(12) STANDARD PATENT (11) Application No. **AU 2018208191 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Anti-GPC3 antibody

(51) International Patent Classification(s)
C12N 15/09 (2006.01) ***C12N 1/21*** (2006.01)
C07K 16/18 (2006.01) ***C12N 5/10*** (2006.01)
C12N 1/15 (2006.01) ***G01N 33/574*** (2006.01)
C12N 1/19 (2006.01) *C12P 21/08* (2006.01)

(21) Application No: **2018208191** (22) Date of Filing: **2018.01.10**

(87) WIPO No: **WO18/131586**

(30) Priority Data

(31) Number	(32) Date	(33) Country
2017-001732	**2017.01.10**	**JP**

(43) Publication Date: **2018.07.19**
(44) Accepted Journal Date: **2024.09.12**

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(56) Related Art
WO 2016/049459 A1
EP 2995682 A1
WO 2013/070468 A1
WO 2016/036973 A1
WENPENG LI ET AL, HUMAN GENE THERAPY, vol. 28, no. 5, 16 August 2016 (2016-08-16), GB, pages 437 - 448, XP055711940, ISSN: 1043-0342, DOI: 10.1089/hum.2016.025

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2018年7月19日(19.07.2018)

WIPO | PCT

(10) 国際公開番号
WO 2018/131586 A1

(51) 国際特許分類:
C12N 15/09 (2006.01) *C12N 1/21* (2006.01)
C07K 16/18 (2006.01) *C12N 5/10* (2006.01)
C12N 1/15 (2006.01) *G01N 33/574* (2006.01)
C12N 1/19 (2006.01) *C12P 21/08* (2006.01)

(21) 国際出願番号： PCT/JP2018/000257

(22) 国際出願日： 2018年1月10日(10.01.2018)

(25) 国際出願の言語： 日本語

(26) 国際公開の言語： 日本語

(30) 優先権データ：
特願 2017-001732 2017年1月10日(10.01.2017) JP

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(81) 指定国(表示のない限り、全ての種類の国内保護が可能): 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,

(54) **Title:** ANTI-GPC3 ANTIBODY

(54) 発明の名称： 抗ＧＰＣ３抗体

(57) **Abstract:** The present invention addresses the problem of providing: an anti-GPC3 antibody that recognizes an epitope different from those recognized by existing antibodies (e.g., GC33 and GC199), and that can specifically bind to GPC3 localized on a cell membrane even as a single-chain antibody; a CAR including said anti-GPC3 single-chain antibody; an immunocompetent cell expressing said CAR; an anti-GPC3 antibody gene or CAR gene; a vector including said anti-GPC3 antibody gene or CAR gene; a host cell into which said vector has been introduced; a method for specifically detecting GPC3; and a kit for specifically detecting GPC3. This antibody includes the specific heavy-chain CDRs 1-3 and the specific light-chain CDRs 1-3 defined in claim 1, and specifically binds to a human-derived GPC3 polypeptide. This antibody specifically binds to GPC3 localized on a cell membrane. A CAR-immunocompetent cell prepared from a CAR including said single-chain antibody is useful in cancer immunotherapy.

(57) 要約：本発明は、既存の抗体（例えば、ＧＣ３３、ＧＣ１９９）とは異なるエピトープを認識し、かつ一本鎖抗体の状態でも細胞膜に局在するＧＰＣ３に特異的に結合できる抗ＧＰＣ３抗体；かかる抗ＧＰＣ３一本鎖抗体を含むＣＡＲ；かかるＣＡＲを発現する免疫担当細胞；上記抗ＧＰＣ３抗体遺伝子又はＣＡＲ遺伝子；かかる抗ＧＰＣ３抗体遺伝子又はＣＡＲ遺伝子を含むベクター；かかるベクターが導入された宿主細胞；ＧＰＣ３を特異的に検出する方法；及びＧＰＣ３を特異的に検出するためのキット；を提供することを課題とする。 請求項１に定義されている特定の重鎖ＣＤＲ１～３と、特定の軽鎖ＣＤＲ１～３とを含み、かつヒト由来ＧＰＣ３ポリペプチドに特異的に結合する抗体は、細胞膜に局在するＧＰＣ３に特異的に結合する。かかる一本鎖抗体を含むＣＡＲを基に作製したＣＡＲ－免疫担当細胞は、がん免疫療法に有用である。

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［続葉有］

SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) 指定国(表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, RU, TJ, TM), ヨーロッパ (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).

