general aspect, the invention relates to an isolated nucleic acid encoding the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[00123] In another general aspect, the invention relates to a vector comprising the isolated nucleic acid encoding the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[00124] In another general aspect, the invention relates to a host cell comprising the vector comprising the isolated nucleic acid encoding the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[00125] In another general aspect, the invention relates to a method of producing the humanized anti-FOLR1 monoclonal 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 under conditions to produce the monoclonal antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or culture.

Pharmaceutical Compositions

[00126] In another general aspect, the invention relates to a pharmaceutical composition comprising an isolated polynucleotide of the invention, an isolated polypeptide of the invention, a host cell of the invention, and/or an engineered immune cell of the invention and a pharmaceutically acceptable carrier.

[00127] In another general aspect, the invention relates to a pharmaceutical composition comprising a humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention and a pharmaceutically acceptable carrier.

[00128] 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, and/or a humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment of the invention together with a pharmaceutically acceptable carrier. Polynucleotides, polypeptides, host cells, engineered immune cells of the invention, and/or a humanized anti-FOLR1 monoclonal antibody or antigen-

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

[00129] 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 a polynucleotide, polypeptide, host cell, and/or engineered immune cell pharmaceutical composition can be used in the invention.

[00130] 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 carriers may be used in formulating the pharmaceutical compositions of the invention.

[00131] In another general aspect, the invention relates to a method of producing a pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

Methods of use

[00132] 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, 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.

[00133] In another general aspect, the invention relates to a method of targeting FOLR1 on a cancer cell surface in a subject in need thereof, comprising administering to the subject in need thereof a pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of the invention.

[00134] In another general aspect, the invention relates to a method of treating cancer in a subject in need thereof, comprising administering to the subject the pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof 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.

[00135] 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 compositions comprise a therapeutically effective amount of the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof. 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.

[00136] 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.

[00137] 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.

[00138] As used herein with reference to a humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof, a therapeutically effective amount means an amount of the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof that modulates an immune response in a subject in need thereof. Also, as used herein with reference to a humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof, a therapeutically effective amount means an amount of the humanized anti-FOLR1 monoclonal 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.

[00139] 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, 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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, intradermaly, 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.

[00144] 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.

[00145] 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.

[00146] 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.

[00147] 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.

[00148] 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, 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.

[00149] According to particular embodiments, provided are compositions used in the treatment of a cancer. 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-TIP-1 mAb, an anti-Claudin18.2 mAb, an anti-CTLA-4 mAb, an anti-PD-L1 mAb, an anti-PD-1 mAb, other immuno-oncology drugs, an antiangiogenic agent, a radiation therapy, an antibody-drug conjugate (ADC), a targeted therapy, or other anticancer drugs.

[00150] 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.

[00151] 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.

[00152] 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 FOLR1. Such agents include, but are not limited to, an anti-FOLR1 monoclonal antibody or bispecific antibody.

[00153] 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.

EMBODIMENTS

[00154] The invention provides also the following non-limiting embodiments.

[00155] Embodiment 1 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 Folate receptor 1 (FOLR1); (b) a hinge region; (c) a transmembrane region; and (d) an intracellular signaling domain.

[00156] Embodiment 2 is the isolated polynucleotide of embodiment 1, 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: 17, 18, 19, 41, 42 and 43, respectively;

(2) SEQ ID NOs: 20, 21, 22, 44, 45 and 46, respectively;

(3) SEQ ID NOs: 23, 24, 25, 47, 48 and 49, respectively;

(4) SEQ ID NOs: 26, 27, 28, 50, 51 and 52, respectively;

(5) SEQ ID NOs: 29, 30, 31, 53, 54 and 55, respectively;

(6) SEQ ID NOs: 32, 33, 34, 56, 57 and 58, respectively;

(7) SEQ ID NOs: 35, 36, 37, 59, 60 and 61, respectively; or

(8) SEQ ID NOs: 38, 39, 40, 62, 63 and 64, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

[00157] Embodiment 3 is the isolated polynucleotide of embodiment 1, 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: 65, 66, 67, 89, 90 and 91, respectively;

(2) SEQ ID NOs: 68, 69, 70, 92, 93 and 94, respectively;

(3) SEQ ID NOs: 71, 72, 73, 95, 96 and 97, respectively;

(4) SEQ ID NOs: 74, 75, 76, 98, 99 and 100, respectively;

(5) SEQ ID NOs: 77, 78, 79, 101, 102 and 103, respectively;

(6) SEQ ID NOs: 80, 81, 82, 104, 105 and 106, respectively;

(7) SEQ ID NOs: 83, 84, 85, 107, 108 and 109, respectively; or

(8) SEQ ID NOs: 86, 87, 88, 110, 111 and 112, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

[00158] Embodiment 4 is the isolated polynucleotide of any one of embodiments 1-3, wherein 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: 1, 3, 5, 7, 9, 11, 13, or 15, 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: 2, 4, 6, 8, 10, 12, 14, or 16.

[00159] Embodiment 5 is the isolated polynucleotide of any one of embodiments 1-4, wherein the antigen binding domain comprises:

(1) 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;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of SEQ ID NO:14; or

(8) 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.

[00160] Embodiment 6 is the isolated polynucleotide of any one of embodiments 1-4, wherein 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: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, 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: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

[00161] Embodiment 7 is the isolated polynucleotide of embodiment 6, wherein the antigen binding domain is humanized and comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

[00162] Embodiment 8 is the isolated polynucleotide of any one of embodiments 1-7, wherein the antigen binding domain is a single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1.

[00163] Embodiment 9 is the isolated polynucleotide of embodiment 8, wherein the single chain variable fragment (scFv) is humanized.

[00164] Embodiment 10 is the isolated polynucleotide of embodiment 8 or 9, wherein the single chain variable fragment (scFv) comprises a polypeptide sequence at least 95% identical to any one of SEQ ID NOs:159-170.

[00165] Embodiment 11 is the isolated polynucleotide of any one of embodiments 1-10, wherein the chimeric antigen receptor (CAR) comprises one or more antigen binding domains.

[00166] Embodiment 12 is the isolated polynucleotide of any one of embodiments 1-11, wherein the intracellular signaling domain of the CAR comprises one or more costimulatory domains and one or more activating domains.

[00167] Embodiment 13 is a chimeric antigen receptor (CAR) encoded by the isolated polynucleotide of any one of embodiments 1-12.

[00168] Embodiment 14 is a vector comprising the isolated polynucleotide of any one of embodiments 1-12.

[00169] Embodiment 15 is a host cell comprising the vector of embodiment 14.

[00170] Embodiment 16 is the host cell of embodiment 15, wherein the cell is a CAR-T cell, preferably a human CAR-T cell.

[00171] Embodiment 17 is the host cell of embodiment 15, wherein the cell is a CAR-NK cell, preferably a human CAR-NK cell.

[00172] Embodiment 18 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 14.

[00173] Embodiment 19 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 1-12 under conditions to produce the CAR-T cell and recovering the CAR-T cell.

[00174] Embodiment 20 is a method of making a host cell expressing a chimeric antigen receptor (CAR), the method comprising transducing a NK cell with the vector of embodiment 14.

[00175] Embodiment 21 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 1-12 under conditions to produce the CAR-NK cell, and recovering the CAR-NK cell.

[00176] Embodiment 22 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 1-12, wherein the isolated polynucleotide is an *in vitro* transcribed RNA or synthetic RNA.

[00177] Embodiment 23 is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject the host cell of any one of embodiments 15-17.

[00178] Embodiment 24 is the method of embodiment 23, 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.

[00179] Embodiment 25 is the method of embodiment 23 or 24, further comprising administering to the subject in need thereof an agent that increases the efficacy of a cell expressing a CAR.

[00180] Embodiment 26 is the method of embodiment 23 or 24, 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.

[00181] Embodiment 27 is the method of embodiment 23 or 24, further comprising administering to the subject in need thereof an agent that treats the disease associated with FOLR1.

[00182] Embodiment 28 is a humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to any one of SEQ ID NO: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

[00183] Embodiment 29 is the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of embodiment 28, wherein the antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

[00184] Embodiment 30 is the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of embodiment 28 or 29, wherein the monoclonal antibody or antigen-binding fragment thereof is capable of binding FOLR1, inducing effector-mediated tumor cell lysis, mediating the recruitment of conjugated drugs, and/or forming a bispecific antibody with another monoclonal antibody or antigen-binding fragment with a cancer-killing effect.

[00185] Embodiment 31 is an isolated nucleic acid encoding the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 28-30.

[00186] Embodiment 32 is a vector comprising the isolated nucleic acid of embodiment 31.

[00187] Embodiment 33 is a host cell comprising the vector of embodiment 32.

[00188] Embodiment 34 is a pharmaceutical composition, comprising the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 28-30 and a pharmaceutically acceptable carrier.

[00189] Embodiment 35 is a method of targeting FOLR1 on a cancer cell surface in a subject in need thereof, comprising administering to the subject in need thereof a pharmaceutical composition comprising the humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 28-30.

[00190] Embodiment 36 is a method of treating cancer in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of embodiment 34.

[00191] Embodiment 37 is the method of embodiment 36, 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.

[00192] Embodiment 38 is a method of producing the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of embodiments 28-30, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment under conditions to produce the monoclonal antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or culture.

[00193] Embodiment 39 is a method of producing the pharmaceutical composition of embodiment 34, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

EXAMPLES

[00194] **Example 1: Identification of antigen binding domains that specifically bind FOLR1**

[00195] The antigen binding domains that specifically bind FOLR1 are anti-FOLR1 mAbs isolated and sequenced as described in PCT/US2019/021084, filed on March 7, 2019, which is incorporated herein by reference in its entirety.

[00196] Sequences of heavy and light chain variable regions for the antigen binding domains that specifically bind FOLR1 are provided in Tables 1 and 2, and the CDR regions for the antigen binding domains that specifically bind FOLR1 are provided in Tables 3-6.

Table 1: Sequences of heavy chain variable regions for the antigen binding domains that specifically bind FOLR1

Name	VH	SEQ ID NO:
F4	EVQLVESGGGLVKPGGSLKLSCAASGFTFSDYGMHWVRQAPEKGLEWVAFISSGSNTIYY ADIVKGRFAISRDNAKNTLFLQMASLRSEDTALYYCARLAEWDVAYWGQGTLVTVSA	1
F5	EVQLVESGGELVKPGGSLKLSCAVSGFTFSNYGMSWVRQTPDKRLEWVATISSGGSYTYY PDSVKGRFTISRDNDKNTLYLQMSSLKSEDTAMYYCSTQGSSGYVGYWGQGTTLTVSS	3

F7	EFQLQQSGPELVKPGASVKISCKASGYSFTDYNMNWVKQSNGKSLEWIGVIDPNYGTTNY NQKFVGKATLTVDQSSITAYMQLNSLTAEDSAVYFCAIKGYGNPAAYWGQGTLVTVSA	5
F8	EVMLVESGGGLVKPGGSLKLSCVASGFTLSTYAMSWVRQTPEKRLEWVATISGGGGDTY HLDTVKGRFTISRDNAKNTLYLQMSSLRSEDTALYYCARQSHYGSSYYFDNWGQGTTLT VSS	7
F10	QVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVRQRPGKGLEWIGRIYPGDGYTH YNGMFKGKATLTADKSSSTGYMQLSSLTSEDSAVYFCTRHGDFPYWYFDVWGTGTTVTV SS	9
F17	DVQLVESGGGLVQPGGSRKLSCAASGFTFSDFGMHWIRQAPERGLEWVAYMSYTPGTFH YADTVKDRFFISRDNAKNTLFLQMTSLRSDDTAMYYCARVHVGTVDYWGQGTSVTVSS	11
F19	EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWVRQSPDKGLEWVAQIGNKFHNY ETYYSDSVKGRFTISRDDSKSSVYLQMNSLRVEDTGIYYCTKLGRGYYVMDYWGQGTSV TVSS	13
F20	QVQLQQSGAELVKPGASVQLSCKASGYTFASYYLYWVKQRPGQGLEWIGEINPRSGGTN FNEKFKSKATVTVDKSSSTAYMQLSSLTSEDSAVYYCSRSGRLRGFYTMDYWGQGTSVT VSS	15

VH: heavy chain variable region

Table 2: Sequences of light chain variable regions for the antigen binding domains that specifically bind FOLR1

Name	**VL**	**SEQ ID NO:**
F4	DIVLTQSPATLSVTPGDRISLSCRASQNINNNLHWYQQKSHESPRLLIKFASQSISGIPSRFSG SGSGTDFTLNINGVETEDFGMYFCQQIYSWPQLTFGAGTRLELK	2
F5	DIQMTQSPSSLSAFLGGKVTITCKASQDITNFIGWYQHKPGKGPRLLISYTSILESGIPSRFSG SGSGRDYSFSISNLEPEDIATYYCLQYYNLWTFGGGTKLEIK	4
F7	DIQMTQSPSSLSASLGGKVTITCKASQDINKYLAWYQHEPGKGPRLLIRYTSILESGIPSRFS GSGSGRDYSFSISNLEPEDIATYYCLQYYNLWTFGGGTKLEIK	6
F8	DIQMTQSPASLSASVGEIVTIICRVSENIDSYLAWYQQKQGKSPQLLVYAATNLADGVPSR FSGSGSGSQYSLKINSLQSEDVARYYCQHYYTTPPTFGGGTKLDIK	8
F10	DIQMTQSPASLSASVGESVTITCRASENIDSYLAWYQQKQGKSPQLLVYAATNLAVGVPS RFSGSGSGTQYTLKINSLQSEDVARYYCQHHYSTPPTFGGGTKLEIK	10
F17	DVVLTQSPATLSVTPGDSVSLSCRASQNINNNLHWFQQKSHESPRLLIKYASQSISGIPSRFS GSGSGTDFTLSINNVETEDFGIYFCQQSNSWPALTFGTGTKVELK	12
F19	DIQMTQTTSSLSASLGDRVTLNCRASQDITNHLNWFQQKPDGTFQLLIYYTSRLHSGVPSR FSGSGSGTDYSLTISNLEQEDFATYFCQQDSQHPWTFGGGTKLEIK	14
F20	NIVMTQSPKSMSVSVGERVTLSCKAGENVGSYVSWYQQKPEQSPELLIYGASNRYTGVPD RFTGSGSATDFTLTISSVQAEDLADYYCGQTYRFLTFGAGTKLELK	16

VL: light chain variable region

Table 3: CDR regions 1-3 of heavy chain for the antigen binding domains that specifically bind FOLR1

Name	**HC CDR1**	**NO**	**HC CDR2**	**NO**	**HC CDR3**	**NO**
F4	GFTFSDYG	17	ISSGSNTI	18	ARLAEWDVAY	19
F5	GFTFSNYG	20	ISSGGSYT	21	STQGSSGYVGY	22
F7	GYSFTDYN	23	IDPNYGTT	24	AIKGYGNPAAY	25
F8	GFTLSTYA	26	ISGGGGDT	27	ARQSHYGSSYYFDN	28
F10	GYAFSSSW	29	IYPGDGYT	30	TRHGDFPYWYFDV	31
F17	GFTFSDFG	32	MSYTPGTF	33	ARVHVGTVDY	34
F19	GFTFSDYW	35	IGNKFHNYET	36	TKLGRGYYVMDY	37
F20	GYTFASYY	38	INPRSGGT	39	SRSGRLRGFYTMDY	40

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

The HC CDRs for the antigen binding domains that specifically bind FOLR1 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 the antigen binding domains that specifically bind FOLR1

Name	LC CDR1	NO	LC CDR2	NO	LC CDR3	NO
F4	QNINNN	41	FAS	42	QQIYSWPQLT	43
F5	QDITNF	44	YTS	45	LQYYNLWT	46
F7	QDINKY	47	YTS	48	LQYYNLWT	49
F8	ENIDSY	50	AAT	51	QHYYTTPPT	52
F10	ENIDSY	53	AAT	54	QHHYSTPPT	55
F17	QNINNN	56	YAS	57	QQSNSWPALT	58
F19	QDITNH	59	YTS	60	QQDSQHPWT	61
F20	ENVGSY	62	GAS	63	GQTYRFLT	64

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

The LC CDRs for the antigen binding domains that specifically bind FOLR1 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 the antigen binding domains that specifically bind FOLR1

Name	HC CDR1	NO	HC CDR2	NO	HC CDR3	NO
F4	GFTFSDYGMH	65	FISSGSNTIYYADIVKG	66	ARLAEWDVAY	67
F5	GFTFSNYGMS	68	TISSGGSYTYYPDSVKG	69	STQGSSGYVGY	70
F7	GYSFTDYNMN	71	VIDPNYGTTNYNQKFVG	72	AIKGYGNPAAY	73
F8	GFTLSTYAMS	74	TISGGGGDTYHLDTVKG	75	ARQSHYGSSYYFDN	76
F10	GYAFSSSWMN	77	RIYPGDGYTHYNGMFKG	78	TRHGDFPYWYFDV	79
F17	GFTFSDFGMH	80	YMSYTPGTFHYADTVKD	81	ARVHVGTVDY	82
F19	GFTFSDYWMN	83	QIGNKFHNYETYYSDSVKG	84	TKLGRGYYVMDY	85
F20	GYTFASYYLY	86	EINPRSGGTNFNEKFKS	87	SRSGRLRGFYTMDY	88

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

The HC CDRs for the antigen binding domains that specifically bind FOLR1 were determined utilizing a combination of IMGT (Lefranc, M.-P. et al., Nucleic Acids Res. 1999; 27:209-212) and Kabat (Elvin A. Kabat et al, Sequences of Proteins of Immunological Interest 5th ed. 1991) methods.

Table 6: CDR regions 1-3 of light chain for the antigen binding domains that specifically bind FOLR1

Name	LC CDR1	NO	LC CDR2	NO	LC CDR3	NO
F4	RASQNINNNLH	89	FASQSIS	90	QQIYSWPQLT	91
F5	KASQDITNFIG	92	YTSILES	93	LQYYNLWT	94
F7	KASQDINKYLA	95	YTSILES	96	LQYYNLWT	97
F8	RVSENIDSYLA	98	AATNLAD	99	QHYYTTPPT	100

F10	RASENIDSYLA	101	AATNLAV	102	QHHYSTPPT	103
F17	RASQNINNNLH	104	YASQSIS	105	QQSNSWPALT	106
F19	RASQDITNHLN	107	YTSRLHS	108	QQDSQHPWT	109
F20	KAGENVGSYVS	110	GASNRYT	111	GQTYRFLT	112

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

The LC CDRs for the antigen binding domains that specifically bind FOLR1 were determined utilizing a combination of IMGT (Lefranc, M.-P. et al., Nucleic Acids Res. 1999; 27:209-212) and Kabat (Elvin A. Kabat et al, Sequences of Proteins of Immunological Interest 5th ed. 1991) methods.

[00197] Example 2: Humanization of mouse anti-FOLR1 mAbs

[00198] The mouse anti-FOLR1 mAbs were humanized to reduce the potential of immunogenicity when used in human patients as described in PCT/US2019/021084, filed on March 7, 2019, which is incorporated herein by reference in its entirety. The sequences of the humanized VH and VL regions are shown in Table 7. The humanized VH and VL were named as follows: F5-H1 refers to the H1 sequence of humanized VH for mouse mAb F5; F5-L1 refers to the L1 sequence of humanized VL for mouse mAb F5. All the other humanized VH and VL regions adopt the same naming rule.