添付公開書類:

— 国際調査報告(条約第21条(3))

— 明細書の別個の部分として表した配列リスト(規則5.2(a))

Description

ANTI-GPC3 ANTIBODY

Technical Field

[0001] The present invention relates to: an antibody specifically binding to GPC3 (glypican-3) (anti-GPC3 antibody); a chimeric antigen receptor (hereinafter, also referred to as "CAR") comprising anti-GPC3 single chain antibody, a transmembrane region fused with a carboxyl (C) terminus of the anti-GPC3 single chain antibody, and an immunocompetent cell activation signal transduction region fused with a C terminus of the transmembrane region; an immunocompetent cell expressing the CAR; an anti-GPC3 antibody gene or a CAR gene; a vector comprising the anti-GPC3 antibody gene or the CAR gene; a host cell in which the vector has been introduced; a method for detecting GPC3; and a kit for detecting GPC3.

Background Art

[0002] Glypican-3 (GPC3) is an extracellular matrix protein that is expressed in embryonic tissues, particularly, the liver or the kidney, and associated with organogenesis. The expression of GPC3 is not observed in human adult tissues except for placenta, but is observed in tissues of various cancers such as hepatocellular carcinoma, melanoma, ovarian clear cell adenocarcinoma, and lung squamous cell carcinoma. Thus, GPC3 is a protein that is expressed in embryonic tissues, as in proteins such as α-fetoprotein (AFP) and carcinoembryonic antigen (CEA), and is therefore classified into embryonal carcinoma

antigens. Specifically, GPC3 is useful as a target molecule of cancer treatment, a tumor marker and a diagnostic marker, because its feature is that the protein is not expressed in normal tissue cells, but is specifically expressed in cancer cells.

[0003] GPC3 is a member of the proteoglycan family that functions as extracellular matrix in cell adhesion in organogenesis or as a receptor of a cell growth factor. A GPI (glycosylphosphatidylinositol) anchor is added to serine at position 560 located on the carboxyl (C)-terminal side of GPC3. The GPI anchor plays a role in localizing GPC3 on cell surface through covalent binding to cell membrane lipid. Also, serine at position 495 and serine at position 509 of GPC3 are modified with a heparan sulfate chain (HS chain). The HS chain is known to regulate a plurality of growth signal transduction pathways such as Wnt signal, FGF signal, and BMP signal transduction pathways. A growth signal transduction pathway involved is known to differ among the types of cancers. For example, in hepatocellular carcinoma (HCC), cells grow by the stimulation of the Wnt signal pathway. A common feature of the glypican family is the number of cysteine as abundant as 16 in an extracellular region, and these cysteine residues are considered to contribute to the stable formation of a conformation by forming a plurality of intramolecular disulfide bonds. The possibility has been reported that GPC3 on cell membrane surface is cleaved between arginine (R) at position 358 and serine (S) at position 359 (R358/S359) by furin convertase. However, since an amino (N)-terminal subunit of GPC3 is cross-linked through

intramolecular disulfide bonds, GPC3, even when cleaved into two subunits, an N-terminal subunit and a C-terminal subunit, by furin convertase may probably retain its full-length structure without dissociating these subunits. The structure of soluble GPC3 remains a controversial subject. Thus, there are many unclear points as to the conformation of GPC3 localized on a cell membrane, also including the structures of isoforms of GPC3.

[0004] GPC3 on a cell membrane has a complicated structure. Therefore, for preparing an antibody against GPC3, it has been considered desirable that the simplest structural region is an epitope. A representative existing anti-GPC3 antibody includes a monoclonal antibody 1G12 which is distributed by BioMosaics, Inc. This antibody is an antibody obtained by immunizing Balb/c mice with an antigen (C-terminal 70-residue polypeptide of GPC3) designed so as to circumvent the complicated structure or localization of GPC3, to prepare hybridomas, and screening the hybridomas using the antigen. Antibodies GC33 and GC199 developed by a Japanese pharmaceutical manufacturer are also monoclonal antibodies established on the basis of the same concept as above and are antibodies obtained with the C-terminal partial fragment of GPC3 as an antigen (patent document 1).

[0004a] It is to be understood that if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art in Australia or any other country.

Prior Art Document

Patent Document

[0005] Patent document 1: Japanese Patent No. 4011100

Summary of the Invention

Object to be Solved by the Invention

[0006] An object of the present invention is to provide: an anti-GPC3 antibody that recognizes an epitope different from that for existing antibodies (e.g., GC33 and GC199) and can specifically bind, even in the form of single chain antibody, to GPC3 localized on a cell membrane; CAR comprising the anti-GPC3 single chain antibody; an immunocompetent cell expressing the CAR; a gene of the anti-GPC3 antibody or a gene of the CAR; a vector comprising the anti-GPC3 antibody gene or the CAR gene; a host cell in which the vector has been introduced; a method for specifically detecting GPC3; and a kit for specifically detecting GPC3.

Means to Solve the Object

[0007] The present inventors are continuing diligent studies to attain the object. In the course of the studies, the present inventors have prepared a novel anti-GPC3 antibody by a phage display method which is an approach different from conventional monoclonal antibody preparation methods involving establishing hybridomas. Specifically, an immune library of antibody genes was synthesized using B cells derived from mice immunized with full-length human GPC3, and the genes were reconstituted into a single chain antibody (scFv) library, which was then incorporated into a phage display and expressed on phage surface, followed by biopanning using recombinant full-length human GPC3 and the GPC3-expressing cell line, and further, if necessary, a competitor C-terminal polypeptide of GPC3

serving as an epitope for the existing antibodies, to prepare an anti-GPC3 antibody. The prepared anti-GPC3 antibody has also been confirmed to be useful for cancer immunotherapy using T cells expressing a chimeric antigen receptor (CAR) (hereinafter, also referred to as "CAR-T cells"). The present invention has been completed on the basis of these findings.

[0008] Specifically, the present invention is as follows.

[1] An antibody specifically binding to a human GPC3 (glypican-3)-derived polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155 (hereinafter, also referred to as the "present antibody"), wherein the antibody

(1-1) comprises a heavy chain complementarity determining region (CDR) 1 consisting of the amino acid sequence represented by SEQ ID NO: 1, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 2, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 3, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 4, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 5, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 6; or

(2-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 11, a heavy chain CDR2 consisting of the amino acid

sequence represented by SEQ ID NO: 12, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 13, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 14, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 15, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 16; or

(3-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 21, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 22, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 23, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 24, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 25, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 26; or

(4-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 31, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 32, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 33, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 34, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID

NO: 35, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 36; or

(5-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 41, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 42, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 43, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 44, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 45, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 46; or

(6-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 51, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 52, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 53, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 54, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 55, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 56; or

(7-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 61, a heavy chain CDR2 consisting of the amino acid

sequence represented by SEQ ID NO: 62, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 63, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 64, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 65, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 66; or

(8-1) comprises heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 71, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 72, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 73, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 74, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 75, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 76; or

(9-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 81, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 82, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 83, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 84, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID

NO: 85, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 86; or

(10-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 91, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 92, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 93, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 94, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 95, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 96; or

(11-1) comprises a heavy chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 101, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 102, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 103, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 104, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 105, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 106.

[2] The antibody according to [1], wherein the antibody

(1-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 7, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 8; or

(2-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 17, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 18; or

(3-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 27, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 28; or

(4-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 37, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 38; or

(5-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 47, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 48; or

(6-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 57, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 58; or

(7-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 67, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 68; or

(8-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 77, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 78; or

(9-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 87, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 88; or

(10-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 97, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 98; or

(11-2) comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 107, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 108.

[3] The antibody according to [1] or [2], wherein the antibody is single chain antibody.