Table 7: Sequences of heavy chain and light chain variable regions of humanized antigen binding domains that specifically bind FOLR1

VH/ VL	SEQUENCE	SEQ ID NO:
F5-H1	EVQLLESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKGLEWVATISSGGSYTY YPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSTQGSSGYVGYWGQGTLVTVSS	113
F5-H2	EVQLVESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKGLEWVATISSGGSYTY YPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSTQGSSGYVGYWGQGTLVTVSS	114
F5-H3	EVQLVESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKGLEWVATISSGGSYTY YPDSVKGRFTISRDNSKNTLYLQMSSLRAEDTAVYYCSTQGSSGYVGYWGQGTLVTVSS	115
F5-H4	EVQLVESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKGLEWVATISSGGSYTY YPDSVKGRFTISRDNDKNTLYLQMSSLRAEDTAVYYCSTQGSSGYVGYWGQGTLVTVSS	116
F5-L1	DIQMTQSPSSVSASVGDRVTITCKASQDITNFIGWYQHKPGKAPKLLISYTSILESGVPSRFS GSGSGRDYTLTISSLQPEDFATYYCLQYYNLWTFGGGTKVEIK	117
F5-L2	DIQMTQSPSSVSASVGDRVTITCKASQDITNFIGWYQHKPGKAPKLLISYTSILESGVPSRFS GSGSGTDYTLTISSLQPEDFATYYCLQYYNLWTFGGGTKVEIK	118
F10-H1	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWMNWVRQAPGQGLEWIGRIYPGDGYTH YNGMFKGRASLTADKSTSTGYMELSSLRSEDTAVFFCTRHGDFPYWYFDVWGRGTLVTV SP	119
F10-H2	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWMNWVRQAPGQGLEWIGRIYPGDGYT HYNGMFKGRASLTADKSTSTGYMELSSLRSEDTAVFFCTRHGDFPYWYFDVWGRGTLV TVSS	120
F10-L1	DIQMTQSPSTLSASVGDRVTITCRASENIDSYLAWYQQKPGRAPKLLVYAATNLAVGVPS RFSGSGSGTEYTLTISSLQSDDFATYYCQHHYSTPPTFGQGTKLEIK	121
F10-L2	DIQMTQSPSTLSASVGDRVTITCRASENIDSYLAWYQQKPGRAPKLLVYAATNLAVGVPS RFSGSGSGTEYTLTISSLQPDDFATYYCQHHYSTPPTFGQGTKLEIK	122

F10-L3	DIQMTQSPSTLSASVGDRVTITCRASENIDSYLAWYQQKPGRAPKLLVYAATNLAVGVPS RFSGSGSGTEYTLTISSLQSEDFATYYCQHHYSTPPTFGQGTKLEIK	123
F17-H1	EVQLVETGGGLIQPGGSLRLSCAASGFTFSDFGMHWIRQAPGKGLEWVAYMSYTPGTFH YADTVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHVGTVDYWGQGTLVTVSS	124
F17-H2	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDFGMHWIRQAPGKGLEWVAYMSYTPGTFH YADTVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHVGTVDYWGQGTLVTVSS	125
F17-L1	EVVLTQSPATLSLSPGERATLSCRASQNINNNLHWFQQKPGQAPRLLIKYASQSISGIPARF SGSGSGTDFTLTISSLEPEDFAVYFCQQSNSWPALTFGQGTKVEIK	126
F17-L2	EVVLTQSPATLSLSPGERATLSCRASQNINNNLHWFQQKPGQAPRLLIKYASQSISGIPARF SGSGSGTDFTLTISSLETEDFAVYFCQQSNSWPALTFGQGTKVEIK	127
F20-H1	QVQLVQSGAEVKKPGSSVKVSCKASGYTFASYYLYWVRQAPGQGLEWIGEINPRSGGTN FNEKFKSRATVTVDKSTSTAYMELSSLRSEDTAVYYCSRSGRLRGFYTMDYWGQGTLVT VSS	128
F20-H2	QVQLVQSGAEVKKPGSSVKVSCKASGYTFASYYLYWVRQAPGQGLEWIGEINPRSGGTN FNEKFKSRATVTVDASTSTAYMELSSLRSEDTAVYYCSRSGRLRGFYTMDYWGQGTLVT VSS	129
F20-H3	QVQLVQSGAEVKKPGSSVKVSCKASGYTFASYYLYWVRQAPGQGLEWIGEINPRSGGTN FNEKFKSKATVTVDKSTNTAYMELSSLRSEDTAVYYCSRSGRLRGFYTMDYWGQGTLVT VSS	130
F20-L1	DIVMTQSPDSLAVSLGERATINCKAGENVGSYVSWYQQKPGQPPKLLIYGASNRYTGVPD RFSGSGSATDFTLTISSLQAEDVAVYYCGQTYRFLTFGQGTKVEIK	131
F20-L2	DIVMTQSPDSLAVSLGERATINCKAGENVGSYVSWYQQKPGQSPKLLIYGASNRYTGVPD RFSGSGSATDFTLTISSLQAEDVAVYYCGQTYRFLTFGQGTKVEIK	132
F20-L3	DIQMTQSPSTLSASVGDRVTITCKAGENVGSYVSWYQQKPGKAPKLLIYGASNRYTGVPA RFSGSGSATEFTLTISSLQPDDFATYYCGQTYRFLTFGQGTKVEVK	133
F20-L4	DIQMTQSPSTLSASVGDRVTITCKAGENVGSYVSWYQQKPGKAPKLLIYGASNRYTGVPA RFSGSGSATEFTLTISSLQPEDFATYYCGQTYRFLTFGQGTKVEVK	134
F4-H1	QVQLVQSGAEVRKPGASVKVSCKASGFTFSDYGMHWVRQAPGQGLEWVAFISSGSNTIY YADIVKGRFTITRNNSTSTLYMELSSLRSEDTAIYYCARLAEWDVAYWGAGTLVTVSS	136
F4-H2	QVQLVQSGAEVKKPGASVKVSCKASGFTFSDYGMHWVRQAPGQGLEWVAFISSGSNTIY YADIVKGRVTITRNNSTSTLYMELSSLRSEDTAIYYCARLAEWDVAYWGAGTLVTVSS	137
F4-H3	EVQLVESGGGLVQPGRSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAGISSGSNTIG YADS\VQGRFTISRDNGKNSLYLQMNSLRAEDTALYYCARLAEWDVAYWGQGTMVTV SS	138
F4-L1	DIQLTQSPSTLSASIGDRVTITCRASQNINNNLHWYQQKPGKAPKLLIKFASQSISGAPSRFS GSGSGTDFTLTISSLQPDDFATYFCQQIYSWPQLTFGGGTKLEIK	139
F4-L2	DIQLTQSPSSLSASVGDRVTITCRASQNINNNLHWYQQKPGKAPKLLIKFASQSISGVPSRFS GSGSGTDFTLTISSLQPDDFATYFCQQIYSWPQLTFGGGTKLEIK	140
F4-L3	EIVLTQSPGTLSLSPGERATLSCRASQNINNNLHWYQQKPGQAPRLLIKFASTRATGIPARF SGSGSGTDFTLTISRLEPEDLAVYFCQQIYSWPQLTFGQGTKVEIK	141
F7-H1	QFQLVQSGAEVKKPGASVKVSCKASGYSFTDYNMHWVRQAPGQGLEWIGWIDPNYGTT NYAQKFQGRATLTVDQSISTAYMELSRLRSDDTAVYFCAIKGYGNPAAYWGQGTLVTVS S	142
F7-H2	EFQLVESGAEVKKPGSSVKVSCKASGYSFTDYNFTWVRQAPGQGLEWIGRIDPNYGTTHY APHLQGRATLTVDQSTSTAYLELRNLRSDDTAVYFCAIKGYGNPAAYWGQGTLVTVSS	143
F7-H3	QVQLVQSGAEVKKPGASVKVSCKASGYSFTDYNFTWVRQAPGQGLEWIGRIDPNYGTTH YAPHLQGRATLTVDQSTSTAYLELRSLRSDDTAVYFCAIKGYGNPAAYWGQGTLVTVSS	144
F7-L1	DIVMTQSPDSLAVSLGERATINCKASQDINKYLAWYQHKPGQPPKLLIRYTSTRESGVPDR FSGSGSGRDYTLTISSLQAEDVAVYYCLQYYNLWTFGGGTKVEIK	145
F7-L2	DIVMTQSPATLSVSPGERATLSCRASQDINKYLAWYQHKPGQAPRLLIRYTSTRATGVPAR FSGSGSGREYTLTISSLQSEDFAVYYCLQYYNLWTFGQGTRLEIK	146
F7-L3	DIVMTQSPATLSVSPGERATLSCRASQDINKYLAWYQHKPGQAPRLLIRYTSTRATGIPAR FSGSGSGTEFTLTISSLQSEDFAVYYCLQYYNLWTFGQGTRLEIK	147
F8-H1	LVNLVESGGGVVQPGRSLRLSCAASGFTLSTYAMHWVRQAPGKGLEWVAVISGGGGDT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVFYCARQSHYGSSYYFDNWGQGTL VTVSS	148
F8-H2	QVQLVESGGGVVQPGRSLRLSCAASGFTLSTYAMNWVRQAPAKGLEWVAIISGGGGDTY YADSVKGRFTISRDNSKNTLYLQMNGLRAEDTAVYYCARQSHYGSSYYFDNWGQGTL VTVSS	149
F8-H3	QVQLVESGGGVVQPGRSLRLSCAASGFTLSTYAMSWVRQAPAKGLEWVAIISGGGGDTY	150

	YADSVKGRFTISRDNSKNTLYLQMNGLRAEDTAVYYCARQSHYGSSYYFDNWGQGTL VTVSS	
F8-L1	EIQMTQSPATLSLSPGERATLSCRVSENIDSYLAWYQQKPGQAPRLLVYAATNRATGIPAR FSGSGSGSDYTLTISSLEPEDFAVYYCQHYYTTPPTFGQGTKVEIK	151
F8-L2	EIVMTQSPDFQSVTPKEKVTITCRVSENIDSYLAWYQQKPDQSPKLLVYAATQSFSGVPSR FSGSGSGSDYTLTINSLEAEDAAAYYCQHYYTTPPTFGPGTKVDIK	152
F8-L3	EIVLTQSPDFQSVTPKEKVTITCRVSENIDSYLAWYQQKPDQSPKLLVYAATQSFSGVPSR FSGSGSGTDFTLTINSLEAEDAAAYYCQHYYTTPPTFGPGTKVDIK	153
F19-H1	QVQLQESGPGLVRPSQTLSLTCTASGFTFSDYWMNWVRQPPGRGLEWVAFIGNKFHNY ETEYNPSVKGRFTILRDDSKNQVSLRLSSVTAADTAVYYCTKLGRGYYVMDYWGQGS LVTVSS	154
F19-H2	QVQLQESGPGLVKPSQTLSLTCTASGFTFSDYWMNWVRQPPGKGLEWVAFIGNKFHNY ETEYNPSVKGRFTILRDDSKNQVSLKLSSVTAADTAVYYCTKLGRGYYVMDYWGQGS LVTVSS	155
F19-H3	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYWMNWVRQAPGKGLEWVAIIGNKFHNY ETYYADSVKGRFTISRDDSKNTVYLQMNGLRAEDTAVYYCTKLGRGYYVMDYWGQGT LVTVSS	156
F19-L1	DIQMTQSPSSLSASVGDRVTITCKASQDITNHLNWFQQKPGKAFKLLIYYTSNLQTGVPSR FSGSGSGTDYTFTISSLQPEDIATYFCQQDSQHPWTFGQGTKVEIK	157
F19-L2	EIVMTQSPDFQSVTPKEKVTITCRASQDITNHLNWFQQKPDQSFKLLIYYTSQSFSGVPSR FSGSGSGTDYTLTINSLEAEDAAAYFCQQDSQHPWTFGPGTKVDIK	158
F8-H4	QVQLVQSGGGLVKPGGSLRLSCAASGFTLSTYAMSWVRQAPGKGLEWVAAISGGGGD TYYADSVKGRFTISRDNSKNTLYLQMSSLRAEDTAVYYCARQSHYGSSYYFDNWGQGT MVTVSS	171
F8-H5	QVQLVQSGGGLVKPGGSLRLSCAASGFTLSTYAMSWVRQAPGKGLEWVAAISGGGGD TYHLDSVKGRFTISRDNSKNTLYLQMSSLRAEDTAVYYCARQSHYGSSYYFDNWGQGT MVTVSS	172
F8-H6	EVQLVVSGGGLIQPGGSLRLSCAASGFTLSTYAMTWVRQAPGKGLEWVAVISGGGGD TYYADSVVGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQSHYGSSYYFDNWGQ GTLVTVSS	173
F19-H4	EVVLVESGGGLVQPGGSLRLSCAASGFTFSDYWISWVRQAPGKGLEWVAHIGNKFHN YETDYADSVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWG QGTLVTVSS	174
F19-H5	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYWISWVRQAPGKGLEWVAHIGNKFHN YETDYADSVKGRFTISKDDSKNTVYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWG QGTLVTVSS	175
F19-H6	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYWMHWVRQAPGKGLEWVAVIGNKFH NYETYYADSVKGRFTISRDDSKNTVYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWG QGTTVTVSS	176
F19-H7	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYWMNWVRQAPGKGLEWVAHIGNKFHN YETDYADSVKGRFTISKDDSKNTVYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWGQ GTLVTVSS	177
F19-H8	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYWMHWVRQAPGKGLEWVAVIGNKFHN YETYYTDSVKGRFTISRDDSKNTVYLQMNTLRAEDTAVYYCTKLGRGYYVMDYWGKG TTVTVSS	178
F19-H9	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDYWMHWVRQAPGKGLEWVAVIGNKFHN YETYYTDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWGKG TTVTVSS	179
F19-H10	QVVLVESGGGLVQPGGSLRLSCAASGFTFSDYWMHWVRQAPGKGLEWVASIGNKFHN YETYYADSVKGRFTISRDDSKNTVYLQMNSLFAEDTAVYYCTKLGRGYYVMDYWGQG TLVTVSS	180
F19-H11	QVQLVESGGGVVQPGGSLRLSCAASGFTFSDYWMHWVRQAPGKGLEWVAFIGNKFH NYETYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWG QGTLVTVSS	181
F19-H12	EVQLVESGGGLVQPGGSLRLSCVASGFTFSDYWMNWVRQAPGKGLEWVAQIGNKFH NYETYYSDSVKGRFTISKDDSKNTVYLQMNSLRAEDTAVYYCTKLGRGYYVMDYWG QGTLVTVSS	182
F5-H5	QVELVESGGGVVQPGRSLRLDCKVSGFTFSNYGMHWVRQAPGKGLEWVAVISSGGS YTYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCSTQGSSGYVGYWGQGT LVTVSS	183

F5-H6	QVQLVESGGGVVQPGRSLRLSCKVSGFTFSNYGMHWVRQAPGKGLEWVAVISSGGS YTYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCSTQGSSGYVGYWGQG TLVTVSS	184
F8-L4	DIQMTQSPSSLSASVGDRVTITCRVSENIDSYLAWYQQKPGKAPKLLVYAATSLQSGV PSRFSGSGSGSDYTLTISSLQPEDFAVYYCQHYYTTPPTFGDGTKVEIK	185
F8-L5	DIQMTQSPSSLSASVGDRVTITCRVSENIDSYLAWYQQKPGKAPKLLVYAATNLASG VPSRFSGSGSGSDYTLTISSLQPEDFAVYYCQHYYTTPPTFGDGTKVEIK	186
F8-L6	DIQMTQSPSTLSASVGDRVTITCRVSENIDSYLAWYQQKPGKAPKLLVYAATSLESG VPSRFSGSGSGSEYTLTISSLQPDDFATYYCQHYYTTPPTFGQGTKVDIK	187
F19-L3	DIQMTQSPSSLSASVGDRVTITCRASQDITNHLNWFQQKPGKAFKLLIYYTSSRASG VPSRFSGSGSGTDYTLTISSLQPEDFATYFCQQDSQHPWTFGQGTKVEIK	188
F19-L4	DIQMTQSPSSLSASVGDRVTITCRASQDITNHLNWFQQKPGKAFKLLIYYTSSLQSG VPSRFSGSGSGTDYTLTISSLQPEDFATYFCQQDSQHPWTFGPGTKVEIK	189
F19-L5	DIQMTQSPSSLSASVGDRVTITCRASQDITNHLNWFQQKPGKAFKLLIYYTSRLHSG VPSRFSGSGSGTDYTLTISSLQPEDFATYFCQQDSQHPWTFGGGTKVEIK	190
F19-L8	DIQMTQSPSSLSASVGDRVTITCRASQDITNHLNWFQQKPGKAFKLLIYYTSSLQSG VPSRFSGSGSGTDYTLTISSLQPEDFATYFCQQDSQHPWTFGGGTKVEIK	191
F19-L9	DIQMTQSPSSLSASVGDRVTITCRASQDITNHLNWYQQKPGKAPKLLIYYTSSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQDSQHPWTFGGGTKVEIK	192
F19-L10	EIVMTQSPATLSLSPGERATLSCRASQDITNHLNWFQQKPGQAFRLLIYYTSSRATG VPARFSGSGSGTDFTLTISSLEPEDFAVYFCQQDSQHPWTFGQGTKVEIK	193
F19-L11	EIVLTQSPATLSLSPGERATLSCRASQDITNHLAWYQQKPGQAPRLLIYYTSNRATG IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQDSQHPWTFGQGTKVEIK	194
F5-L3	AIQMTQSPSSLSASVGDRVTITCRASQDITNFLGWYQHKPGEAPKLLISYTSVLQSG VPSRFSGSGSGRDYTLTISSLQPEDFATYYCLQYYNLWTFGQGTKVEIK	195
F5-L4	EIVMTQSPDFQSVTPKEKVTITCRASQDITNFIGWYQHKPDQSPKLLISYTSQSFSGV PSRFSGSGSGRDYTLTINSLEAEDAAAYYCLQYYNLWTFGPGTKVDIK	196
F5-L5	EIVMTQSPATLSLSPGERATLSCRASQDITNFLGWYQHKPGQAPRLLISYTSNRATG IPARFSGSGSGRDYTLTISSLEPEDFAVYYCLQYYNLWTFGQGTKVEIK	197
F5-L6	EIVMTQSPATLSLSPGERATLSCRASQDITNFLGWYQQKPGQAPRLLISYTSIRATGI PARFSGSGSGTDYTLTISSLEPEDFAVYYCLQYYNLWTFGQGTKVEIK	198

[00199] The humanized VH and VL regions were fused to the constant regions of human IgG1 heavy chain and kappa light chain, respectively. The humanized mAbs were named as follows: F5-H1L1 refers to the mAb with the F5-H1 heavy chain variable region and the F5-L1 light chain variable region; all the other humanized mAbs adopt the same naming rule.

[00200] Example 3: Conversion of humanized mAbs to single chain variable fragments (scFvs)

[00201] The humanized mAbs were converted to scFvs, each of which consists of one VH and one VL with a $(G_4S)_n$ linker in between (where "n" represents the number of the G_4S repeats). Either the VH or the VL region was placed at the N-terminus of the fusion protein to identify the most effective scFv designs. The sequences of the designed scFvs are shown in Table 8. The scFvs were named as following: F5-H2$(G_4S)_3$L2 refers to the scFv with F5-H2 heavy chain variable region, the $(G_4S)_3$ linker and F5-L2 light chain variable region; all the other scFvs adopt the same naming rule.

Table 9: Sequences of humanized scFvs that specifically bind FOLR1

Name	SEQUENCE	SEQ ID NO:
F5-H2(G_4S)$_3$L2	EVQLVESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKGLEWVATISSG GSYTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSTQGSSGYVGY WGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCKASQD ITNFIGWYQHKPGKAPKLLISYTSILESGVPSRFSGSGSGTDYTLTISSLQPEDFAT YYCLQYYNLWTFGGGTKVEIK	159
F5-H2(G_4S)$_4$L2	EVQLVESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKGLEWVATISSG GSYTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCSTQGSSGYVGY WGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITC KASQDITNFIGWYQHKPGKAPKLLISYTSILESGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCLQYYNLWTFGGGTKVEIK	160
F5-L2(G_4S)$_3$H2	DIQMTQSPSSVSASVGDRVTITCKASQDITNFIGWYQHKPGKAPKLLISYTSILESG VPSRFSGSGSGTDYTLTISSLQPEDFATYYCLQYYNLWTFGGGTKVEIKGGGGSG GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAVSGFTFSNYGMSWVRQAPGKG LEWVATISSGGSYTYYPDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCST QGSSGYVGYWGQGTLVTVSS	161
F10-H1(G_4S)$_3$L2	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWMNWVRQAPGQGLEWIGRIYP GDGYTHYNGMFKGRASLTADKSTSTGYMELSSLRSEDTAVFFCTRHGDFPYWY FDVWGRGTLVTVSPGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCRA SENIDSYLAWYQQKPGRAPKLLVYAATNLAVGVPSRFSGSGSGTEYTLTISSLQP DDFATYYCQHHYSTPPTFGQGTKLEIK	162
F10-H1(G_4S)$_4$L2	EVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWMNWVRQAPGQGLEWIGRIYP GDGYTHYNGMFKGRASLTADKSTSTGYMELSSLRSEDTAVFFCTRHGDFPYWY FDVWGRGTLVTVSPGGGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRV TITCRASENIDSYLAWYQQKPGRAPKLLVYAATNLAVGVPSRFSGSGSGTEYTLT ISSLQPDDFATYYCQHHYSTPPTFGQGTKLEIK	163
F10-L2(G_4S)$_3$H1	DIQMTQSPSTLSASVGDRVTITCRASENIDSYLAWYQQKPGRAPKLLVYAATNL AVGVPSRFSGSGSGTEYTLTISSLQPDDFATYYCQHHYSTPPTFGQGTKLEIKGGG GSGGGGSGGGGSEVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWMNWVRQA PGQGLEWIGRIYPGDGYTHYNGMFKGRASLTADKSTSTGYMELSSLRSEDTAVF FCTRHGDFPYWYFDVWGRGTLVTVSP	164
F17-H1(G_4S)$_3$L2	EVQLVETGGGLIQPGGSLRLSCAASGFTFSDFGMHWIRQAPGKGLEWVAYMSYT PGTFHYADTVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHVGTVDYW GQGTLVTVSSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCRASQNIN NNLHWFQQKPGQAPRLLIKYASQSISGIPARFSGSGSGTDFTLTISSLETEDFAVYF CQQSNSWPALTFGQGTKVEIK	165
F17-H1(G_4S)$_4$L2	EVQLVETGGGLIQPGGSLRLSCAASGFTFSDFGMHWIRQAPGKGLEWVAYMSYT PGTFHYADTVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHVGTVDYW GQGTLVTVSSGGGGSGGGGSGGGGSGGGGSEVVLTQSPATLSLSPGERATLSCR ASQNINNNLHWFQQKPGQAPRLLIKYASQSISGIPARFSGSGSGTDFTLTISSLETE DFAVYFCQQSNSWPALTFGQGTKVEIK	166
F17-L2(G_4S)$_3$H1	EVVLTQSPATLSLSPGERATLSCRASQNINNNLHWFQQKPGQAPRLLIKYASQSIS GIPARFSGSGSGTDFTLTISSLETEDFAVYFCQQSNSWPALTFGQGTKVEIKGGGG SGGGGSGGGGSEVQLVETGGGLIQPGGSLRLSCAASGFTFSDFGMHWIRQAPGK GLEWVAYMSYTPGTFHYADTVKDRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARVHVGTVDYWGQGTLVTVSS	167
F20-H1(G_4S)$_3$L3	QVQLVQSGAEVKKPGSSVKVSCKASGYTFASYYLYWVRQAPGQGLEWIGEINP RSGGTNFNEKFKSRATVTVDKSTSTAYMELSSLRSEDTAVYYCSRSGRLRGFYT MDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTITCK AGENVGSYVSWYQQKPGKAPKLLIYGASNRYTGVPARFSGSGSATEFTLTISSLQ PDDFATYYCGQTYRFLTFGQGTKVEVK	168
F20-H1(G_4S)$_4$L3	QVQLVQSGAEVKKPGSSVKVSCKASGYTFASYYLYWVRQAPGQGLEWIGEINP RSGGTNFNEKFKSRATVTVDKSTSTAYMELSSLRSEDTAVYYCSRSGRLRGFYT MDYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSTLSASVGDRV TITCKAGENVGSYVSWYQQKPGKAPKLLIYGASNRYTGVPARFSGSGSATEFTLT ISSLQPDDFATYYCGQTYRFLTFGQGTKVEVK	169
F20-	DIQMTQSPSTLSASVGDRVTITCKAGENVGSYVSWYQQKPGKAPKLLIYGASNR	170

L3(G_4S)$_3$H1	YTGVPARFSGSGSATEFTLTISSLQPDDFATYYCGQTYRFLTFGQGTKVEVKGGG GSGGGGSGGGGSQVQLVQSGAEVKKPGSSVKVSCKASGYTFASYYLYWVRQAP GQGLEWIGEINPRSGGTNFNEKFKSRATVTVDKSTSTAYMELSSLRSEDTAVYYC SRSGRLRGFYTMDYWGQGTLVTVSS	

[00202] Example 4: ELISA binding analysis of humanized mAbs and scFvs

[00203] To test the binding of mAbs and scFvs to human FOLR1, mAbs and fusion proteins of scFvs fused to one G_4S linker and human IgG4 Fc (with the order of scFv, G_4S linker and Fc from the N-terminus to the C-terminus) were produced by transient expression in either ExpiCHO or Expi293 cells. The method for the ELISA binding analysis of the mAbs or humanized scFvs is described in PCT/US2019/021084, filed on March 7, 2019. The results of the ELISA assay are shown in FIGs. 1A-1L and FIGs. 3A-3G

[00204] Example 5: FACS analysis of mAbs and humanized scFvs

[00205] The mAbs and the scFv fusion proteins were also tested for their ability to bind SK-OV-3 cells that express endogenous FOLR1. The method for the FACS analysis of the mAbs or the humanized scFvs is described in PCT/US2019/021084, filed on March 7, 2019, with minor modifications. SK-OV-3 cells were plated at 100,000 cells per well. In each well of the plate, propidium iodide was incubated together with the secondary antibody to label dead cells. The binding results are shown in FIGs. 2A-2E and FIGs. 4A-4G

[00206] Example 6: Construction of chimeric antigen receptor constructs comprising anti-FOLR1 monoclonal antibodies or antigen-binding fragments thereof

[00207] To construct a CAR, each mAb is converted into a scFv, using the VH, VL and a (G_4S)n linker, and the scFv is fused to the N-terminus of the hinge and transmembrane domains derived from human CD8α (aa 114-188, Boursier JP et al., J Biol Chem. 1993; 268(3):2013-20). The C-terminal intracellular signaling domain of the CAR is constructed by fusing the intracellular costimulatory domain of CD28 (aa 162-202, Aruffo A and Seed B, Proc Natl Acad Sci USA. 1987;84(23):8573-7) followed by the activation domain from CD3 zeta chain (aa 52-162, Letourneur F and Klausner RD, Proc Natl Acad Sci USA. 1991;88(20):8905-9). The DNA sequence encoding the CAR is assembled and cloned into a retroviral vector to generate the CAR construct using standard molecular biology cloning techniques.

[00208] 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 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 folate receptor 1 (FOLR1);

(b) a hinge region;

(c) a transmembrane region; and

(d) an intracellular signaling domain.

2. The isolated polynucleotide of claim 1, 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: 17, 18, 19, 41, 42 and 43, respectively;

(2) SEQ ID NOs: 20, 21, 22, 44, 45 and 46, respectively;

(3) SEQ ID NOs: 23, 24, 25, 47, 48 and 49, respectively;

(4) SEQ ID NOs: 26, 27, 28, 50, 51 and 52, respectively;

(5) SEQ ID NOs: 29, 30, 31, 53, 54 and 55, respectively;

(6) SEQ ID NOs: 32, 33, 34, 56, 57 and 58, respectively;

(7) SEQ ID NOs: 35, 36, 37, 59, 60 and 61, respectively; or

(8) SEQ ID NOs: 38, 39, 40, 62, 63 and 64, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

3. The isolated polynucleotide of claim 1, 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: 65, 66, 67, 89, 90 and 91, respectively;

(2) SEQ ID NOs: 68, 69, 70, 92, 93 and 94, respectively;

(3) SEQ ID NOs: 71, 72, 73, 95, 96 and 97, respectively;

(4) SEQ ID NOs: 74, 75, 76, 98, 99 and 100, respectively;

(5) SEQ ID NOs: 77, 78, 79, 101, 102 and 103, respectively;

(6) SEQ ID NOs: 80, 81, 82, 104, 105 and 106, respectively;

(7) SEQ ID NOs: 83, 84, 85, 107, 108 and 109, respectively; or

(8) SEQ ID NOs: 86, 87, 88, 110, 111 and 112, respectively;

wherein the antigen binding domain specifically binds FOLR1, preferably human FOLR1.

4. The isolated polynucleotide of any one of claims 1-3, wherein the antigen binding domain comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16.

5. The isolated polynucleotide of any one of claims 1-4, wherein the antigen binding domain comprises:

(1) 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;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:3, and a light chain variable region having the polypeptide sequence of SEQ ID NO:4;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:5, and a light chain variable region having the polypeptide sequence of SEQ ID NO:6;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:7, and a light chain variable region having the polypeptide sequence of SEQ ID NO:8;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:9, and a light chain variable region having the polypeptide sequence of SEQ ID NO:10;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:11, and a light chain variable region having the polypeptide sequence of SEQ ID NO:12;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:13, and a light chain variable region having the polypeptide sequence of SEQ ID NO:14; or

(8) 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.

6. The isolated polynucleotide of any one of claims 1-4, 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: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

7. The isolated polynucleotide of claim 6, wherein the antigen binding domain is humanized and comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

8. The isolated polynucleotide of any one of claims 1-7, wherein the antigen binding domain is a single chain variable fragment (scFv) that specifically binds FOLR1, preferably human FOLR1.

9. The isolated polynucleotide of claim 8, wherein the single chain variable fragment (scFv) is humanized.

10. The isolated polynucleotide of claim 8 or 9, wherein the single chain variable fragment (scFv) comprises a polypeptide sequence at least 95% identical to any one of SEQ ID NOs: 159-170.

11. The isolated polynucleotide of any one of claims 1-10, wherein the chimeric antigen receptor (CAR) comprises one or more antigen binding domains.

12. The isolated polynucleotide of any one of claims 1-11, wherein the intracellular signaling domain comprises one or more costimulatory domains and one or more activating domains.

13. A chimeric antigen receptor (CAR) encoded by the isolated polynucleotide of any one of claims 1-12.

14. A vector comprising the isolated polynucleotide of any one of claims 1-12.

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

16. The host cell of claim 15, wherein the host cell is a T cell, preferably a human T cell.

17. The host cell of claim 15, wherein the host cell is a NK cell, preferably a human NK cell.

18. 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 14.

19. 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 1-12 under conditions to produce the CAR-T cell and recovering the CAR-T cell.

20. 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 14.

21. 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 1-12 under conditions to produce the CAR-NK cell and recovering the CAR-NK cell.

22. 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 1-12, wherein the isolated polynucleotide is an *in vitro* transcribed RNA or synthetic RNA.

23. 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 15-17.

24. The method of claim 23, 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.

25. The method of claim 23 or 24, further comprising administering to the subject in need thereof an agent that increases the efficacy of a cell expressing a CAR.

26. The method of claim 23 or 24, 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.

27. The method of claim 23 or 24, further comprising administering to the subject in need thereof an agent that treats the disease associated with FOLR1.

28. A humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region having a polypeptide sequence at least 95% identical to any one of SEQ ID NO: 113, 114, 115, 116, 119, 120, 124, 125, 128, 129, 130, 136, 137, 138, 142, 143, 144, 148, 149, 150, 154, 155, 156 or 171-184, or a light chain variable region having a polypeptide sequence at least 95% identical to SEQ ID NO: 117, 118, 121, 122, 123, 126, 127, 131, 132, 133, 134, 139, 140, 141, 145, 146, 147, 151, 152, 153, 157, 158 or 185-198.

29. The humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of claim 28, wherein the antibody or antigen-binding fragment thereof comprises:

(1) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(2) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:113, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(3) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(4) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:114, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(5) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(6) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:115, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(7) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:117;

(8) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:116, and a light chain variable region having the polypeptide sequence of SEQ ID NO:118;

(9) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:121;

(10) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:122;

(11) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:119, and a light chain variable region having the polypeptide sequence of SEQ ID NO:123;

(12) 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:121;

(13) 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:122;

(14) 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:123;

(15) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:126;

(16) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:124, and a light chain variable region having the polypeptide sequence of SEQ ID NO:127;

(17) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(18) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(19) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(20) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:128, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(21) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(22) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(23) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(24) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:129, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(25) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:131;

(26) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:132;

(27) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:133;

(28) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:130, and a light chain variable region having the polypeptide sequence of SEQ ID NO:134;

(29) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(30) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(31) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:136, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(32) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(33) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(34) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:137, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(35) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:139;

(36) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:140;

(37) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:138, and a light chain variable region having the polypeptide sequence of SEQ ID NO:141;

(38) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:145;

(39) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:146;

(40) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:142, and a light chain variable region having the polypeptide sequence of SEQ ID NO:147;

(41) 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:145;

(42) 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:146;

(43) 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:147;

(44) 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:145;

(45) 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:146;

(46) 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:147;

(47) 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;

(48) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:150, and a light chain variable region having the polypeptide sequence of SEQ ID NO:153;

(49) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(50) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(51) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:171, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(52) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:185;

(53) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:186;

(54) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:173, and a light chain variable region having the polypeptide sequence of SEQ ID NO:187;

(55) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:182, and a light chain variable region having the polypeptide sequence of SEQ ID NO:190;

(56) 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:195;

(57) 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:196;

(58) 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:197;

(59) 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;

(60) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:195;

(61) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:196;

(62) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:197; or

(63) a heavy chain variable region having the polypeptide sequence of SEQ ID NO:184, and a light chain variable region having the polypeptide sequence of SEQ ID NO:198.

30. The humanized anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of claim 28 or 29, wherein the monoclonal antibody or antigen-binding fragment thereof is capable of binding FOLR1, inducing effector-mediated tumor cell lysis, mediating the recruitment of conjugated drugs, and/or forming a bispecific antibody with another monoclonal antibody or antigen-binding fragment with a cancer-killing effect.

31. An isolated nucleic acid encoding the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of claims 28-30.

32. A vector comprising the isolated nucleic acid of claim 31.

33. A host cell comprising the vector of claim 32.

34. A pharmaceutical composition, comprising the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of claims 28-30 and a pharmaceutically acceptable carrier.

35. A method of targeting FOLR1 on a cancer cell surface in a subject in need thereof, comprising administering to the subject in need thereof a pharmaceutical composition comprising the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of claims 28-30.

36. A method of treating cancer in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 34.

37. The method of claim 36, 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.

38. A method of producing the anti-FOLR1 monoclonal antibody or antigen-binding fragment thereof of any one of claims 28-30, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment under conditions to produce

the monoclonal antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or culture.

39. A method of producing the pharmaceutical composition of claim 34, comprising combining the monoclonal antibody or antigen-binding fragment thereof with a pharmaceutically acceptable carrier to obtain the pharmaceutical composition.

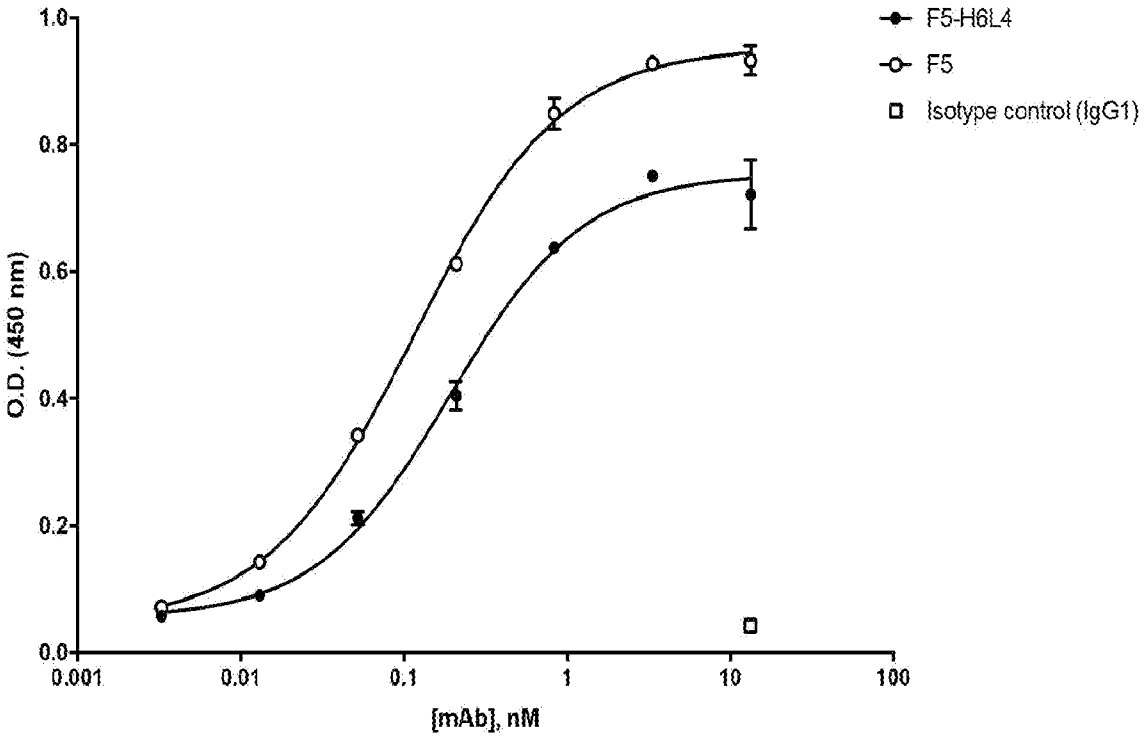

F5-H6L4
F5
Isotype control (IgG1)
O.D. (450 nm)
1.0
0.8
0.6
0.4
0.2
0.0
0.001
0.01
0.1
1
10
100
[mAb], nM

FIG. 1A

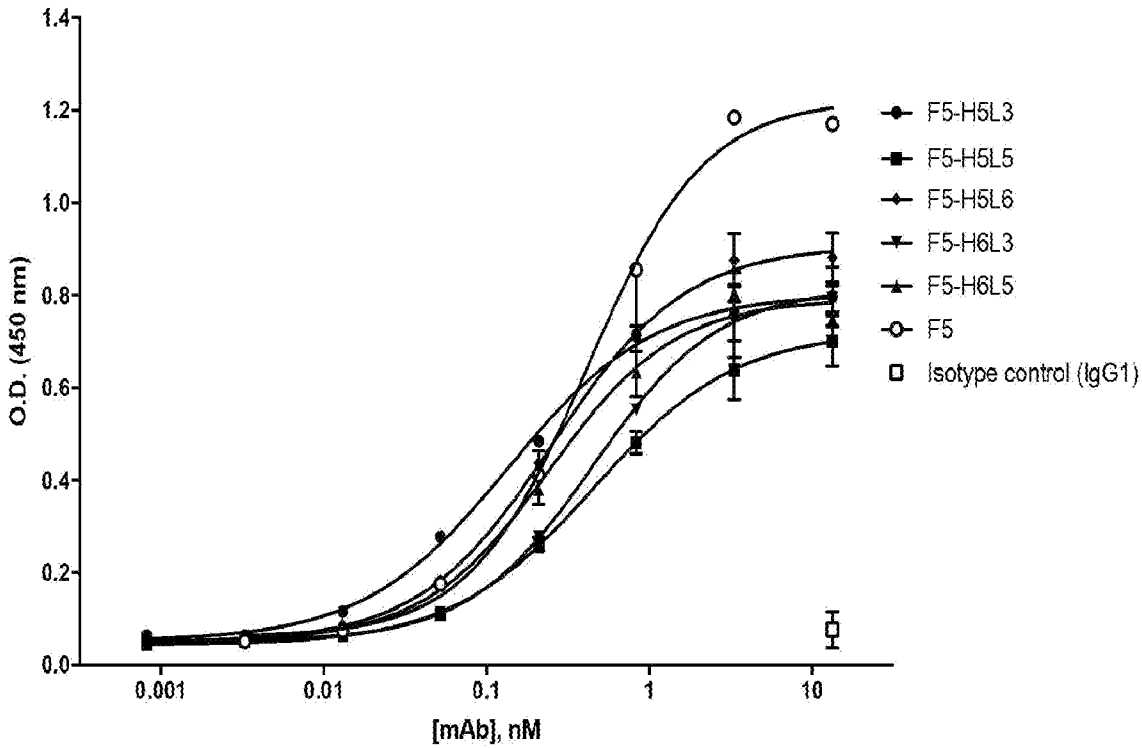

F5-H5L3
F5-H5L5
F5-H5L6
F5-H6L3
F5-H6L5
F5
Isotype control (IgG1)
O.D. (450 nm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.001
0.01
0.1
1
10
[mAb], nM

FIG. 1B

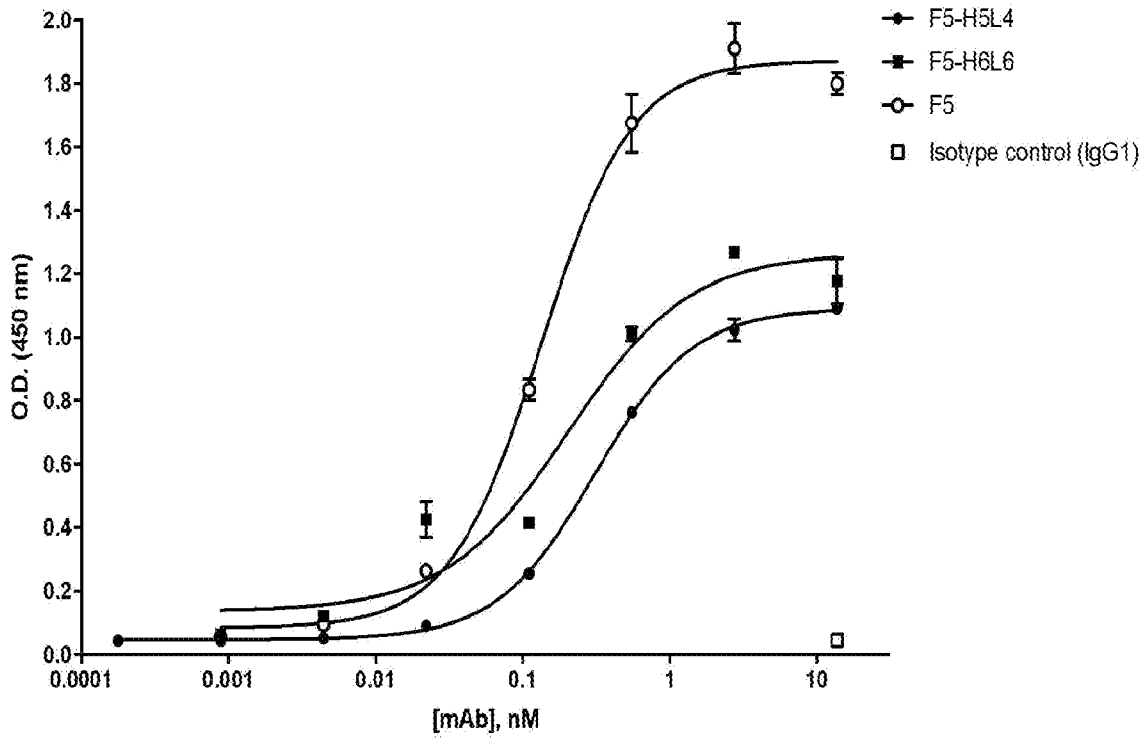

F5-H5L4
F5-H6L6
F5
Isotype control (IgG1)
O.D. (450 nm)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
[mAb], nM

FIG. 1C

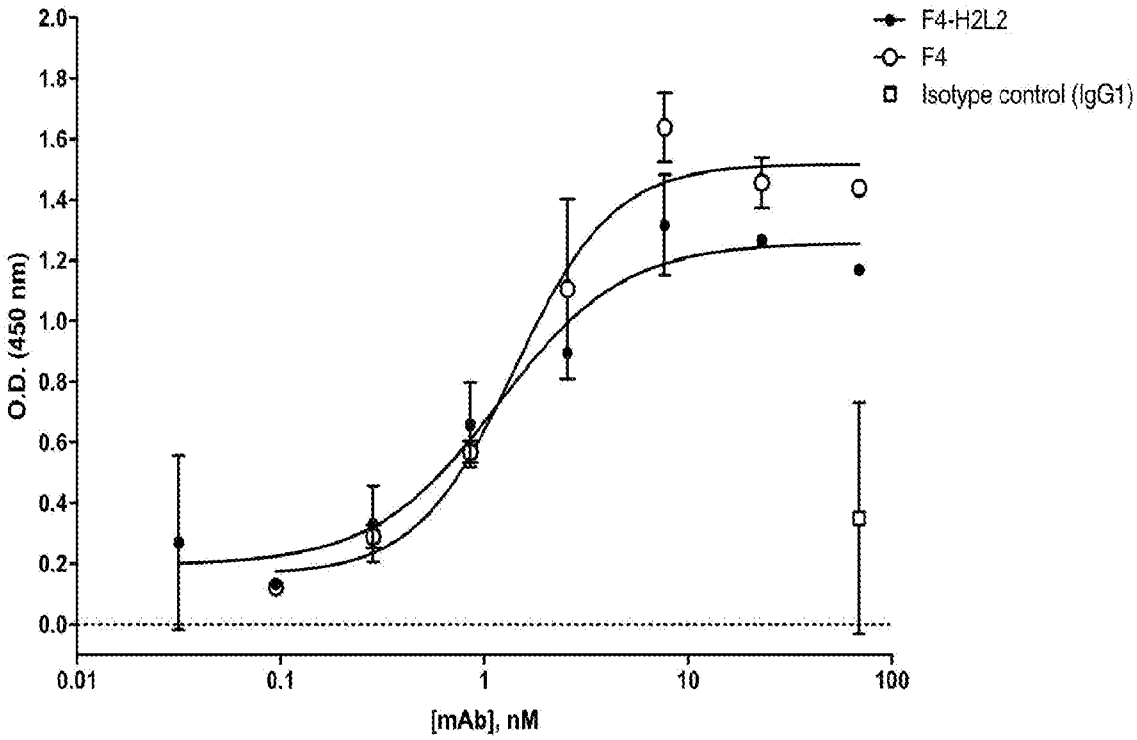

F4-H2L2
F4
Isotype control (IgG1)
O.D. (450 nm)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.01
0.1
1
10
100
[mAb], nM