[4] The antibody according to [3], wherein the single chain antibody

(1-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 165; or

(2-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 166; or

(3-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 167; or

(4-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 168; or

(5-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 169; or

(6-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 170; or

(7-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 171; or

(8-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 172; or

(9-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 173; or

(10-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 174; or

(11-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 175.

[5] The antibody according to [3], wherein the single chain antibody

(1-3'-1) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 178; or

(1-3'-2) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 179; or

(1-3'-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 180; or

(2-3'-1) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 181; or

(2-3'-2) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 182; or

(2-3'-3) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 183; or

(2-3'-4) comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 184.

[6] The antibody according to [1] or [2], wherein the antibody

(1-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 9, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 10; or

(2-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 19, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 20; or

(3-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 29, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 30; or

(4-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 39, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 40; or

(5-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 49, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 50; or

(6-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 59, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 60; or

(7-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 69, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 70; or

(8-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 79, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 80; or

(9-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 89, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 90; or

(10-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 99, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 100; or

(11-4) comprises a heavy chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 109, and a light chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 110.

[7] CAR comprising the antibody according to any one of [3] to [5] (hereinafter, also referred to as the "present single chain antibody"), a transmembrane region fused with a carboxyl terminus of the present single chain antibody, and an immunocompetent cell activation signal transduction region fused with a carboxyl terminus of the transmembrane region (hereinafter, also referred to as the "present CAR").

[8] The CAR according to [7], comprising the amino acid sequence represented by any of SEQ ID NOs: 185 to 187.

[9] An immunocompetent cell expressing the CAR according to [7] or [8] (hereinafter, also referred to as the "present immunocompetent cell").

[10] The immunocompetent cell according to [9], further expressing interleukin 7 (IL-7) and chemokine ligand 19 (CCL19).

[11] An antibody gene encoding the antibody according to any one of [1] to [6] (hereinafter, also referred to as the "present antibody gene"), or a CAR gene encoding the CAR according to [7] or [8] (hereinafter, also referred to as the "present CAR gene").

[12] An antibody gene encoding the antibody according to any one of [1] to [4] and [6].

[13] A vector comprising a promoter, and the antibody gene according to [11] or the CAR gene encoding the CAR according to [11] operably linked downstream of the promoter (hereinafter, also referred to as the "present vector").

[14] A vector comprising a promoter, and the antibody gene according to [12] operably linked downstream of the promoter.

[15] A host cell in which the vector according to [13] or [14] has been introduced (hereinafter, also referred to as the "present host cell").

[16] A method for detecting GPC3 (glypican-3), comprising the step of detecting GPC3 using the antibody according to any one of [1] to [6] (hereinafter, also referred to as the "present detection method").

[17] A kit for the detection of GPC3 (glypican-3), comprising the antibody according to any one of [1] to [6], or a labeled form thereof (hereinafter, also referred to as the "present kit for detection").

[0009] Examples of other embodiments of the present invention can include the present antibody for use in the detection of GPC3, and a method for producing the present antibody, comprising the steps of: immunizing nonhuman animals (e.g., mice and rats) with full-length human GPC3 consisting of the amino acid sequence represented by SEQ ID NO: 157; synthesizing cDNA by reverse transcription reaction from total RNA of B cells derived from the immunized nonhuman animals, and amplifying antibody genes to prepare an antibody gene library; and constructing a scFv phage library from the antibody gene library, and infecting *E. coli* with the library so that cells express scFv, followed by biopanning using the full-length human GPC3 and the GPC3-expressing cell line, and further, if necessary, a competitor C-terminal polypeptide of GPC3 (human-derived GPC3 polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 156).

Effect of the Invention

[0010] The present antibody is an antibody specifically binding to GPC3 localized on a cell membrane not only in the form of IgG but in the form of scFv. CAR-T cells using the present antibody as scFv in CAR have excellent cytotoxic activity and the ability to produce IFN-γ. Hence, the present antibody is useful for cancer immunotherapy.