FIG. 1D

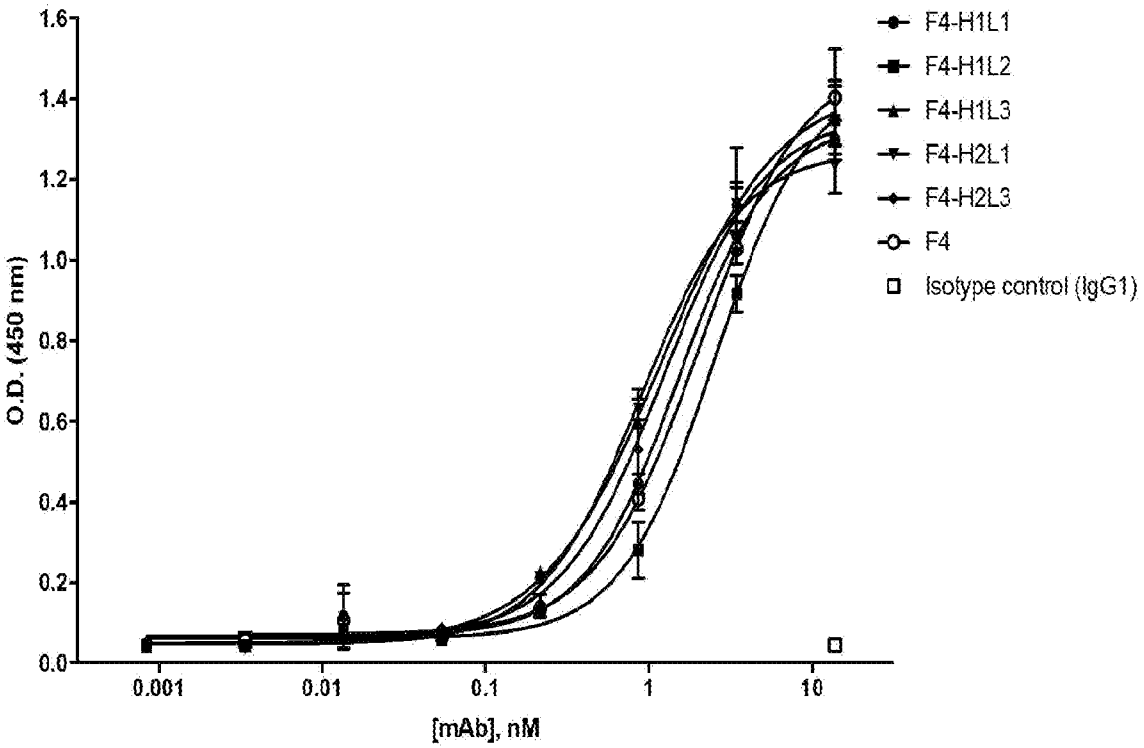

F4-H1L1
F4-H1L2
F4-H1L3
F4-H2L1
F4-H2L3
F4
Isotype control (IgG1)
O.D. (450 nm)
[mAb], nM
0.001
0.01
0.1
1
10
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6

FIG. 1E

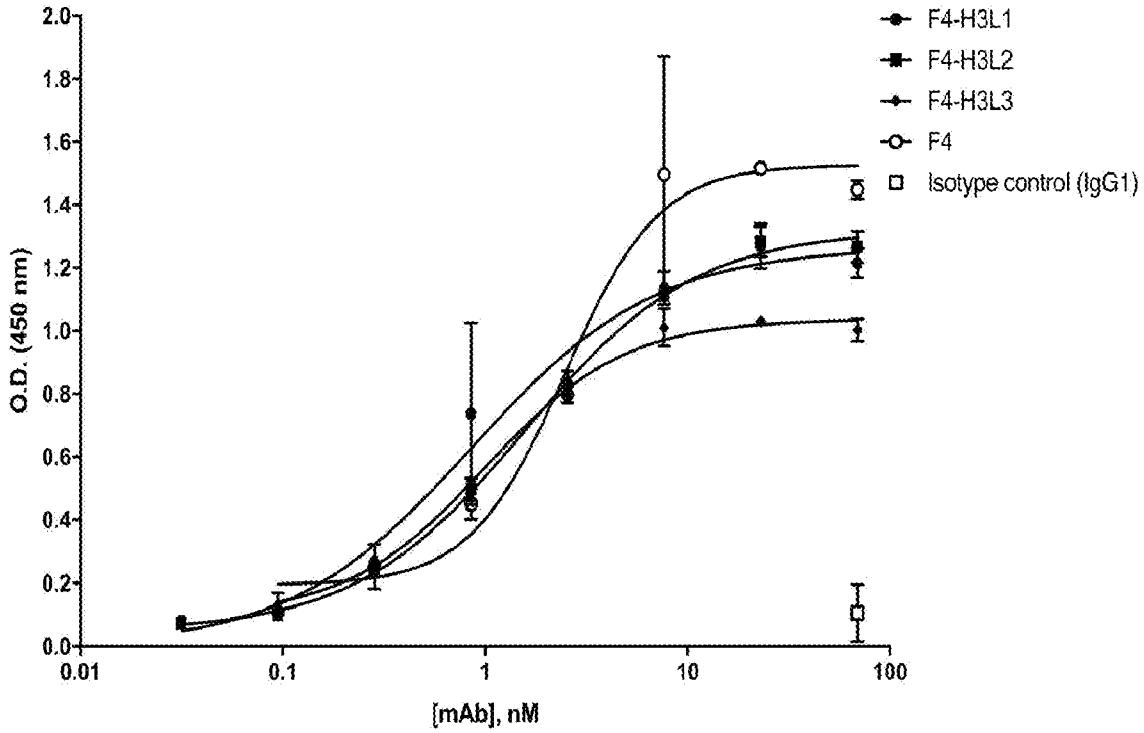

F4-H3L1
F4-H3L2
F4-H3L3
F4
Isotype control (IgG1)
O.D. (450 nm)
[mAb], nM
0.01
0.1
1
10
100
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0

FIG. 1F

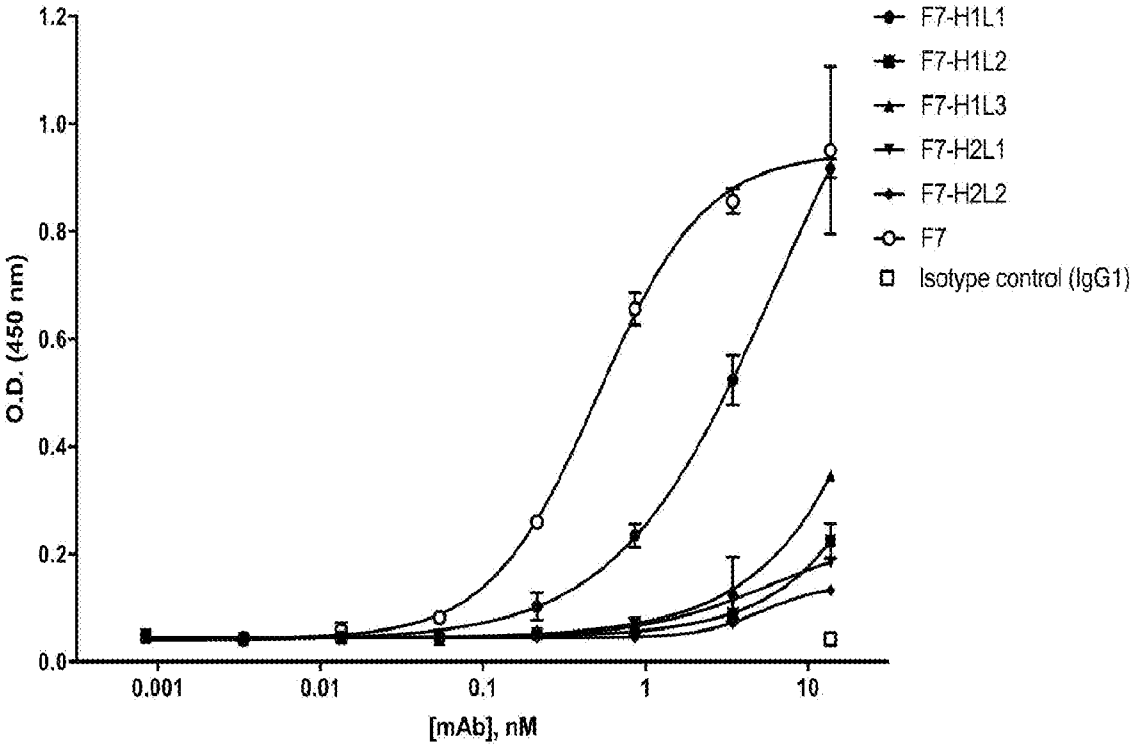

F7-H1L1
F7-H1L2
F7-H1L3
F7-H2L1
F7-H2L2
F7
Isotype control (IgG1)
O.D. (450 nm)
[mAb], nM
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.001
0.01
0.1
1
10

FIG. 1G

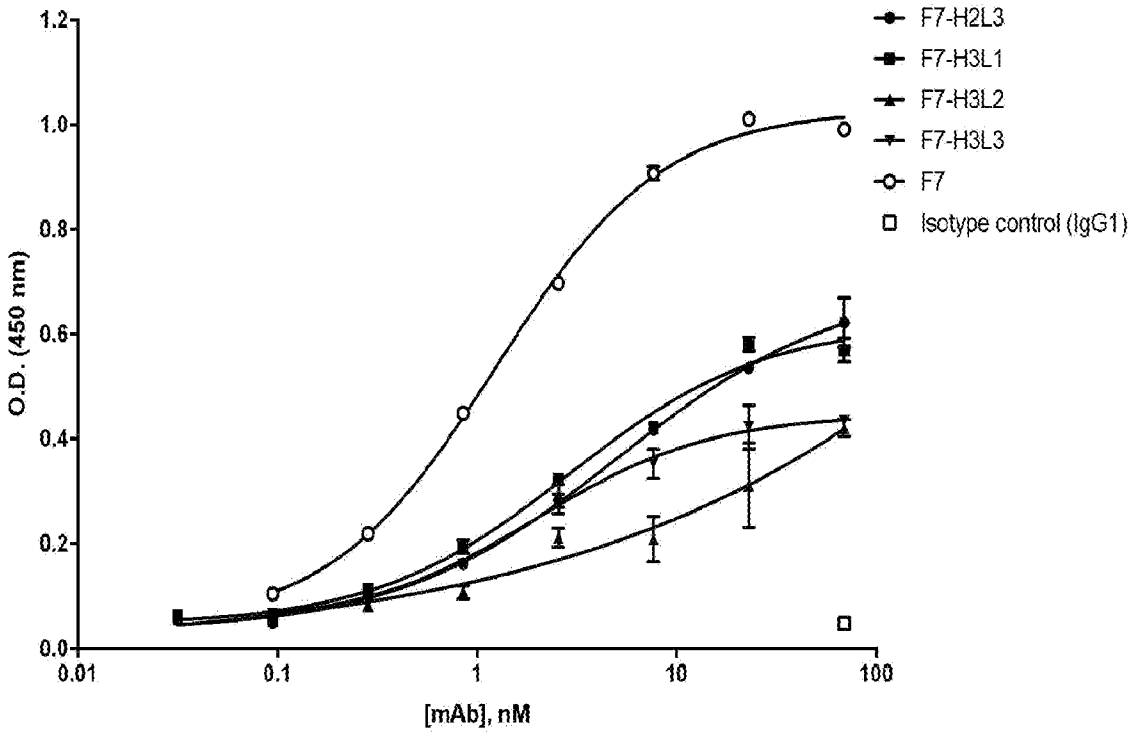

F7-H2L3
F7-H3L1
F7-H3L2
F7-H3L3
F7
Isotype control (IgG1)
O.D. (450 nm)
[mAb], nM
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.01
0.1
1
10
100

FIG. 1H

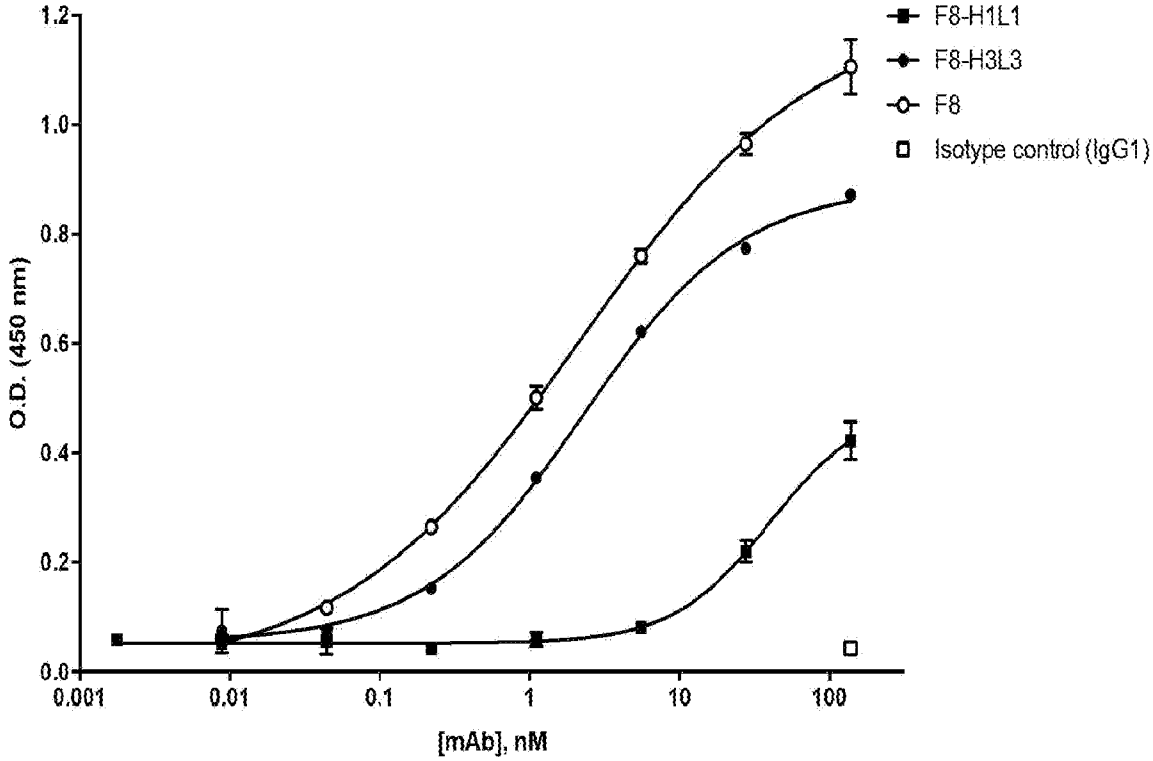

F8-H1L1
F8-H3L3
F8
Isotype control (IgG1)
O.D. (450 nm)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.001
0.01
0.1
1
10
100
[mAb], nM

FIG. 1I

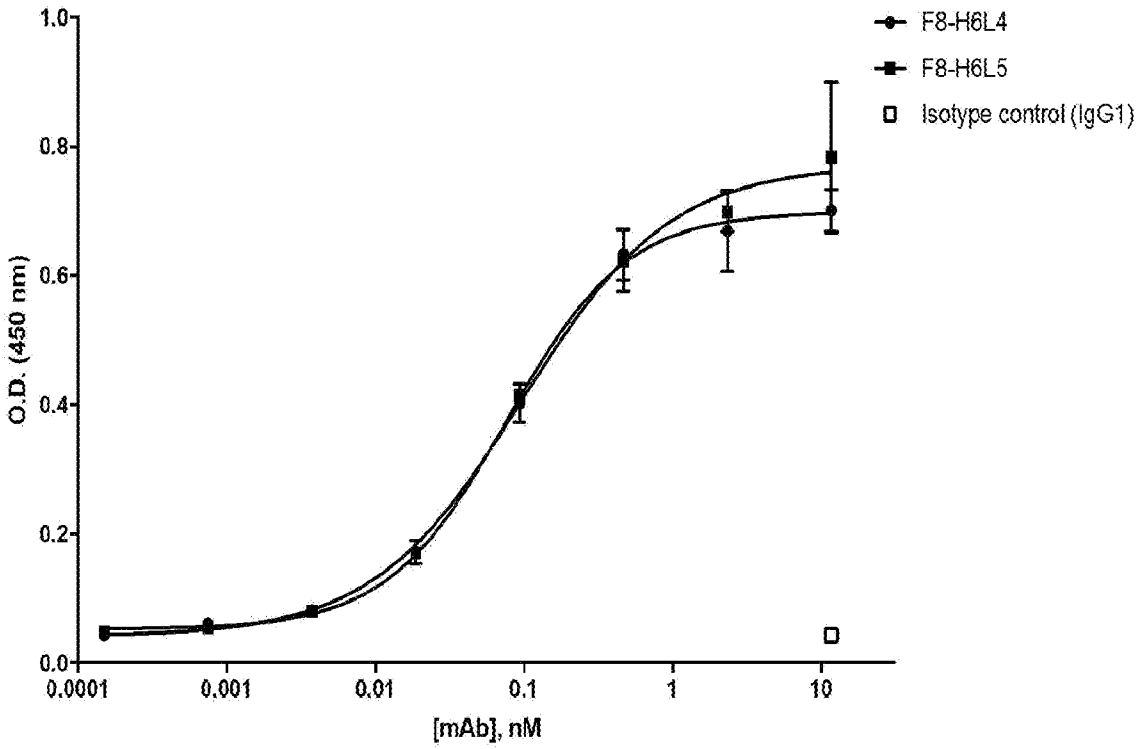

F8-H6L4
F8-H6L5
Isotype control (IgG1)
O.D. (450 nm)
1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
[mAb], nM

FIG. 1J

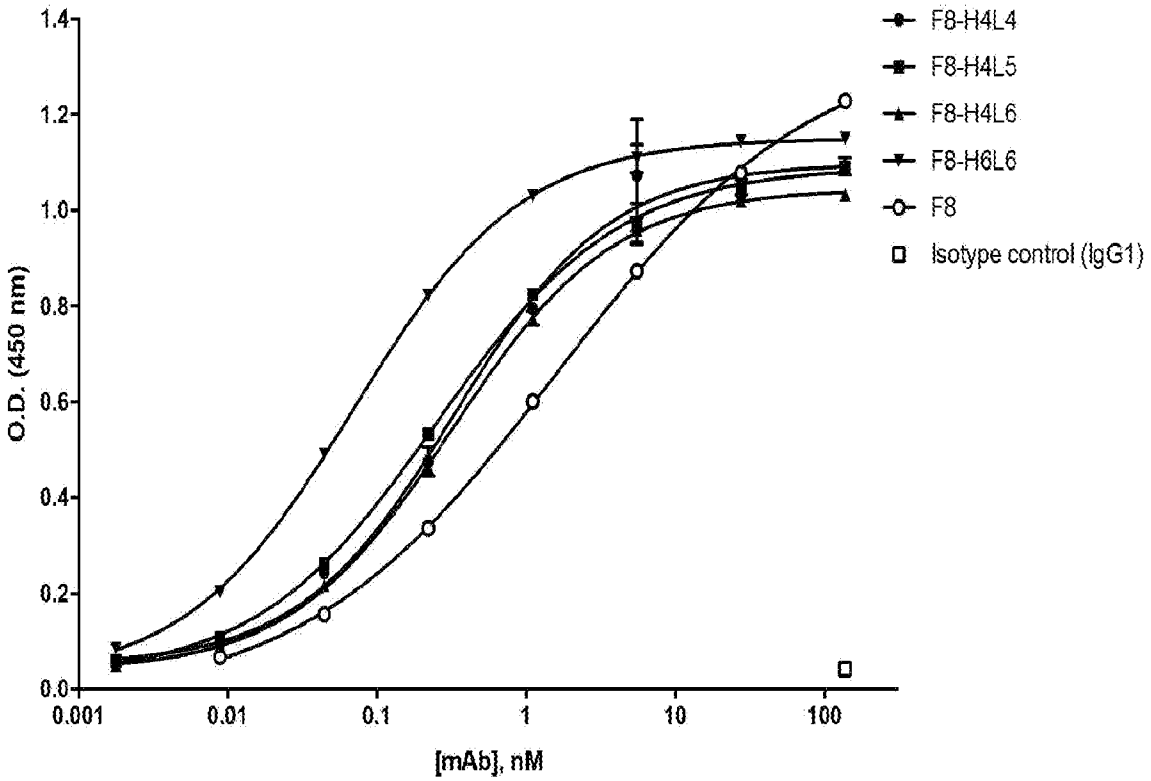

F8-H4L4
F8-H4L5
F8-H4L6
F8-H6L6
F8
Isotype control (IgG1)
O.D. (450 nm)
[mAb], nM
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0.001
0.01
0.1
1
10
100

FIG. 1K

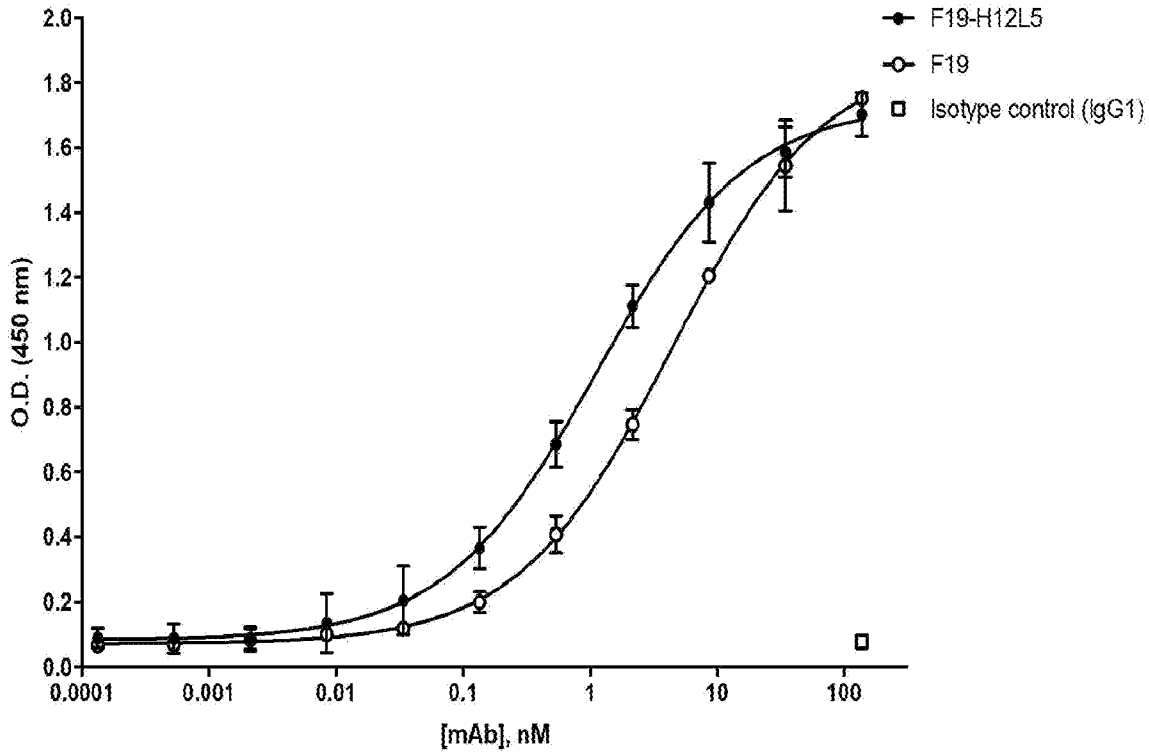

F19-H12L5
F19
Isotype control (IgG1)
O.D. (450 nm)
[mAb], nM
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0.0001
0.001
0.01
0.1
1
10
100

FIG. 1L

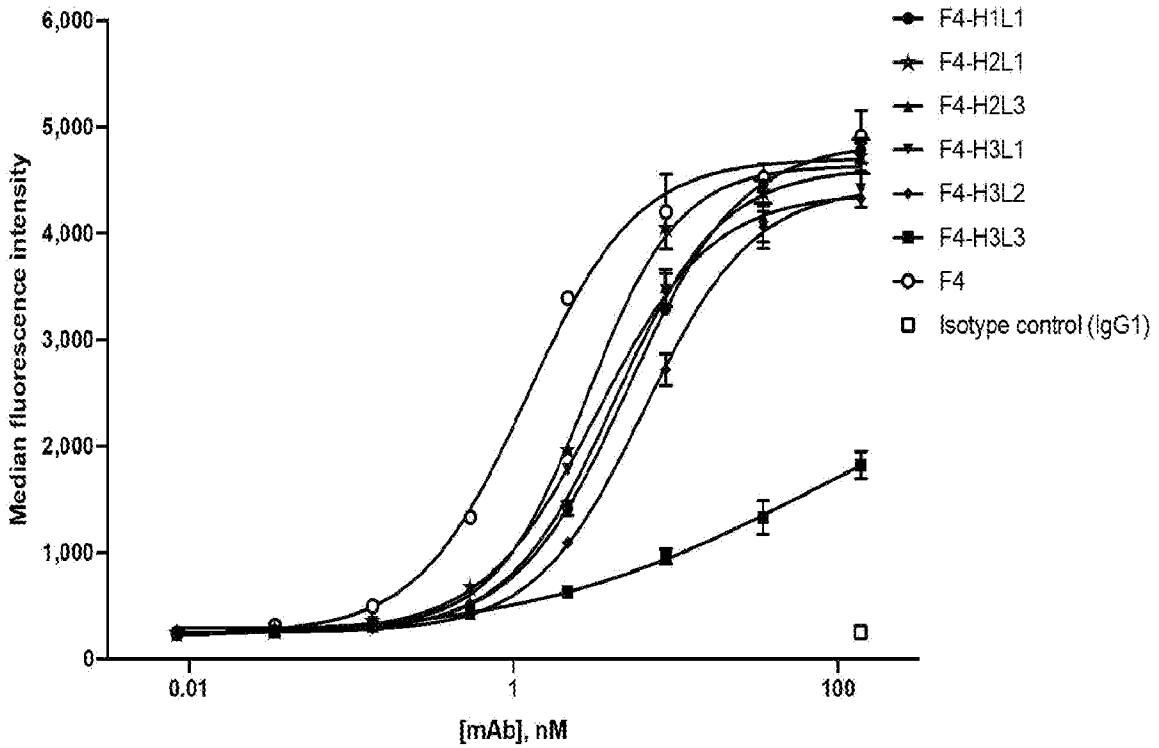

6,000
5,000
4,000
3,000
2,000
1,000
0
Median fluorescence intensity
0.01
1
100
[mAb], nM
F4-H1L1
F4-H2L1
F4-H2L3
F4-H3L1
F4-H3L2
F4-H3L3
F4
Isotype control (IgG1)

FIG.2A

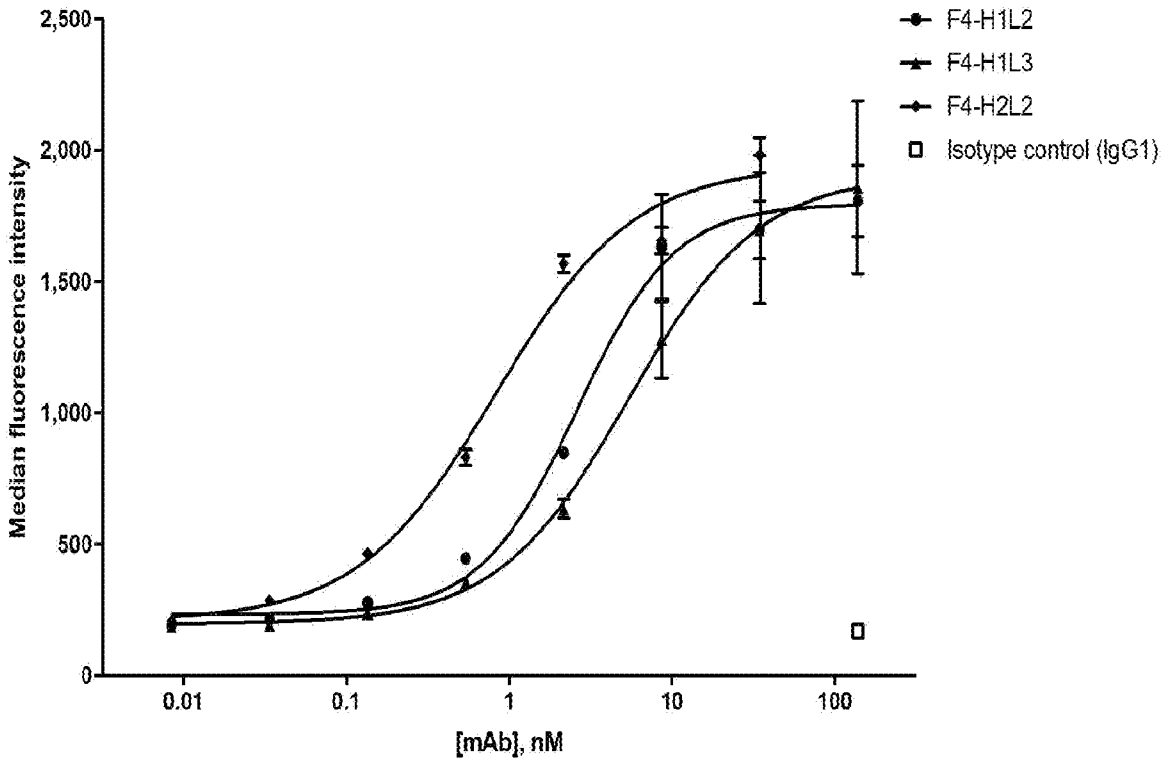

2,500
2,000
1,500
1,000
500
0
Median fluorescence intensity
0.01
0.1
1
10
100
[mAb], nM
F4-H1L2
F4-H1L3
F4-H2L2
Isotype control (IgG1)

FIG. 2B

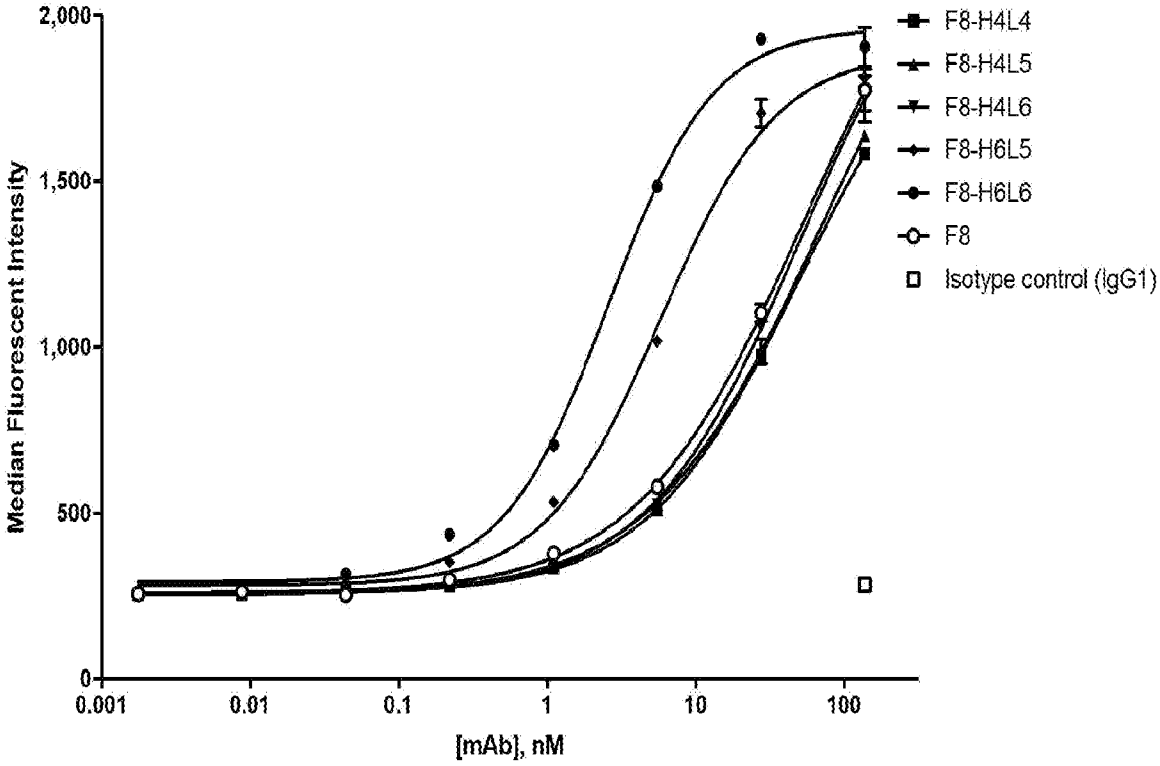

Median Fluorescent Intensity
2,000
1,500
1,000
500
0
0.001
0.01
0.1
1
10
100
[mAb], nM
F8-H4L4
F8-H4L5
F8-H4L6
F8-H6L5
F8-H6L6
F8
Isotype control (IgG1)

FIG. 2C

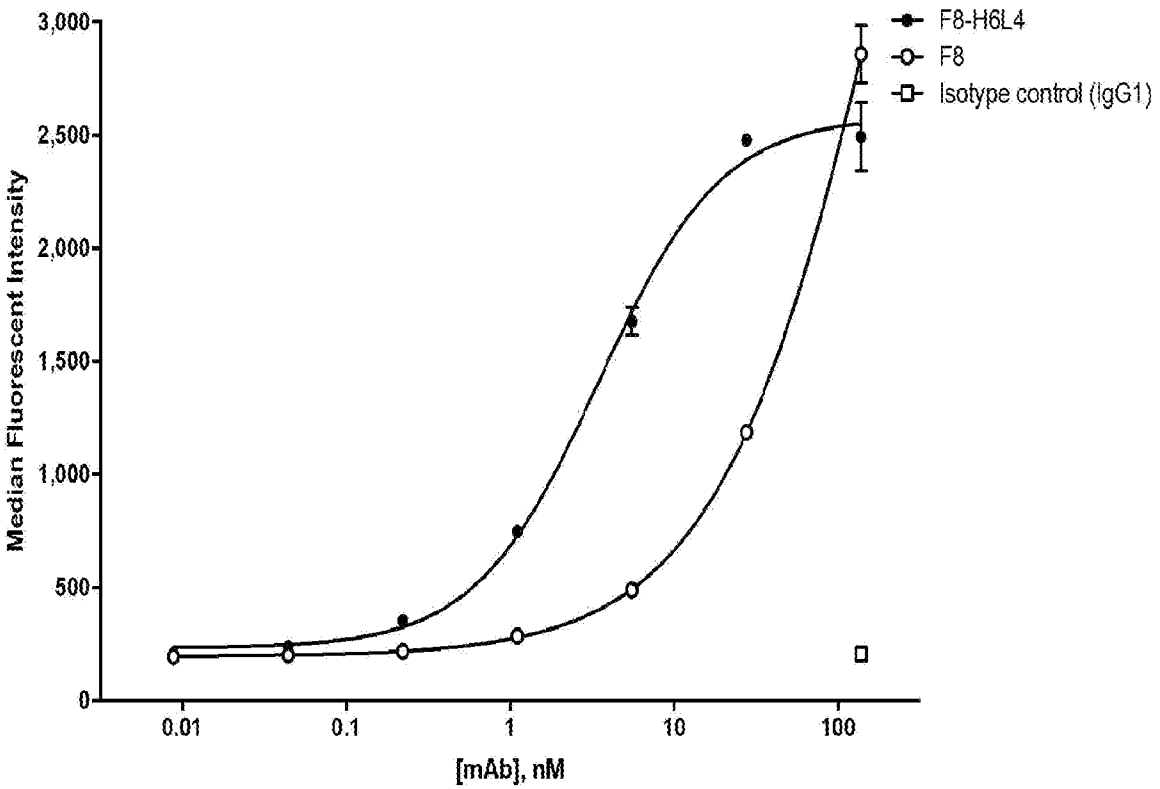

Median Fluorescent Intensity
3,000
2,500
2,000
1,500
1,000
500
0
0.01
0.1
1
10
100
[mAb], nM
F8-H6L4
F8
Isotype control (IgG1)

FIG. 2D

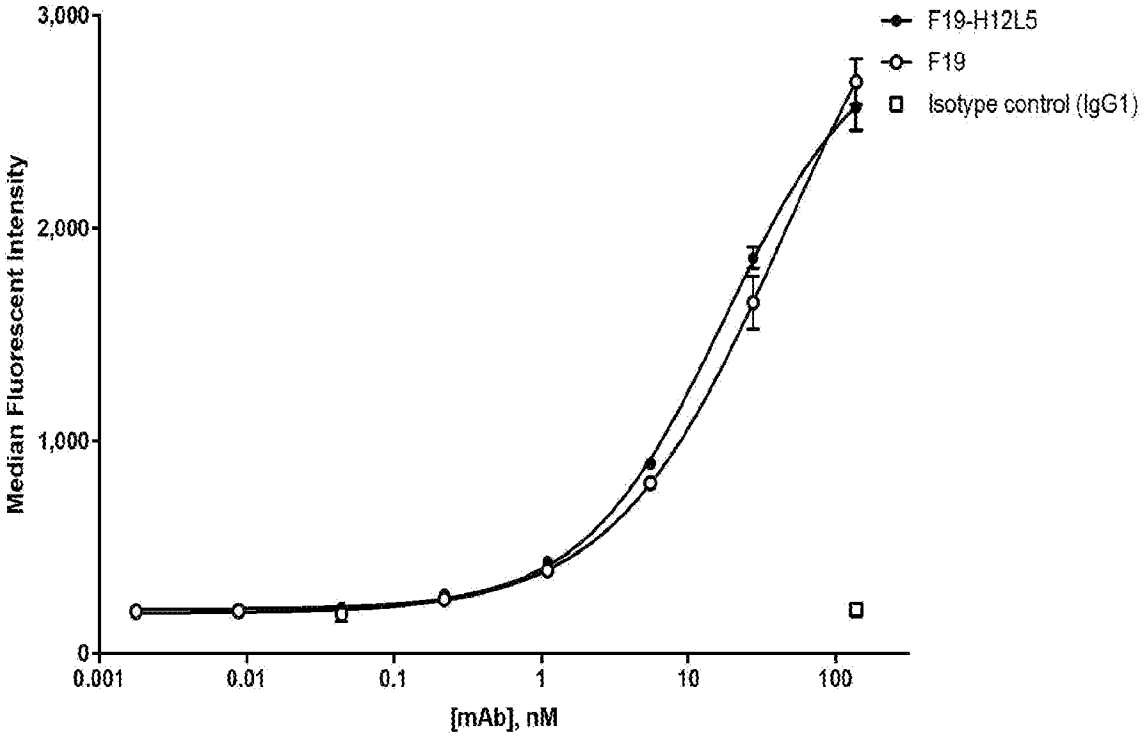

3,000
2,000
1,000
0
Median Fluorescent Intensity
0.001
0.01
0.1
1
10
100
[mAb], nM
F19-H12L5
F19
Isotype control (IgG1)

FIG. 2E

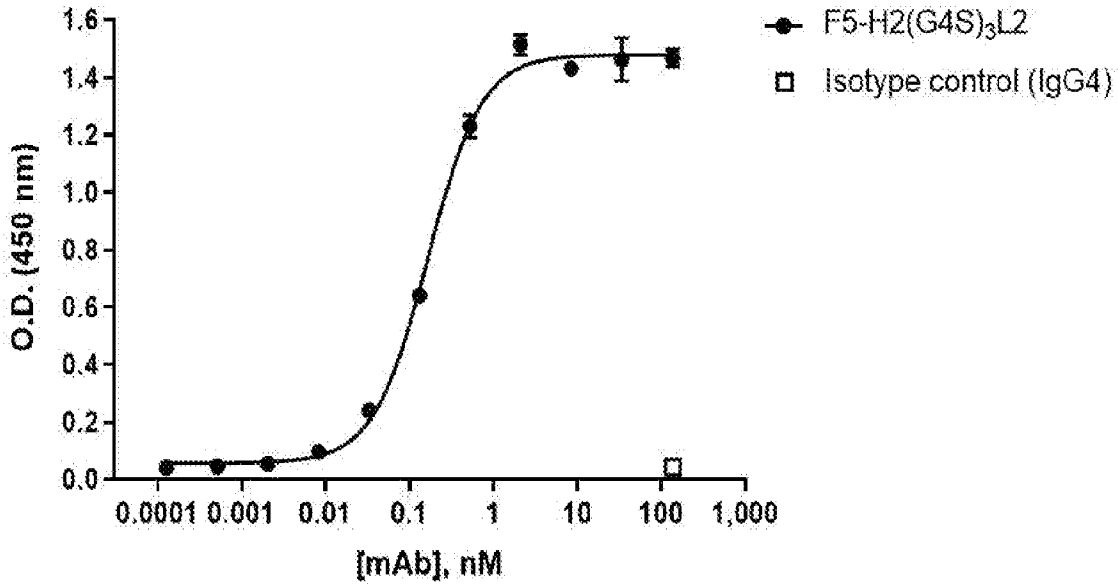

1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
O.D. (450 nm)
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F5-H2(G4S)3L2
Isotype control (IgG4)

FIG. 3A

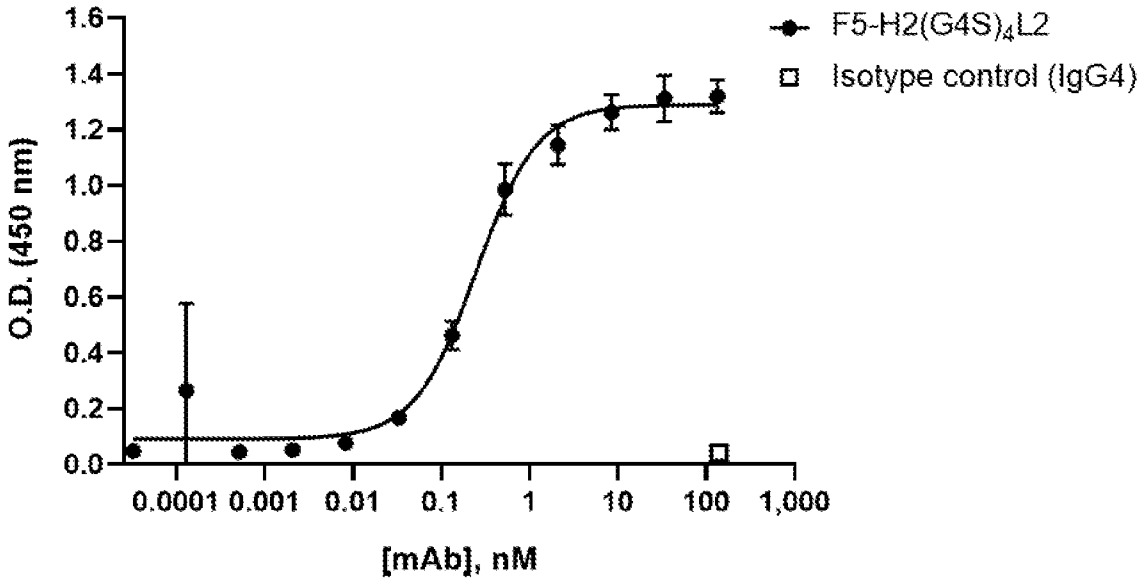

F5-H2(G4S)4L2
Isotype control (IgG4)
O.D. (450 nm)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM

FIG. 3B

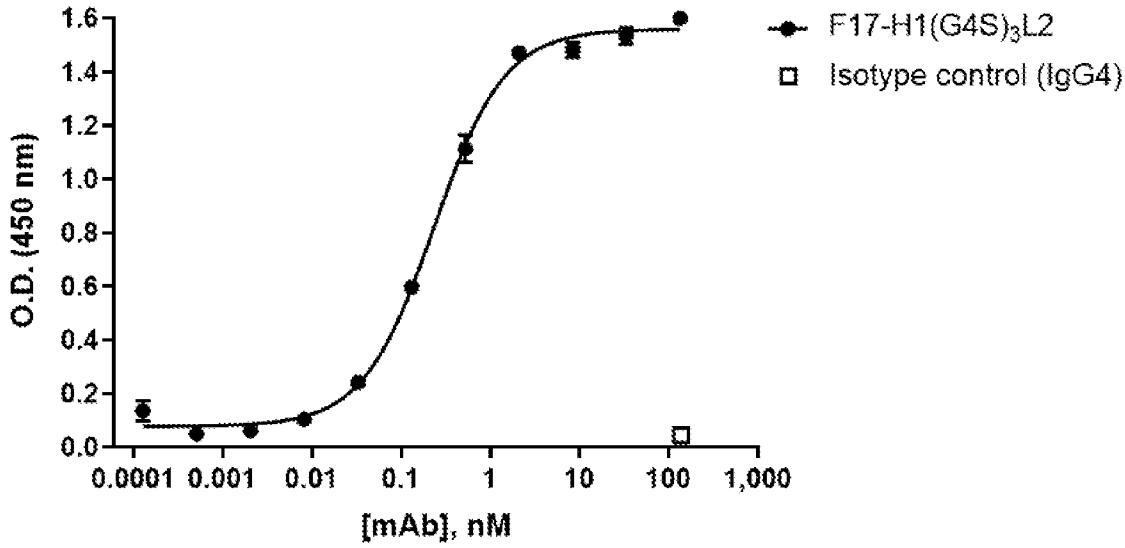

F17-H1(G4S)3L2
Isotype control (IgG4)
O.D. (450 nm)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM

FIG. 3C

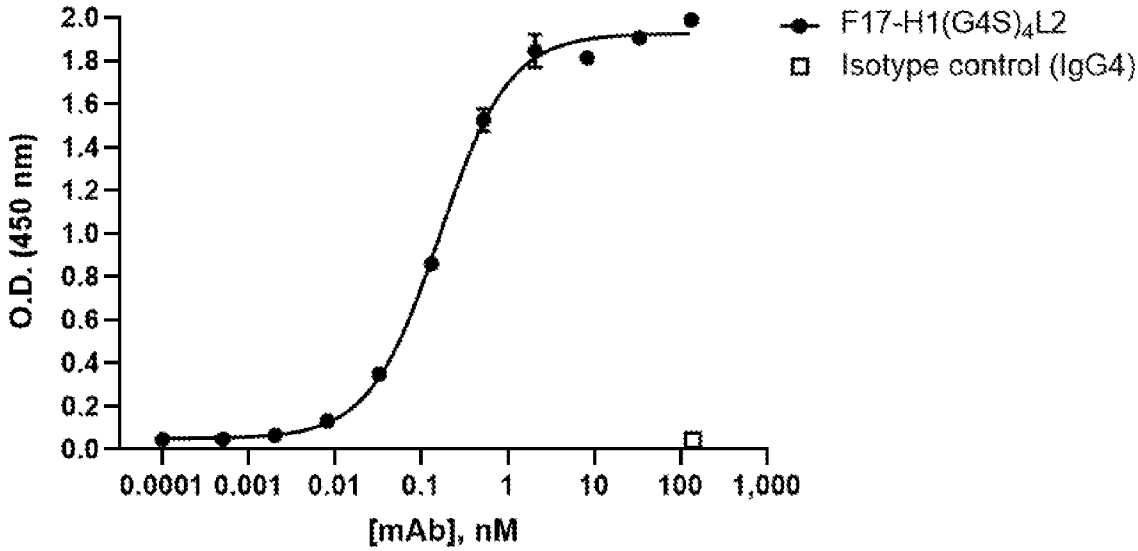

F17-H1(G4S)4L2
Isotype control (IgG4)
O.D. (450 nm)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM

FIG. 3D

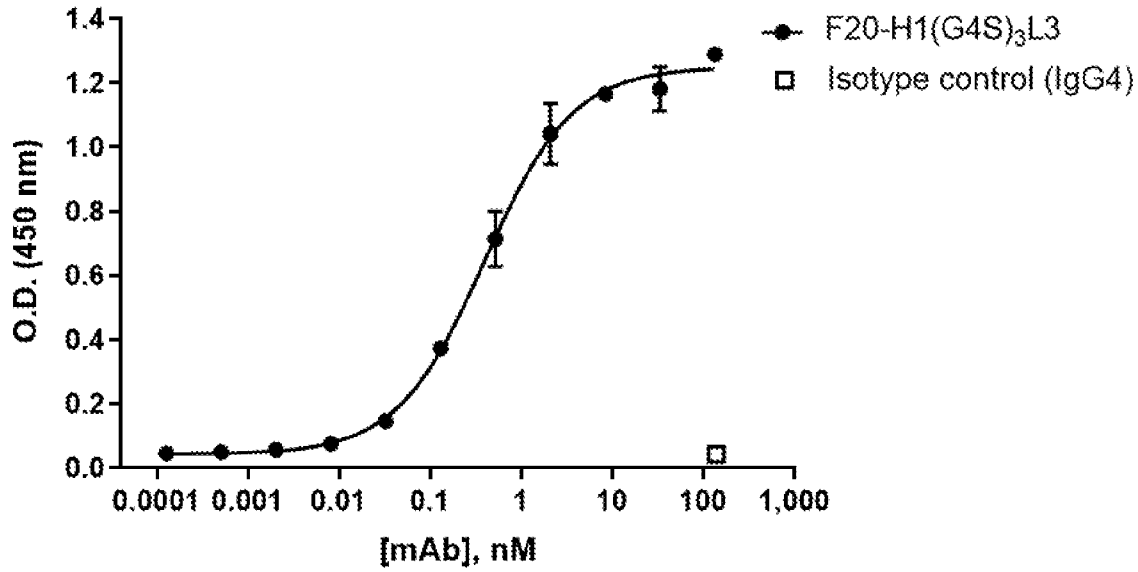

F20-H1(G4S)3L3
Isotype control (IgG4)
O.D. (450 nm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM

FIG. 3E

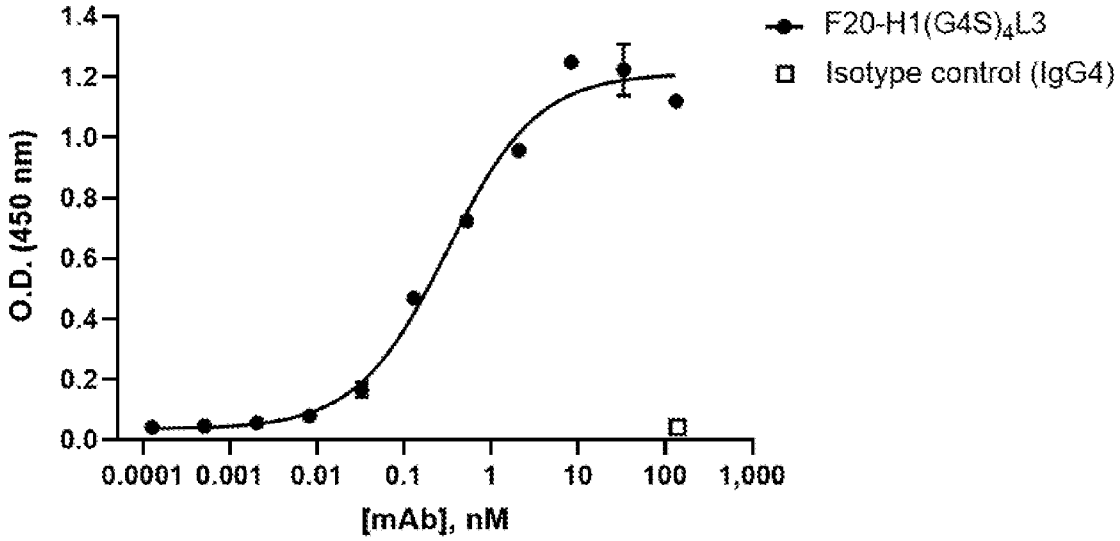

F20-H1(G4S)4L3
Isotype control (IgG4)
O.D. (450 nm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM

FIG. 3F

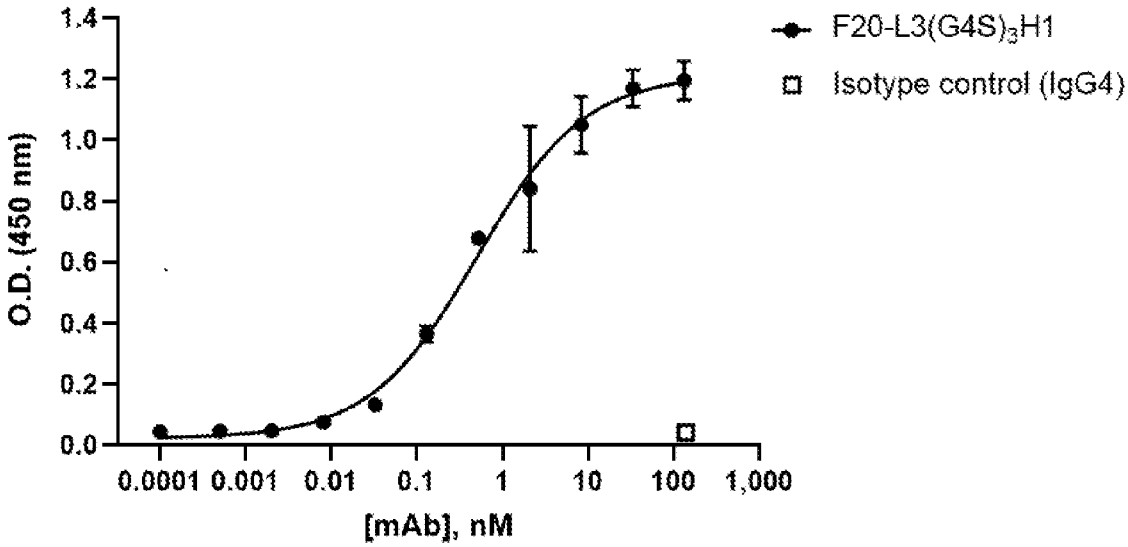

F20-L3(G4S)3H1
Isotype control (IgG4)
O.D. (450 nm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM

FIG. 3G

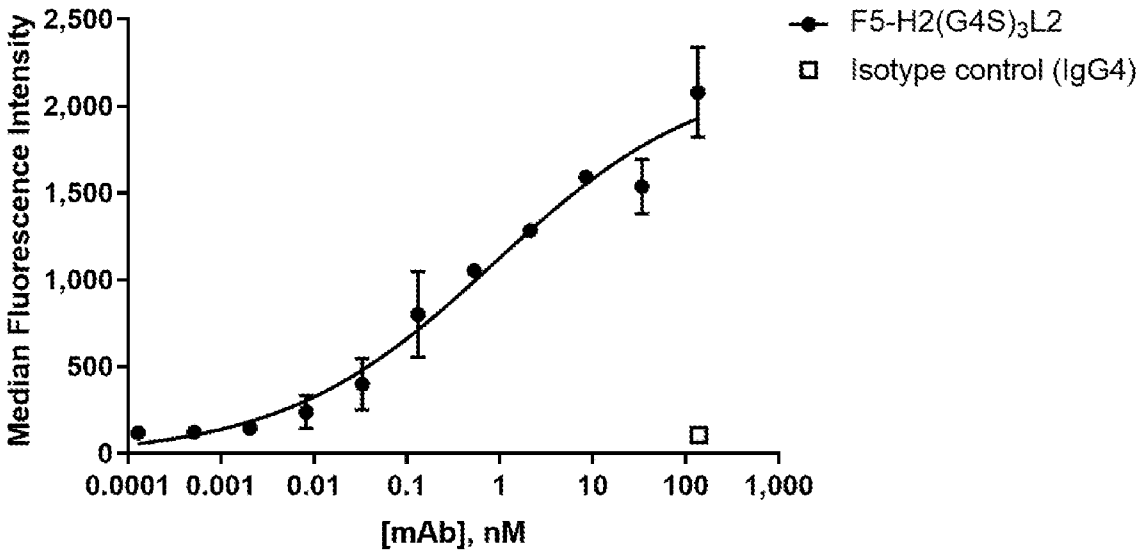

Median Fluorescence Intensity
2,500
2,000
1,500
1,000
500
0
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F5-H2(G4S)3L2
Isotype control (IgG4)

FIG. 4A

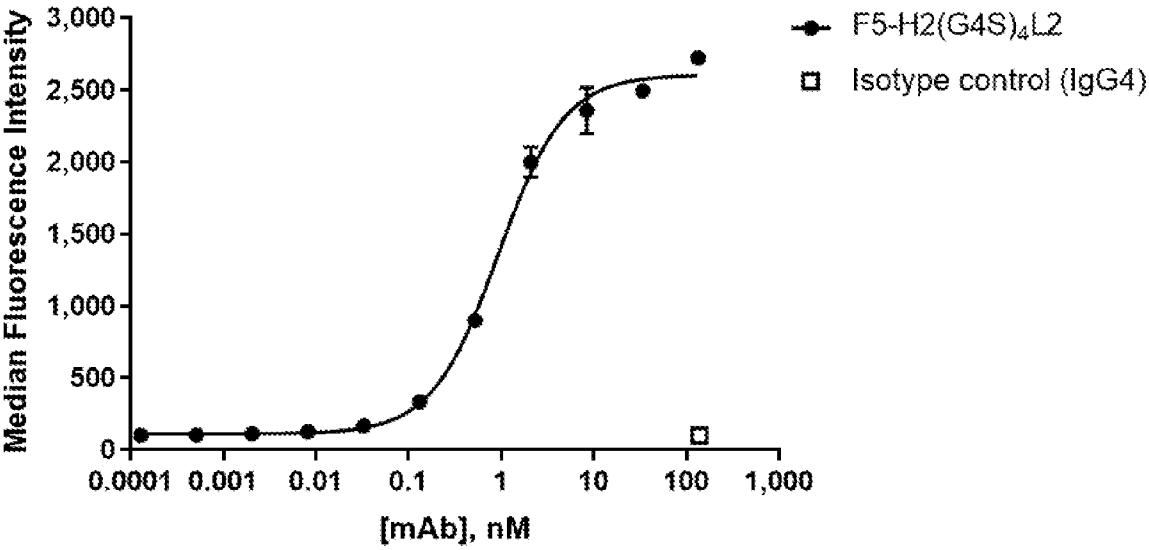

Median Fluorescence Intensity
3,000
2,500
2,000
1,500
1,000
500
0
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F5-H2(G4S)4L2
Isotype control (IgG4)

FIG. 4B

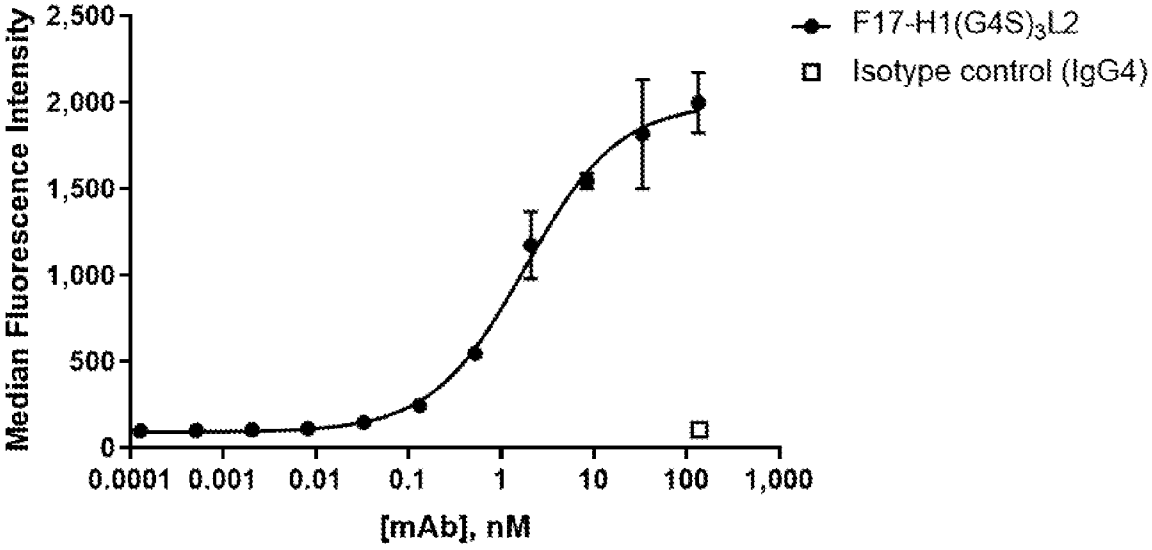

Median Fluorescence Intensity
2,500
2,000
1,500
1,000
500
0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM
F17-H1(G4S)3L2
Isotype control (IgG4)

FIG. 4C

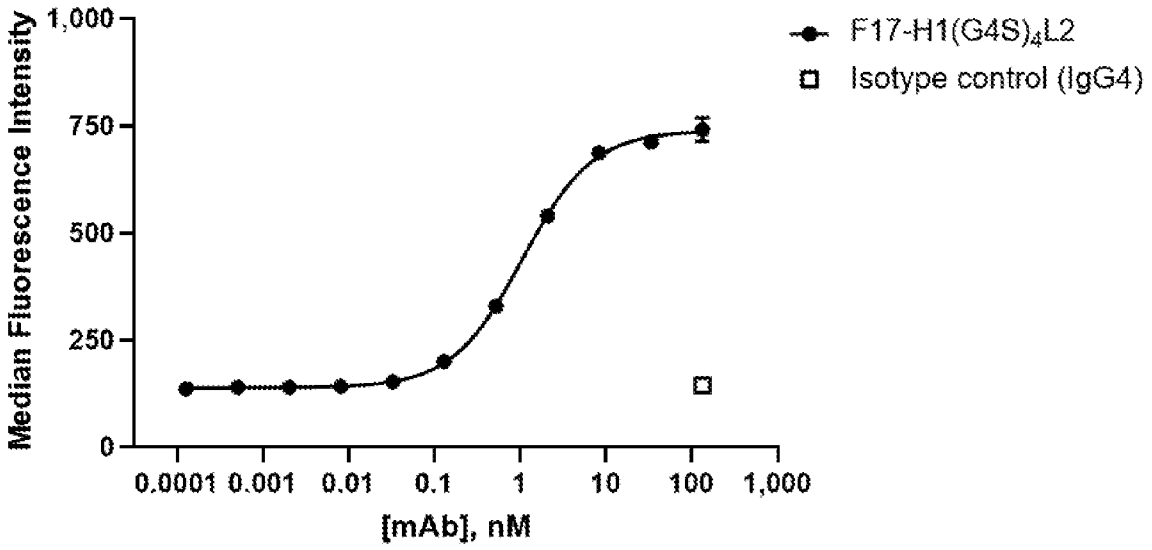

Median Fluorescence Intensity
1,000
750
500
250
0
0.0001 0.001 0.01 0.1 1 10 100 1,000
[mAb], nM
F17-H1(G4S)4L2
Isotype control (IgG4)

FIG. 4D

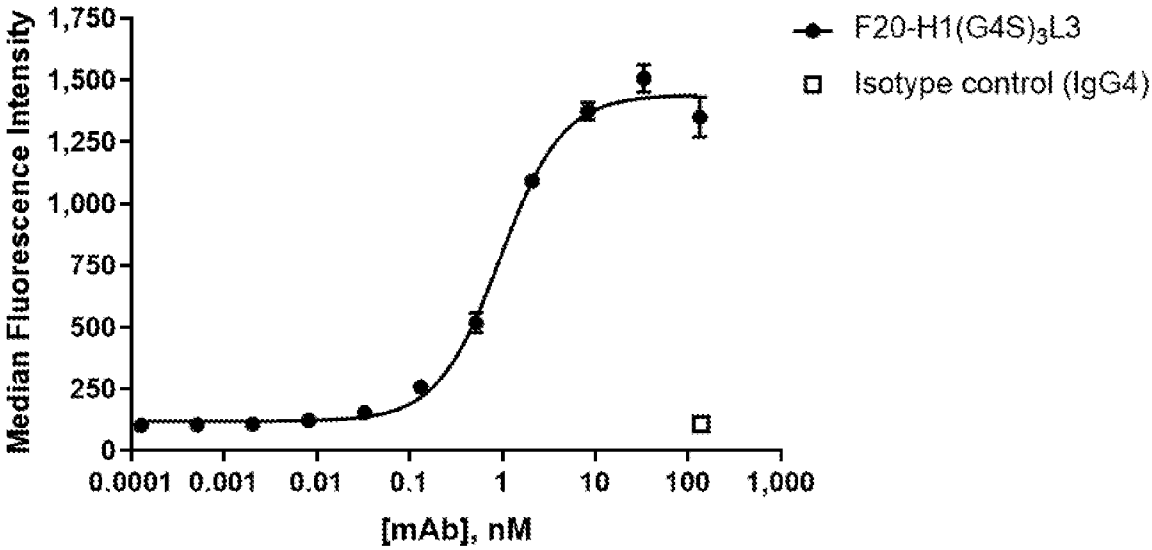

Median Fluorescence Intensity
1,750
1,500
1,250
1,000
750
500
250
0
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F20-H1(G4S)3L3
Isotype control (IgG4)

FIG. 4E

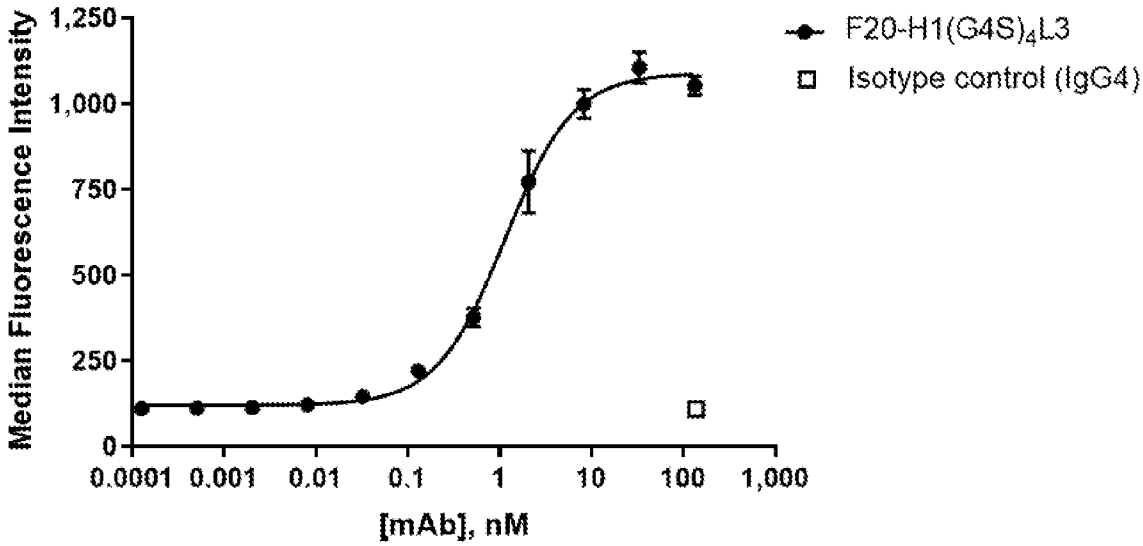

Median Fluorescence Intensity
1,250
1,000
750
500
250
0
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F20-H1(G4S)4L3
Isotype control (IgG4)

FIG. 4F

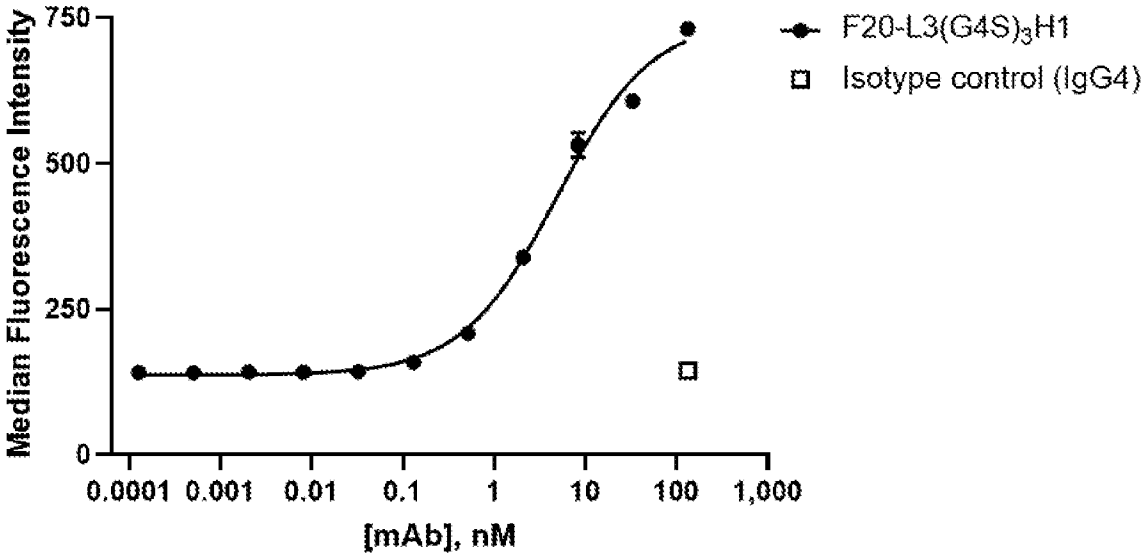

Median Fluorescence Intensity
750
500
250
0
0.0001
0.001
0.01
0.1
1
10
100
1,000
[mAb], nM
F20-L3(G4S)3H1
Isotype control (IgG4)

FIG. 4G

SEQUENCE LISTING

<110> Phanes Therapeutics, Inc.