Brief Description of Drawings

[0011] [Figure 1] Figure 1 is a diagram showing each round (step) of biopanning consisting of 5 types of series (A to E series). A series involves performing 3 rounds of biopanning with recombinant GPC3 immobilized on magnetic beads as a bait, and performing biopanning in rounds 4 and 5 with a GPC3-expressing cell line as a bait (round 5 was carried out only for 1413 #3). In rounds 1 to 4, existing anti-GPC3 antibodies (GC33 and GC199) were added as competitive antibodies. B series involves performing biopanning with GPC3-expressing cells as a bait in the presence of the competitive antibodies after round 2 of A series. E series involves performing biopanning with recombinant GPC3 immobilized on magnetic beads as a bait under conditions of no competitive antibody after round 3 of A series. In C series, 4 rounds in total of biopanning with a GPC3-expressing cell line as a bait in 2 rounds and recombinant GPC3 immobilized on magnetic beads as a bait in 2 rounds were performed in the absence of the competitive

antibodies. D series involves performing the same biopanning as that of A series in the absence of the competitive antibodies.

[Figure 2] Figure 2 is a diagram showing results of performing flow cytometry (FCM) using 18 types of anti-GPC3 scFv clones (TF1413-02d023, 02d028, 02d030, 02d039, 02e003, 02e004, 02e014, 02e030, 02e040, 03e001, 03e004, 03e005, 03e015, 03e016, 03e019, 03e027, 03e034, and 03e045) and existing anti-GPC3 antibodies (GC33 and GC199), and 3 types of cell lines (GPC3 N-terminal fragment-expressing cell line, GPC3 C-terminal fragment-expressing cell line, and GPC3 [full-length]-expressing cell line). The numeric values in the diagram are indicated by relative values when the fluorescence intensity of a cell line expressing no GPC3 (SK-Hep-1 cell line) was defined as 1 in FCM.

[Figure 3] Figure 3 is a diagram showing results of performing FCM using IgG antibodies prepared from 11 types of scFv clones (TF1413-02d028, 02d039, 02e004, 02e014, 02e030, 02e040, 03e001, 03e004, 03e005, 03e015, and 03e034) and existing anti-GPC3 antibodies (GC33 and GC199), and 3 types of cell lines (GPC3 N-terminal fragment-expressing cell line, GPC3 C-terminal fragment-expressing cell line, and GPC3 [full-length]-expressing cell line).

[Figure 4] Figure 4 is a diagram showing results of performing FACS (fluorescence activated cell sorting) using a GPC3-expressing cell line treated with 3 types of methods (EDTA, trypsin, and "EDTA + collagenase"), 3 types of antibody combinations (anti-mouse IgG antibody labeled with APC [hereinafter, also referred to as "APC ant-mouse IgG

antibody"], and a combination of the APC anti-mouse IgG antibody and a scFv clone [TF1413-02d028] antibody).

[Figure 5] Figure 5 is a diagram showing results of analyzing GPC3 CAR-T cells (T cells expressing CAR of scFv recognizing GPC3) derived from 5 types of scFv clones (TF1413-02d028, TF1413-02d039, TF1413-02e014, TF1413-02e030, and TF1413-03e005) for cytotoxic activity against a Sk-HEP-1 GPC3 cell line. In each graph, the right peak depicts CD45-positive cells (GPC3 CAR-T cells), and the left peak depicts CD45-negative cells (residual cancer cells [Sk-HEP-1 GPC3 cells]). The ordinate of each graph depicts the number of cells. The numeric value in each graph depicts the ratio (%) of the number of CD45-positive cells to the total number of cells (CD45-positive cells and CD45-negative cells). T cells expressing no GPC3 CAR ("Non infection" in the diagram) were used as a control.

[Figure 6] Figure 6 is a graph showing the ratio of CD45-negative cells in Figure 5 (Figure 6A) and the number of CD45-negative cells (Figure 6B). In a pair of bar graphs, the left bar graph depicts "mock" (Sk-HEP-1 mock cell line), and the right bar graph depicts "GPC3" (Sk-HEP-1 GPC3 cell line).

[Figure 7] Figure 7 is a diagram showing results of analyzing GPC3 CAR-T cells derived from 5 types of scFv clones (TF1413-02d028, TF1413-02d039, TF1413-02e014, TF1413-02e030, and TF1413-03e005) for the ability to produce IFN-γ against a Sk-HEP-1 GPC3

cell line. T cells expressing no GPC3 CAR ("Non infection" in the diagram) were used as a control.