<120> Humanized Anti-Folate Receptor 1 Chimeric Antigen Receptors and Uses Thereof

<130> 065799.21WO1

<150> US 62/832,975
<151> 2019-04-12

<150> US 62/863,330
<151> 2019-06-19

<150> US 62/931,988
<151> 2019-11-07

<160> 198

<170> PatentIn version 3.5

<210> 1
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 Heavy Chain Variable Region

<400> 1

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

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

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

Ala Phe Ile Ser Ser Gly Ser Asn Thr Ile Tyr Tyr Ala Asp Ile Val
50 55 60

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

Leu Gln Met Ala Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

```
Ala Arg Leu Ala Glu Trp Asp Val Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ala
        115


<210>  2
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F4 Light Chain Variable Region

<400>  2

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


Asp Arg Ile Ser Leu Ser Cys Arg Ala Ser Gln Asn Ile Asn Asn Asn
            20                  25                  30


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


Lys Phe Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60


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


Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ile Tyr Ser Trp Pro Gln
                85                  90                  95


Leu Thr Phe Gly Ala Gly Thr Arg Leu Glu Leu Lys
            100                 105


<210>  3
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
```

<223> F5 Heavy Chain Variable Region

<400> 3

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


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


Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
        35                  40                  45


Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60


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


Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Thr Leu Thr Val Ser Ser
        115
```

<210> 4
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 Light Chain Variable Region

<400> 4

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


Gly Lys Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile Thr Asn Phe
            20                  25                  30
```

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

Ser Tyr Thr Ser Ile Leu Glu Ser 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 Tyr Asn Leu Trp Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 5
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 Heavy Chain Variable Region

<400> 5

```
Glu Phe 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 Ser Phe Thr Asp Tyr
            20                  25                  30

Asn Met Asn Trp Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Asp Pro Asn Tyr Gly Thr Thr Asn Tyr Asn Gln Lys Phe
    50                  55                  60

Val Gly Lys Ala Thr Leu Thr Val Asp Gln Ser Ser Ile Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Asn Ser Leu Thr Ala Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95
```

Ala Ile Lys Gly Tyr Gly Asn Pro Ala Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 6
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 Light Chain Variable Region

<400> 6

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

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

Arg Tyr Thr Ser Ile Leu Glu Ser 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 Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 7
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 Heavy Chain Variable Region

<400> 7

Glu Val Met Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Gly Asp Thr Tyr His Leu Asp Thr Val
50 55 60

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

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 8
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 Light Chain Variable Region

<400> 8

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

Glu Ile Val Thr Ile Ile Cys Arg Val Ser Glu Asn Ile Asp Ser Tyr
20 25 30

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

```
Tyr Ala Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Ser Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Val Ala Arg Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
            100                 105
```

<210> 9
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 Heavy Chain Variable Region

<400> 9

```
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 Ser Ser
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Arg Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Tyr Pro Gly Asp Gly Tyr Thr His Tyr Asn Gly Met Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Gly Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95

Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val Trp Gly Thr
            100                 105                 110
```

Gly Thr Thr Val Thr Val Ser Ser
        115   120

<210> 10
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 Light Chain Variable Region

<400> 10

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

Glu Ser Val Thr Ile Thr Cys Arg Ala Ser Glu Asn Ile Asp Ser Tyr
            20   25   30

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

Tyr Ala Ala Thr Asn Leu Ala Val Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Gln Tyr Thr Leu Lys Ile Asn Ser Leu Gln Ser
65   70   75   80

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 11
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 Heavy Chain Variable Region

<400> 11

```
Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15


Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
            20                  25                  30


Gly Met His Trp Ile Arg Gln Ala Pro Glu Arg Gly Leu Glu Trp Val
        35                  40                  45


Ala Tyr Met Ser Tyr Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val
    50                  55                  60


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


Leu Gln Met Thr Ser Leu Arg Ser Asp Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Val His Val Gly Thr Val Asp Tyr Trp Gly Gln Gly Thr Ser
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  12
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F17 Light Chain Variable Region

<400>  12

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


Asp Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Asn Ile Asn Asn Asn
            20                  25                  30


Leu His Trp Phe Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile
        35                  40                  45
```

```
Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Gly Ile Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Ala
                85                  90                  95

Leu Thr Phe Gly Thr Gly Thr Lys Val Glu Leu Lys
            100                 105
```

<210> 13
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 Heavy Chain Variable Region

<400> 13

```
Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ser Pro Asp Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Gln Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr Tyr Ser Asp
    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 Ser Leu Arg Val Glu Asp Thr Gly Ile Tyr
                85                  90                  95

Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Ser Val Thr Val Ser Ser
        115   120

<210> 14
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 Light Chain Variable Region

<400> 14

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

Asp Arg Val Thr Leu Asn Cys Arg Ala Ser Gln Asp Ile Thr Asn His
            20   25   30

Leu Asn Trp Phe Gln Gln Lys Pro Asp Gly Thr Phe Gln Leu Leu Ile
        35   40   45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65   70   75   80

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100   105

<210> 15
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 Heavy Chain Variable Region

<400> 15

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

```
Ser Val Gln Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ala Ser Tyr
            20                  25                  30

Tyr Leu Tyr Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60

Lys Ser Lys Ala Thr Val 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

Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

<210> 16
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 Light Chain Variable Region

<400> 16

```
Asn Ile Val Met Thr Gln Ser Pro Lys Ser Met Ser Val Ser Val Gly
1               5                   10                  15

Glu Arg Val Thr Leu Ser Cys Lys Ala Gly Glu Asn Val Gly Ser Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln Lys Pro Glu Gln Ser Pro Glu Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60
```

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Asp Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 17
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 HCDR1

<400> 17

Gly Phe Thr Phe Ser Asp Tyr Gly
1 5

<210> 18
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 HCDR2

<400> 18

Ile Ser Ser Gly Ser Asn Thr Ile
1 5

<210> 19
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 HCDR3

<400> 19

Ala Arg Leu Ala Glu Trp Asp Val Ala Tyr
1 5 10

<210> 20
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 HCDR1

<400> 20

Gly Phe Thr Phe Ser Asn Tyr Gly
1   5

<210> 21
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 HCDR2

<400> 21

Ile Ser Ser Gly Gly Ser Tyr Thr
1   5

<210> 22
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 HCDR3

<400> 22

Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr
1   5   10

<210> 23
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR1

<400> 23

Gly Tyr Ser Phe Thr Asp Tyr Asn
1 5

<210> 24
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR2

<400> 24

Ile Asp Pro Asn Tyr Gly Thr Thr
1 5

<210> 25
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR3

<400> 25

Ala Ile Lys Gly Tyr Gly Asn Pro Ala Ala Tyr
1 5 10

<210> 26
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 HCDR1

<400> 26

Gly Phe Thr Leu Ser Thr Tyr Ala
1 5

<210> 27
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 HCDR2

<400> 27

Ile Ser Gly Gly Gly Gly Asp Thr
1 5

<210> 28
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 HCDR3

<400> 28

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn
1 5 10

<210> 29
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 HCDR1

<400> 29

Gly Tyr Ala Phe Ser Ser Ser Trp
1 5

<210> 30
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 HCDR2

<400> 30

Ile Tyr Pro Gly Asp Gly Tyr Thr
1 5

<210> 31
<211> 13
<212> PRT
<213> Artificial Sequence

<220>

<223> F10 HCDR3

<400> 31

Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val
1   5   10

<210> 32
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 HCDR1

<400> 32

Gly Phe Thr Phe Ser Asp Phe Gly
1   5

<210> 33
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 HCDR2

<400> 33

Met Ser Tyr Thr Pro Gly Thr Phe
1   5

<210> 34
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 HCDR3

<400> 34

Ala Arg Val His Val Gly Thr Val Asp Tyr
1   5   10

<210> 35
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 HCDR1

<400> 35

Gly Phe Thr Phe Ser Asp Tyr Trp
1   5

<210> 36
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 HCDR2

<400> 36

Ile Gly Asn Lys Phe His Asn Tyr Glu Thr
1   5   10

<210> 37
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 HCDR3

<400> 37

Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr
1   5   10

<210> 38
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 HCDR1

<400> 38

Gly Tyr Thr Phe Ala Ser Tyr Tyr
1   5

<210> 39
<211> 8

<212> PRT
<213> Artificial Sequence

<220>
<223> F20 HCDR2

<400> 39

Ile Asn Pro Arg Ser Gly Gly Thr
1   5

<210> 40
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 HCDR3

<400> 40

Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr
1   5   10

<210> 41
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 LCDR1

<400> 41

Gln Asn Ile Asn Asn Asn
1   5

<210> 42
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 LCDR2

<400> 42

Phe Ala Ser
1

<210> 43
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 LCDR3

<400> 43

Gln Gln Ile Tyr Ser Trp Pro Gln Leu Thr
1   5   10

<210> 44
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 LCDR1

<400> 44

Gln Asp Ile Thr Asn Phe
1   5

<210> 45
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 LCDR2

<400> 45

Tyr Thr Ser
1

<210> 46
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 LCDR3

<400> 46

Leu Gln Tyr Tyr Asn Leu Trp Thr
1   5

<210> 47
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR1

<400> 47

Gln Asp Ile Asn Lys Tyr
1 5

<210> 48
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR2

<400> 48

Tyr Thr Ser
1

<210> 49
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR3

<400> 49

Leu Gln Tyr Tyr Asn Leu Trp Thr
1 5

<210> 50
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 LCDR1

<400> 50

Glu Asn Ile Asp Ser Tyr
1 5

<210> 51
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 LCDR2

<400> 51

Ala Ala Thr
1

<210> 52
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 LCDR3

<400> 52

Gln His Tyr Tyr Thr Thr Pro Pro Thr
1 5

<210> 53
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 LCDR1

<400> 53

Glu Asn Ile Asp Ser Tyr
1 5

<210> 54
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 LCDR2

<400> 54

Ala Ala Thr
1

<210> 55
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 LCDR3

<400> 55

Gln His His Tyr Ser Thr Pro Pro Thr
1 5

<210> 56
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 LCDR1

<400> 56

Gln Asn Ile Asn Asn Asn
1 5

<210> 57
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 LCDR2

<400> 57

Tyr Ala Ser
1

<210> 58
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> F17 LCDR3

<400> 58

Gln Gln Ser Asn Ser Trp Pro Ala Leu Thr
1   5   10

<210> 59
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 LCDR1

<400> 59

Gln Asp Ile Thr Asn His
1   5

<210> 60
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 LCDR2

<400> 60

Tyr Thr Ser
1

<210> 61
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 LCDR3

<400> 61

Gln Gln Asp Ser Gln His Pro Trp Thr
1   5

<210> 62
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 LCDR1

<400> 62

Glu Asn Val Gly Ser Tyr
1   5

<210> 63
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 LCDR2

<400> 63

Gly Ala Ser
1

<210> 64
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 LCDR3

<400> 64

Gly Gln Thr Tyr Arg Phe Leu Thr
1   5

<210> 65
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 HCDR1

<400> 65

Gly Phe Thr Phe Ser Asp Tyr Gly Met His
1   5   10

<210> 66
<211> 17

<212> PRT
<213> Artificial Sequence

<220>
<223> F4 HCDR2

<400> 66

Phe Ile Ser Ser Gly Ser Asn Thr Ile Tyr Tyr Ala Asp Ile Val Lys
1   5   10   15

Gly

<210> 67
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 HCDR3

<400> 67

Ala Arg Leu Ala Glu Trp Asp Val Ala Tyr
1   5   10

<210> 68
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 HCDR1

<400> 68

Gly Phe Thr Phe Ser Asn Tyr Gly Met Ser
1   5   10

<210> 69
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 HCDR2

<400> 69

Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val Lys
1 5 10 15

Gly

<210> 70
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 HCDR3

<400> 70

Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr
1 5 10

<210> 71
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR1

<400> 71

Gly Tyr Ser Phe Thr Asp Tyr Asn Met Asn
1 5 10

<210> 72
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR2

<400> 72

Val Ile Asp Pro Asn Tyr Gly Thr Thr Asn Tyr Asn Gln Lys Phe Val
1 5 10 15

Gly

<210> 73
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 HCDR3

<400> 73

Ala Ile Lys Gly Tyr Gly Asn Pro Ala Ala Tyr
1 5 10

<210> 74
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 HCDR1

<400> 74

Gly Phe Thr Leu Ser Thr Tyr Ala Met Ser
1 5 10

<210> 75
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 HCDR2

<400> 75

Thr Ile Ser Gly Gly Gly Gly Asp Thr Tyr His Leu Asp Thr Val Lys
1 5 10 15

Gly

<210> 76
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 HCDR3

<400> 76

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn
1 5 10

<210> 77
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 HCDR1

<400> 77

Gly Tyr Ala Phe Ser Ser Ser Trp Met Asn
1 5 10

<210> 78
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 HCDR2

<400> 78

Arg Ile Tyr Pro Gly Asp Gly Tyr Thr His Tyr Asn Gly Met Phe Lys
1 5 10 15

Gly

<210> 79
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 HCDR3

<400> 79

Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val
1 5 10

<210> 80
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> F17 HCDR1

<400> 80

Gly Phe Thr Phe Ser Asp Phe Gly Met His
1   5   10

<210> 81
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 HCDR2

<400> 81

Tyr Met Ser Tyr Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val Lys
1   5   10   15

Asp

<210> 82
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 HCDR3

<400> 82

Ala Arg Val His Val Gly Thr Val Asp Tyr
1   5   10

<210> 83
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 HCDR1

<400> 83

Gly Phe Thr Phe Ser Asp Tyr Trp Met Asn
1 5 10

<210> 84
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 HCDR2

<400> 84

Gln Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr Tyr Ser Asp Ser
1 5 10 15

Val Lys Gly

<210> 85
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 HCDR3

<400> 85

Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr
1 5 10

<210> 86
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 HCDR1

<400> 86

Gly Tyr Thr Phe Ala Ser Tyr Tyr Leu Tyr
1 5 10

<210> 87
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 HCDR2

<400> 87

Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe Lys
1   5   10   15

Ser

<210> 88
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 HCDR3

<400> 88

Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr
1   5   10

<210> 89
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 LCDR1

<400> 89

Arg Ala Ser Gln Asn Ile Asn Asn Asn Leu His
1   5   10

<210> 90
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 LCDR2

<400> 90

Phe Ala Ser Gln Ser Ile Ser
1   5

<210> 91
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F4 LCDR3

<400> 91

Gln Gln Ile Tyr Ser Trp Pro Gln Leu Thr
1   5   10

<210> 92
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 LCDR1

<400> 92

Lys Ala Ser Gln Asp Ile Thr Asn Phe Ile Gly
1   5   10

<210> 93
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 LCDR2

<400> 93

Tyr Thr Ser Ile Leu Glu Ser
1   5

<210> 94
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F5 LCDR3

<400> 94

Leu Gln Tyr Tyr Asn Leu Trp Thr
1   5

<210> 95
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR1

<400> 95

Lys Ala Ser Gln Asp Ile Asn Lys Tyr Leu Ala
1   5   10

<210> 96
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR2

<400> 96

Tyr Thr Ser Ile Leu Glu Ser
1   5

<210> 97
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F7 LCDR3

<400> 97

Leu Gln Tyr Tyr Asn Leu Trp Thr
1   5

<210> 98
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 LCDR1

<400> 98

Arg Val Ser Glu Asn Ile Asp Ser Tyr Leu Ala
1 5 10

<210> 99
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 LCDR2

<400> 99

Ala Ala Thr Asn Leu Ala Asp
1 5

<210> 100
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F8 LCDR3

<400> 100

Gln His Tyr Tyr Thr Thr Pro Pro Thr
1 5

<210> 101
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 LCDR1

<400> 101

Arg Ala Ser Glu Asn Ile Asp Ser Tyr Leu Ala
1 5 10

<210> 102
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> F10 LCDR2

<400> 102

Ala Ala Thr Asn Leu Ala Val
1   5

<210> 103
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F10 LCDR3

<400> 103

Gln His His Tyr Ser Thr Pro Pro Thr
1   5

<210> 104
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 LCDR1

<400> 104

Arg Ala Ser Gln Asn Ile Asn Asn Asn Leu His
1   5   10

<210> 105
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 LCDR2

<400> 105

Tyr Ala Ser Gln Ser Ile Ser
1   5

<210> 106
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> F17 LCDR3

<400> 106

Gln Gln Ser Asn Ser Trp Pro Ala Leu Thr
1   5   10

<210> 107
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 LCDR1

<400> 107

Arg Ala Ser Gln Asp Ile Thr Asn His Leu Asn
1   5   10

<210> 108
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 LCDR2

<400> 108

Tyr Thr Ser Arg Leu His Ser
1   5

<210> 109
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> F19 LCDR3

<400> 109

Gln Gln Asp Ser Gln His Pro Trp Thr
1   5

<210> 110
<211> 11

<212> PRT
<213> Artificial Sequence

<220>
<223> F20 LCDR1

<400> 110

Lys Ala Gly Glu Asn Val Gly Ser Tyr Val Ser
1   5   10

<210> 111
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 LCDR2

<400> 111

Gly Ala Ser Asn Arg Tyr Thr
1   5

<210> 112
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> F20 LCDR3

<400> 112

Gly Gln Thr Tyr Arg Phe Leu Thr
1   5

<210> 113
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H1 Heavy Chain Variable Region

<400> 113

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 Val Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


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


Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60


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


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  114
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F5-H2 Heavy Chain Variable Region

<400>  114

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 Val Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


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


Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60
```

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


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115
```

<210> 115
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H3 Heavy Chain Variable Region

<400> 115

```
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 Val Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


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


Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60


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


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


Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110
```

Leu Val Thr Val Ser Ser
115

<210> 116
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H4 Heavy Chain Variable Region

<400> 116

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 Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

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

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

Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 117
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L1 Light Chain Variable Region

<400> 117

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 Thr Asn Phe
20 25 30

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

Ser Tyr Thr Ser Ile Leu Glu 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 Leu Gln Tyr Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 118
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L2 Light Chain Variable Region

<400> 118

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 Thr Asn Phe
20 25 30

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

Ser Tyr Thr Ser Ile Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

```
Ser Gly Ser Gly Thr 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 Tyr Asn Leu Trp Thr
                85                  90                  95


Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210>  119
<211>  120
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F10-H1 Heavy Chain Variable Region

<400>  119

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 Ala Phe Ser Ser Ser
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Arg Ile Tyr Pro Gly Asp Gly Tyr Thr His Tyr Asn Gly Met Phe
    50                  55                  60


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


Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Phe Phe Cys
                85                  90                  95


Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val Trp Gly Arg
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Pro
        115                 120
```

<210> 120
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> F10-H2 Heavy Chain Variable Region

<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 Ala Phe Ser Ser Ser
20 25 30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Tyr Pro Gly Asp Gly Tyr Thr His Tyr Asn Gly Met Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Phe Phe Cys
85 90 95

Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val Trp Gly Arg
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 121
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F10-L1 Light Chain Variable Region

<400> 121

```
Asp Ile 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 Ala Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30


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


Tyr Ala Ala Thr Asn Leu Ala Val Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Ser Thr Pro Pro
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  122
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F10-L2 Light Chain Variable Region

<400>  122

Asp Ile 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 Ala Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30


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


Tyr Ala Ala Thr Asn Leu Ala Val Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

```
Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Ser Thr Pro Pro
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  123
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F10-L3 Light Chain Variable Region

<400>  123

Asp Ile 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 Ala Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30


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


Tyr Ala Ala Thr Asn Leu Ala Val Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Ser Thr Pro Pro
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210>  124
<211>  117
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> F17-H1 Heavy Chain Variable Region

<400> 124

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
            20   25   30

Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45

Ala Tyr Met Ser Tyr Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val
    50   55   60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Val His Val Gly Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 125
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> F17-H2 Heavy Chain Variable Region

<400> 125

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
            20   25   30

```
Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Tyr Met Ser Tyr Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val
    50                  55                  60


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


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ala Arg Val His Val Gly Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  126
<211>  108
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F17-L1 Light Chain Variable Region

<400>  126

Glu Val Val Leu 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 Asn Ile Asn Asn Asn
            20                  25                  30


Leu His Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 127
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> F17-L2 Light Chain Variable Region

<400> 127

Glu Val Val Leu 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 Asn Ile Asn Asn Asn
20 25 30

Leu His Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 128
<211> 121
<212> PRT
<213> Artificial Sequence

<220>

<223> F20-H1 Heavy Chain Variable Region

<400> 128

```
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 Ala Ser Tyr
            20                  25                  30


Tyr Leu Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60


Lys Ser Arg Ala Thr Val 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


Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 129
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-H2 Heavy Chain Variable Region

<400> 129

```
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 Ala Ser Tyr
            20                  25                  30
```

```
Tyr Leu Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60

Lys Ser Arg Ala Thr Val Thr Val Asp Ala 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

Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met 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> F20-H3 Heavy Chain Variable Region

<400> 130

```
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 Ala Ser Tyr
            20                  25                  30

Tyr Leu Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60

Lys Ser Lys Ala Thr Val Thr Val Asp Lys Ser Thr Asn 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

Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 131
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-L1 Light Chain Variable Region

<400> 131

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Gly Glu Asn Val Gly Ser Tyr
20 25 30

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

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

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 132
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-L2 Light Chain Variable Region

<400> 132

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Gly Glu Asn Val Gly Ser Tyr
            20   25   30

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

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

Ser Gly Ser Ala Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
65   70   75   80

Glu Asp Val Ala Val Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr
                85   90   95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 133
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-L3 Light Chain Variable Region

<400> 133

Asp Ile 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 Lys Ala Gly Glu Asn Val Gly Ser Tyr
            20   25   30

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

```
Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Val Lys
            100                 105
```

<210> 134
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-L4 Light Chain Variable Region

<400> 134

```
Asp Ile 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 Lys Ala Gly Glu Asn Val Gly Ser Tyr
            20                  25                  30

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

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Val Lys
            100                 105
```