Mode of Carrying Out the Invention

[0012] The present antibody is an antibody comprising the heavy (H) chain and light (L) chain CDR1 to CDR3 described above in any of (1-1) to (11-1), and specifically binding to, as an epitope, at least a portion (usually within the range of 3 to 30 amino acid residues, preferably 4 to 20 amino acid residues, more preferably 5 to 15 amino acid residues) of a human-derived GPC3 polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155 (amino [N]-terminal polypeptide consisting of amino acid residues 32 to 471 [exons 1 to 7] of human-derived full-length GPC3 consisting of the amino acid sequence represented by SEQ ID NO: 157). This antibody specifically binds not only in the form of IgG but in the form of scFv to GPC3 localized on a cell membrane, and usually comprises a H chain variable region comprising the H chain CDR1 to CDR3 described above in any of (1-1) to (11-1), and a L chain variable region comprising the L chain CDR1 to CDR3 described above in any of (1-1) to (11-1). In this context, the phrase "specifically binding" means that the antibody recognizes and binds to the polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155 through a recognition mechanism with high antigen-antibody specificity. Thus, the present antibody does not specifically bind to a human-derived GPC3 polypeptide consisting of the amino acid sequence

represented by SEQ ID NO: 156 (carboxyl [C]-terminal polypeptide consisting of amino acid residues 472 to 580 [exons 8 and 9] of human-derived full-length GPC3 consisting of the amino acid sequence represented by SEQ ID NO: 157).

[0013] The present antibody is not particularly limited by its origin, type, class, morphology, etc. The present antibody includes, for example: a human-derived antibody; an antibody derived from a nonhuman animal such as a mouse or a rat; a polyclonal antibody, an oligoclonal antibody (mixture of several to several tens of antibodies), and a monoclonal antibody; and a chimeric antibody or a humanized antibody in which a partial region (e.g., constant regions) of an antibody has been substituted by a region derived from a different organism species, an antibody fragment such as a $F(ab')_2$ antibody fragment obtained by digesting a monoclonal antibody with pepsin, a Fab' antibody fragment obtained by reducing a $F(ab')_2$ antibody fragment, and Fab obtained by digesting a monoclonal antibody with papain, and a recombinant antibody such as scFv containing an antibody heavy (H) chain variable region and an antibody light (H) chain variable region linked through amino acid cross-links. In the case of using the present antibody as CAR, scFv is preferred.

[0014] The present antibody is preferably in a separated form. In this context, the term "separated" means that the antibody is present in a state different from the state where the antibody is originally present in such a way that the antibody is taken out of an environment

originally involving the antibody or expressed in an environment different from the environment originally involving the antibody by an artificial operation. Specifically, the "separated antibody" does not include an antibody that is derived from a certain individual and is in a state contained in the body of the individual without an external operation (artificial operation) or in a tissue or a body fluid (blood, plasma, serum, etc.) derived from the body. The present antibody is preferably an antibody prepared by an artificial operation (e.g., the recombinant antibody described above). Such an "antibody derived from a cell prepared by an artificial operation or an antibody produced from the cell" does not include an antibody that is not subjected to an artificial operation, for example, an antibody produced from a naturally occurring B cell.

[0015] In the present antibody, a framework region (FR) is usually linked to the N terminus and/or C terminus of each of H chain and L chain CDR1 to CDR3 regions. Among such FRs, examples of the H chain FRs can include H chain FR1 linked to the N terminus of H chain CDR1, H chain FR2 linked to the C terminus of H chain CDR1 (N terminus of H chain CDR2), H chain FR3 linked to the C terminus of H chain CDR2 (N terminus of H chain CDR3), and H chain FR4 linked to the C terminus of H chain CDR3. Among the FRs, examples of the L chain FRs can include L chain FR1 linked to the N terminus of L chain CDR1, L chain FR2 linked to the C terminus of L chain CDR1 (N terminus of L chain CDR2),

L chain FR3 linked to the C terminus of L chain CDR2 (N terminus of L chain CDR3), and L chain FR4 linked to the C terminus of L chain CDR3.