<210> 135
<211> 257
<212> PRT
<213> Homo sapiens

<400> 135

```
Met Ala Gln Arg Met Thr Thr Gln Leu Leu Leu Leu Leu Val Trp Val
1               5                  10                  15


Ala Val Val Gly Glu Ala Gln Thr Arg Ile Ala Trp Ala Arg Thr Glu
            20                  25                  30


Leu Leu Asn Val Cys Met Asn Ala Lys His His Lys Glu Lys Pro Gly
        35                  40                  45


Pro Glu Asp Lys Leu His Glu Gln Cys Arg Pro Trp Arg Lys Asn Ala
    50                  55                  60


Cys Cys Ser Thr Asn Thr Ser Gln Glu Ala His Lys Asp Val Ser Tyr
65                  70                  75                  80


Leu Tyr Arg Phe Asn Trp Asn His Cys Gly Glu Met Ala Pro Ala Cys
                85                  90                  95


Lys Arg His Phe Ile Gln Asp Thr Cys Leu Tyr Glu Cys Ser Pro Asn
            100                 105                 110


Leu Gly Pro Trp Ile Gln Gln Val Asp Gln Ser Trp Arg Lys Glu Arg
        115                 120                 125


Val Leu Asn Val Pro Leu Cys Lys Glu Asp Cys Glu Gln Trp Trp Glu
    130                 135                 140


Asp Cys Arg Thr Ser Tyr Thr Cys Lys Ser Asn Trp His Lys Gly Trp
145                 150                 155                 160


Asn Trp Thr Ser Gly Phe Asn Lys Cys Ala Val Gly Ala Ala Cys Gln
                165                 170                 175


Pro Phe His Phe Tyr Phe Pro Thr Pro Thr Val Leu Cys Asn Glu Ile
```

```
            180                 185                 190

Trp Thr His Ser Tyr Lys Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg
        195                 200                 205

Cys Ile Gln Met Trp Phe Asp Pro Ala Gln Gly Asn Pro Asn Glu Glu
    210                 215                 220

Val Ala Arg Phe Tyr Ala Ala Ala Met Ser Gly Ala Gly Pro Trp Ala
225                 230                 235                 240

Ala Trp Pro Phe Leu Leu Ser Leu Ala Leu Met Leu Leu Trp Leu Leu
                245                 250                 255

Ser
```

<210> 136
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> F4-H1 Heavy Chain Variable Region

<400> 136

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Arg Lys Pro Gly Ala
1               5                   10                  15

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

Gly Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
        35                  40                  45

Ala Phe Ile Ser Ser Gly Ser Asn Thr Ile Tyr Tyr Ala Asp Ile Val
    50                  55                  60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
```

85 90 95

Ala Arg Leu Ala Glu Trp Asp Val Ala Tyr Trp Gly Ala Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 137
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> F4-H2 Heavy Chain Variable Region

<400> 137

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 Phe Thr Phe Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Ala Phe Ile Ser Ser Gly Ser Asn Thr Ile Tyr Tyr Ala Asp Ile Val
50 55 60

Lys Gly Arg Val Thr Ile Thr Arg Asn Asn Ser Thr Ser Thr Leu Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Leu Ala Glu Trp Asp Val Ala Tyr Trp Gly Ala Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 138

<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> F4-H3 Heavy Chain Variable Region

<400> 138

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 Asp Tyr
20 25 30

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

Ala Gly Ile Ser Ser Gly Ser Asn Thr Ile Gly Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Leu Ala Glu Trp Asp Val Ala Tyr Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> 139
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> F4-L1 Light Chain Variable Region

<400> 139

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

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Asn Asn Asn
            20                  25                  30

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

Lys Phe Ala Ser Gln Ser Ile Ser Gly Ala Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ile Tyr Ser Trp Pro Gln
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 140
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> F4-L2 Light Chain Variable Region

<400> 140

```
Asp Ile Gln Leu 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 Asn Ile Asn Asn Asn
            20                  25                  30

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

Lys Phe Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

Asp Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ile Tyr Ser Trp Pro Gln
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 141
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> F4-L3 Light Chain Variable Region

<400> 141

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn Ile Asn Asn Asn
20 25 30

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

Lys Phe Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 142
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-H1 Heavy Chain Variable Region

<400> 142

Gln Phe 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 Ser Phe Thr Asp Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Asn Tyr Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Ala Thr Leu Thr Val Asp Gln 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 Ile Lys Gly Tyr Gly Asn Pro Ala Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 143
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-H2 Heavy Chain Variable Region

<400> 143

Glu Phe Gln Leu Val Glu 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 Ser Phe Thr Asp Tyr
20 25 30

Asn Phe Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

```
        35                  40                  45

Gly Arg Ile Asp Pro Asn Tyr Gly Thr Thr His Tyr Ala Pro His Leu
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Val Asp Gln Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Leu Glu Leu Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
                85                  90                  95

Ala Ile Lys Gly Tyr Gly Asn Pro Ala Ala Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115


<210>  144
<211>  118
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F7-H3 Heavy Chain Variable Region

<400>  144

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 Ser Phe Thr Asp Tyr
            20                  25                  30

Asn Phe Thr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Asp Pro Asn Tyr Gly Thr Thr His Tyr Ala Pro His Leu
    50                  55                  60

Gln Gly Arg Ala Thr Leu Thr Val Asp Gln Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Leu Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Phe Cys
```

85 90 95

Ala Ile Lys Gly Tyr Gly Asn Pro Ala Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 145
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-L1 Light Chain Variable Region

<400> 145

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Asp Ile Asn Lys Tyr
20 25 30

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

Arg Tyr Thr Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Ala
65 70 75 80

Glu Asp Val Ala Val Tyr Tyr Cys Leu Gln Tyr Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 146
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-L2 Light Chain Variable Region

<400> 146

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Asn Lys Tyr
            20   25   30

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

Arg Tyr Thr Ser Thr Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Arg Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Ser
65   70   75   80

Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Tyr Tyr Asn Leu Trp Thr
                85   90   95

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100   105

<210> 147
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F7-L3 Light Chain Variable Region

<400> 147

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asp Ile Asn Lys Tyr
            20   25   30

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

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


Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80


Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Tyr Tyr Asn Leu Trp Thr
                85                  90                  95


Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
            100                 105


<210>  148
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F8-H1 Heavy Chain Variable Region

<400>  148

Leu Val Asn Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Thr Tyr
            20                  25                  30


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


Ala Val Ile Ser Gly Gly Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Phe Tyr Cys
                85                  90                  95


Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 149
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-H2 Heavy Chain Variable Region

<400> 149

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1   5   10   15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Thr Tyr
            20   25   30

Ala Met Asn Trp Val Arg Gln Ala Pro Ala Lys Gly Leu Glu Trp Val
        35   40   45

Ala Ile Ile Ser Gly Gly Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
    50   55   60

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

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
            100   105   110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 150
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-H3 Heavy Chain Variable Region

<400> 150

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Thr Tyr
20 25 30

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

Ala Ile Ile Ser Gly Gly Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 151
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-L1 Light Chain Variable Region

<400> 151

Glu Ile Gln 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 Val Ser Glu Asn Ile Asp Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Val

35 40 45

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

Ser Gly Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
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> F8-L2 Light Chain Variable Region

<400> 152

Glu Ile Val Met Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Val Ser Glu Asn Ile Asp Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Val
35 40 45

Tyr Ala Ala Thr Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ser Asp Tyr Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Ala Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys

100 105

<210> 153
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-L3 Light Chain Variable Region

<400> 153

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Val Ser Glu Asn Ile Asp Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Val
35 40 45

Tyr Ala Ala Thr Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Ala Ala Ala Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 154
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H1 Heavy Chain Variable Region

<400> 154

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

```
Thr Leu Ser Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Val
        35                  40                  45

Ala Phe Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Glu Tyr Asn Pro
    50                  55                  60

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

Val Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Ser Leu Val Thr Val Ser Ser
        115                 120
```

<210> 155
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H2 Heavy Chain Variable Region

<400> 155

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

Thr Leu Ser Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Phe Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Glu Tyr Asn Pro
    50                  55                  60
```

```
Ser Val Lys Gly Arg Phe Thr Ile Leu Arg Asp Asp Ser Lys Asn Gln
65                  70                  75                  80


Val Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Ser Leu Val Thr Val Ser Ser
        115                 120


<210>  156
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F19-H3 Heavy Chain Variable Region

<400>  156

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Ile Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr 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 Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120

<210> 157
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L1 Light Chain Variable Region

<400> 157

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 Thr Asn His
            20   25   30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Phe Lys Leu Leu Ile
        35   40   45

Tyr Tyr Thr Ser Asn Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Asp Ser Gln His Pro Trp
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 158
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L2 Light Chain Variable Region

<400> 158

Glu Ile Val Met Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys

1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Thr Asn His
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Asp Gln Ser Phe Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80

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

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 159
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H2(G4S)3L2

<400> 159

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 Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr 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 Val
130 135 140

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln
145 150 155 160

Asp Ile Thr Asn Phe Ile Gly Trp Tyr Gln His Lys Pro Gly Lys Ala
165 170 175

Pro Lys Leu Leu Ile Ser Tyr Thr Ser Ile Leu Glu Ser Gly Val Pro
180 185 190

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile
195 200 205

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr
210 215 220

Tyr Asn Leu Trp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
225 230 235

<210> 160
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H2(G4S)4L2

<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 Val Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

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

Ala Thr Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr 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 Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
145                 150                 155                 160

Cys Lys Ala Ser Gln Asp Ile Thr Asn Phe Ile Gly Trp Tyr Gln His
                165                 170                 175

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Ser Tyr Thr Ser Ile Leu
            180                 185                 190

Glu Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
    210                 215                 220
```

Tyr Cys Leu Gln Tyr Tyr Asn Leu Trp Thr Phe Gly Gly Gly Thr Lys
225 230 235 240

Val Glu Ile Lys

<210> 161
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L2(G4S)3H2

<400> 161

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 Thr Asn Phe
20 25 30

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

Ser Tyr Thr Ser Ile Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr 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 Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser
115 120 125

Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala
130 135 140

```
Val Ser Gly Phe Thr Phe Ser Asn Tyr Gly Met Ser Trp Val Arg Gln
145                 150                 155                 160


Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser Ser Gly Gly
                165                 170                 175


Ser Tyr Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
            180                 185                 190


Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
        195                 200                 205


Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser Thr Gln Gly Ser Ser Gly
    210                 215                 220


Tyr Val Gly Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235


<210>  162
<211>  242
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F10-H1(G4S)3L2

<400>  162

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 Ala Phe Ser Ser Ser
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Arg Ile Tyr Pro Gly Asp Gly Tyr Thr His Tyr Asn Gly Met Phe
    50                  55                  60


Lys Gly Arg Ala Ser Leu Thr Ala Asp Lys Ser Thr Ser Thr Gly Tyr
65                  70                  75                  80
```

```
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Phe Phe Cys
                85                  90                  95

Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val Trp Gly Arg
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Pro 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

Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Glu Asn Ile Asp Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Arg Ala Pro Lys Leu Leu Val Tyr Ala Ala Thr Asn Leu Ala Val Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

His His Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu
225                 230                 235                 240

Ile Lys
```

<210> 163
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> F10-H1(G4S)4L2

<400> 163

```
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 Ala Phe Ser Ser Ser
            20                  25                  30

Trp Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Tyr Pro Gly Asp Gly Tyr Thr His Tyr Asn Gly Met Phe
    50                  55                  60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Phe Phe Cys
                85                  90                  95

Thr Arg His Gly Asp Phe Pro Tyr Trp Tyr Phe Asp Val Trp Gly Arg
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Pro 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 Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160

Ile Thr Cys Arg Ala Ser Glu Asn Ile Asp Ser Tyr Leu Ala Trp Tyr
                165                 170                 175

Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Val Tyr Ala Ala Thr
            180                 185                 190

Asn Leu Ala Val Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205

Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala
```

```
    210                 215                 220

Thr Tyr Tyr Cys Gln His His Tyr Ser Thr Pro Pro Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 164
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> F10-L2(G4S)3H1

<400> 164

```
Asp Ile 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 Ala Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30

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

Tyr Ala Ala Thr Asn Leu Ala Val Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln His His Tyr Ser Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser
            100                 105                 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Gln
        115                 120                 125

Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys
```

```
    130                 135                 140

Lys Ala Ser Gly Tyr Ala Phe Ser Ser Ser Trp Met Asn Trp Val Arg
145                 150                 155                 160

Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Arg Ile Tyr Pro Gly
                165                 170                 175

Asp Gly Tyr Thr His Tyr Asn Gly Met Phe Lys Gly Arg Ala Ser Leu
            180                 185                 190

Thr Ala Asp Lys Ser Thr Ser Thr Gly Tyr Met Glu Leu Ser Ser Leu
        195                 200                 205

Arg Ser Glu Asp Thr Ala Val Phe Phe Cys Thr Arg His Gly Asp Phe
    210                 215                 220

Pro Tyr Trp Tyr Phe Asp Val Trp Gly Arg Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Pro
```

<210> 165
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> F17-H1(G4S)3L2

<400> 165

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
            20                  25                  30

Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Tyr Met Ser Tyr Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val
```

```
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Val His Val Gly Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Glu Val Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
    130                 135                 140

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Asn
145                 150                 155                 160

Ile Asn Asn Asn Leu His Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro
                165                 170                 175

Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ala
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Glu Thr Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Ser Asn
    210                 215                 220

Ser Trp Pro Ala Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225                 230                 235                 240
```

<210> 166
<211> 245
<212> PRT
<213> Artificial Sequence

<220>
<223> F17-H1(G4S)4L2

<400> 166

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
            20                  25                  30

Gly Met His Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Tyr Met Ser Tyr Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val
    50                  55                  60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Val His Val Gly Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Val Leu Thr Gln Ser
    130                 135                 140

Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys
145                 150                 155                 160

Arg Ala Ser Gln Asn Ile Asn Asn Asn Leu His Trp Phe Gln Gln Lys
                165                 170                 175

Pro Gly Gln Ala Pro Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile
            180                 185                 190

Ser Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        195                 200                 205
```

```
Thr Leu Thr Ile Ser Ser Leu Glu Thr Glu Asp Phe Ala Val Tyr Phe
    210                 215                 220


Cys Gln Gln Ser Asn Ser Trp Pro Ala Leu Thr Phe Gly Gln Gly Thr
225                 230                 235                 240


Lys Val Glu Ile Lys
                245


<210>  167
<211>  240
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F17-L2(G4S)3H1

<400>  167

Glu Val Val Leu 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 Asn Ile Asn Asn Asn
            20                  25                  30


Leu His Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45


Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60


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


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


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


Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
        115                 120                 125
```

```
Glu Thr Gly Gly Gly Leu Ile Gln Pro Gly Gly Ser Leu Arg Leu Ser
    130                 135                 140

Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe Gly Met His Trp Ile
145                 150                 155                 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Tyr Met Ser Tyr
                165                 170                 175

Thr Pro Gly Thr Phe His Tyr Ala Asp Thr Val Lys Asp Arg Phe Thr
            180                 185                 190

Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
        195                 200                 205

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Val His Val
    210                 215                 220

Gly Thr Val Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225                 230                 235                 240
```

<210> 168
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-H1(G4S)3L3

<400> 168

```
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 Ala Ser Tyr
            20                  25                  30

Tyr Leu Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60
```

```
Lys Ser Arg Ala Thr Val 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


Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125


Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
    130                 135                 140


Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys
145                 150                 155                 160


Ala Gly Glu Asn Val Gly Ser Tyr Val Ser Trp Tyr Gln Gln Lys Pro
                165                 170                 175


Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala Ser Asn Arg Tyr Thr
            180                 185                 190


Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Ala Thr Glu Phe Thr
        195                 200                 205


Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220


Gly Gln Thr Tyr Arg Phe Leu Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240


Val Lys
```

<210> 169
<211> 247
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-H1(G4S)4L3

<400> 169

```
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 Ala Ser Tyr
            20                  25                  30


Tyr Leu Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Asn Pro Arg Ser Gly Gly Thr Asn Phe Asn Glu Lys Phe
    50                  55                  60


Lys Ser Arg Ala Thr Val 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


Ser Arg Ser Gly Arg Leu Arg Gly Phe Tyr Thr Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125


Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln
    130                 135                 140


Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val
145                 150                 155                 160


Thr Ile Thr Cys Lys Ala Gly Glu Asn Val Gly Ser Tyr Val Ser Trp
                165                 170                 175


Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly Ala
            180                 185                 190


Ser Asn Arg Tyr Thr Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser
```

```
        195                 200                 205

Ala Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe
    210                 215                 220

Ala Thr Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr Phe Gly Gln
225                 230                 235                 240

Gly Thr Lys Val Glu Val Lys
                245
```

<210> 170
<211> 242
<212> PRT
<213> Artificial Sequence

<220>
<223> F20-L3(G4S)3H1

<400> 170

```
Asp Ile 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 Lys Ala Gly Glu Asn Val Gly Ser Tyr
            20                  25                  30

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

Tyr Gly Ala Ser Asn Arg Tyr Thr Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Ala Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gly Gln Thr Tyr Arg Phe Leu Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Val Glu Val Lys Gly Gly Gly Gly Ser Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser
```

```
        115                 120                 125

Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys
    130                 135                 140

Ala Ser Gly Tyr Thr Phe Ala Ser Tyr Tyr Leu Tyr Trp Val Arg Gln
145                 150                 155                 160

Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Glu Ile Asn Pro Arg Ser
                165                 170                 175

Gly Gly Thr Asn Phe Asn Glu Lys Phe Lys Ser Arg Ala Thr Val Thr
            180                 185                 190

Val Asp Lys Ser Thr Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
        195                 200                 205

Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Ser Gly Arg Leu Arg
    210                 215                 220

Gly Phe Tyr Thr Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
225                 230                 235                 240

Ser Ser
```

<210> 171
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-H4 Heavy Chain Variable Region

<400> 171

```
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Thr Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
```

```
        35                  40                  45

Ala Ala Ile Ser Gly Gly Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
            100                 105                 110

Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210>  172
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F8-H5 Heavy Chain Variable Region

<400>  172

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Thr Tyr
            20                  25                  30

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

Ala Ala Ile Ser Gly Gly Gly Gly Asp Thr Tyr His Leu Asp Ser Val
    50                  55                  60

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

Leu Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
```

85 90 95

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 173
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-H6 Heavy Chain Variable Region

<400> 173

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Thr Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Gly Gly Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gln Ser His Tyr Gly Ser Ser Tyr Tyr Phe Asp Asn Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 174

<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H4 Heavy Chain Variable Region

<400> 174

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 Phe Thr Phe Ser Asp Tyr
20 25 30

Trp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala His Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Asp 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 Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 175
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H5 Heavy Chain Variable Region

<400> 175

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 Asp Tyr
            20                  25                  30


Trp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala His Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Asp Tyr Ala Asp
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Lys 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 Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  176
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F19-H6 Heavy Chain Variable Region

<400>  176

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30


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


Ala Val Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr 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 Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210>  177
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F19-H7 Heavy Chain Variable Region

<400>  177

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 Asp Tyr
            20                  25                  30


Trp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala His Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Asp Tyr Ala Asp
    50                  55                  60


Ser Val Lys Gly Arg Phe Thr Ile Ser Lys 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 Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 178
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H8 Heavy Chain Variable Region

<400> 178

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

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

Ala Val Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr Tyr Thr 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 Thr Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
100 105 110

Lys Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 179
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H9 Heavy Chain Variable Region

<400> 179

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

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

Ala Val Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr Tyr Thr Asp
50 55 60

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

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
100 105 110

Lys Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 180
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H10 Heavy Chain Variable Region

<400> 180

Gln 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 Phe Thr Phe Ser Asp Tyr
20 25 30

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

```
        35                  40                  45

Ala Ser Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr 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 Phe Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  181
<211>  121
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F19-H11 Heavy Chain Variable Region

<400>  181

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

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

Ala Phe Ile Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr Tyr Ala Asp
    50                  55                  60

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

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
```

85 90 95

Tyr Cys Thr Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 182
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-H12 Heavy Chain Variable Region

<400> 182

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 Asp 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 Gly Asn Lys Phe His Asn Tyr Glu Thr Tyr Tyr Ser Asp
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Lys 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 Lys Leu Gly Arg Gly Tyr Tyr Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 183

<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H5 Heavy Chain Variable Region

<400> 183

Gln Val Glu Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Asp Cys Lys Val Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

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

Ala Val Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 184
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-H6 Heavy Chain Variable Region

<400> 184

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Lys Val Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30


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


Ala Val Ile Ser Ser Gly Gly Ser Tyr Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60


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


Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95


Ser Thr Gln Gly Ser Ser Gly Tyr Val Gly Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  185
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  F8-L4 Light Chain Variable Region

<400>  185

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 Val Ser Glu Asn Ile Asp Ser Tyr
            20                  25                  30


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


Tyr Ala Ala Thr Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

Ser Gly Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Asp Gly Thr Lys Val Glu Ile Lys
100 105

<210> 186
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F8-L5 Light Chain Variable Region

<400> 186

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 Val Ser Glu Asn Ile Asp Ser Tyr
20 25 30

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

Tyr Ala Ala Thr Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Asp Gly Thr Lys Val Glu Ile Lys
100 105

<210> 187
<211> 107
<212> PRT

<213> Artificial Sequence

<220>
<223> F8-L6 Light Chain Variable Region

<400> 187

Asp Ile 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 Val Ser Glu Asn Ile Asp Ser Tyr
20 25 30

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

Tyr Ala Ala Thr Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Ser Glu Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln His Tyr Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 188
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L3 Light Chain Variable Region

<400> 188

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 Thr Asn His
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Phe Lys Leu Leu Ile

```
        35                  40                  45

Tyr Tyr Thr Ser Ser Arg Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 189
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L4 Light Chain Variable Region

<400> 189

```
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 Thr Asn His
            20                  25                  30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Phe Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys
```

100 105

<210> 190
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L5 Light Chain Variable Region

<400> 190

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 Thr Asn His
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Phe Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 191
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L8 Light Chain Variable Region

<400> 191

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 Thr Asn His
            20                  25                  30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Phe Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 192
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L9 Light Chain Variable Region

<400> 192

```
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 Thr Asn His
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
```

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 193
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L10 Light Chain Variable Region

<400> 193

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 Asp Ile Thr Asn His
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Phe Arg Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 194
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> F19-L11 Light Chain Variable Region

<400> 194

Glu Ile Val Leu 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 Asp Ile Thr Asn His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro 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 Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 195
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L3 Light Chain Variable Region

<400> 195

Ala 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 Thr Asn Phe
20 25 30

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

Ser Tyr Thr Ser Val 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 Leu Gln Tyr Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 196
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L4 Light Chain Variable Region

<400> 196

Glu Ile Val Met Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Thr Asn Phe
20 25 30

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

Ser Tyr Thr Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Arg Asp Tyr Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Ala Tyr Tyr Cys Leu Gln Tyr Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> 197

<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L5 Light Chain Variable Region

<400> 197

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 Asp Ile Thr Asn Phe
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Tyr Tyr Asn Leu Trp Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 198
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> F5-L6 Light Chain Variable Region

<400> 198

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 Asp Ile Thr Asn Phe
20 25 30

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


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


Ser Gly 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 Leu Gln Tyr Tyr Asn Leu Trp Thr
                85                  90                  95


Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```