[0016] Examples of the H chain FR1 can specifically include: (1-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 7, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 17, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 27, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 37, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 47, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-HFR1) a polypeptide consisting of amino acid residues

1 to 30 of the amino acid sequence represented by SEQ ID NO: 57, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 67, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 77, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 87, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 97, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-HFR1) a polypeptide consisting of amino acid residues 1 to 30 of the amino acid sequence represented by SEQ ID NO: 107, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0017] Examples of the H chain FR2 can specifically include: (1-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 7, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 17, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 27, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 37, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 47, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 57, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-HFR2) a polypeptide

consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 67, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 77, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 87, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 97, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-HFR2) a polypeptide consisting of amino acid residues 36 to 49 of the amino acid sequence represented by SEQ ID NO: 107, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0018] Examples of the H chain FR3 can specifically include: (1-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 7, or a polypeptide consisting of an amino acid sequence having at least 80% or

higher sequence identity to the amino acid sequence of the polypeptide; (2-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 17, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 27, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-HFR3) a polypeptide consisting of amino acid residues 67 to 99 of the amino acid sequence represented by SEQ ID NO: 37, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-HFR3) a polypeptide consisting of amino acid residues 67 to 99 of the amino acid sequence represented by SEQ ID NO: 47, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 57, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 67, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-HFR3) a

polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 77, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-HFR3) a polypeptide consisting of amino acid residues 67 to 99 of the amino acid sequence represented by SEQ ID NO: 87, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 97, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-HFR3) a polypeptide consisting of amino acid residues 67 to 98 of the amino acid sequence represented by SEQ ID NO: 107, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0019] Examples of the H chain FR4 can specifically include: (1-HFR4) a polypeptide consisting of amino acid residues 109 to 118 of the amino acid sequence represented by SEQ ID NO: 7, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-HFR4) a polypeptide consisting of amino acid residues 108 to 117 of the amino acid sequence represented by SEQ ID NO: 17, or a polypeptide consisting of an amino acid sequence

having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-HFR4) a polypeptide consisting of amino acid residues 106 to 115 of the amino acid sequence represented by SEQ ID NO: 27, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-HFR4) a polypeptide consisting of amino acid residues 111 to 120 of the amino acid sequence represented by SEQ ID NO: 37, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-HFR4) a polypeptide consisting of amino acid residues 108 to 117 of the amino acid sequence represented by SEQ ID NO: 47, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-HFR4) a polypeptide consisting of amino acid residues 107 to 116 of the amino acid sequence represented by SEQ ID NO: 57, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-HFR4) a polypeptide consisting of amino acid residues 106 to 115 of the amino acid sequence represented by SEQ ID NO: 67, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-HFR4) a polypeptide consisting of amino acid residues 106 to 115 of the amino acid sequence represented by SEQ ID NO: 77, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the

polypeptide; (9-HFR4) a polypeptide consisting of amino acid residues 111 to 120 of the amino acid sequence represented by SEQ ID NO: 87, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-HFR4) a polypeptide consisting of amino acid residues 110 to 119 of the amino acid sequence represented by SEQ ID NO: 97, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-HFR4) a polypeptide consisting of amino acid residues 109 to 118 of the amino acid sequence represented by SEQ ID NO: 107, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0020] Examples of the L chain FR1 can specifically include: (1-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 8, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 18, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 28, or a polypeptide consisting of an amino acid

sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 38, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 48, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 58, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 68, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 78, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 88, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-LFR1) a

polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 98, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-LFR1) a polypeptide consisting of amino acid residues 1 to 23 of the amino acid sequence represented by SEQ ID NO: 108, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0021] Examples of the L chain FR2 can specifically include: (1-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 8, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-LFR2) a polypeptide consisting of amino acid residues 40 to 54 of the amino acid sequence represented by SEQ ID NO: 18, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 28, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 38, or a polypeptide consisting of an

amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-LFR2) a polypeptide consisting of amino acid residues 41 to 55 of the amino acid sequence represented by SEQ ID NO: 48, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 58, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 68, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 78, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 88, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 98, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid

sequence of the polypeptide; and (11-LFR2) a polypeptide consisting of amino acid residues 35 to 49 of the amino acid sequence represented by SEQ ID NO: 108, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0022] Examples of the L chain FR3 can specifically include: (1-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 8, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-LFR3) a polypeptide consisting of amino acid residues 62 to 93 of the amino acid sequence represented by SEQ ID NO: 18, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 28, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 38, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-LFR3) a polypeptide consisting of amino acid residues 63 to 94 of the amino acid sequence represented by SEQ ID NO: 48, or a polypeptide

consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 58, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 68, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 78, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 88, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 98, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-LFR3) a polypeptide consisting of amino acid residues 57 to 88 of the amino acid sequence represented by SEQ ID NO: 108, or a

polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0023] Examples of the L chain FR4 can specifically include: (1-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 8, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (2-LFR4) a polypeptide consisting of amino acid residues 103 to 113 of the amino acid sequence represented by SEQ ID NO: 18, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (3-LFR4) a polypeptide consisting of amino acid residues 97 to 107 of the amino acid sequence represented by SEQ ID NO: 28, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (4-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 38, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (5-LFR4) a polypeptide consisting of amino acid residues 104 to 114 of the amino acid sequence represented by SEQ ID NO: 48, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (6-LFR4) a polypeptide consisting of

amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 58, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (7-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 68, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (8-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 78, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (9-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 88, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; (10-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 98, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide; and (11-LFR4) a polypeptide consisting of amino acid residues 98 to 108 of the amino acid sequence represented by SEQ ID NO: 108, or a polypeptide consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence of the polypeptide.

[0024] The FRs of the present antibody are preferably FRs of a known human antibody. Examples of such "FRs of a known human antibody" can include FRs of a human antibody registered in a sequence database known in the art such as GenBank, and FRs selected from a common sequence (human most homologous consensus sequence; Kabat, E. A. et al., Sequences of Proteins of Immunological Interest, US Dept. Health and Human Services, 1991) derived from each subgroup of a human antibody.

[0025] The H chain CDR1 in the present antibody usually resides at positions H31 to H35 based on Kabat numbering (see the document "Kabat, E.A. et al., (1991) NIH Publication No. 91-3242, sequences of proteins of immunological interest"). The H chain CDR2 in the present antibody usually resides at positions H50 to H52, H52A, and H53 to H65 based on Kabat numbering. The H chain CDR3 in the present antibody usually resides at positions H95 to H100, H100A, H100B, H101, and H102 based on Kabat numbering. The L chain CDR1 in the present antibody usually resides at positions L24 to L34 based on Kabat numbering. The L chain CDR2 in the present antibody usually resides at positions L50 to L56 based on Kabat numbering. The L chain CDR3 in the present antibody usually resides at positions L89 to L97 based on Kabat numbering.

[0026] Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (1-1) as the present antibody can include an antibody comprising the H

chain and L chain variable (V) regions described above in (1-2) and can specifically include: the single chain antibody described above in (1-3); the single chain antibody described above in (1-3'-1), the single chain antibody described above in (1-3'-2), and the single chain antibody described above in (1-3'-3); and an antibody comprising the H chain and the L chain described above in (1-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (2-1) can include an antibody comprising the H chain and L chain V regions described above in (2-2) and can specifically include: the single chain antibody described above in (2-3); the single chain antibody described above in (2-3'-1), the single chain antibody described above in (2-3'-2), the single chain antibody described above in (2-3'-3), and the single chain antibody described above in (2-3'-4); and an antibody comprising the H chain and the L chain described above in (2-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (3-1) can include an antibody comprising the H chain and L chain V regions described above in (3-2) and can specifically include: the single chain antibody described above in (3-3); and an antibody comprising the H chain and the L chain described above in (3-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (4-1) can include an antibody comprising the H chain and L chain V regions described above in (4-2) and can specifically include: the single chain antibody described above in (4-3); and an antibody comprising the H chain and the L chain described above in (4-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (5-1)

can include an antibody comprising the H chain and L chain V regions described above in (5-2) and can specifically include: the single chain antibody described above in (5-3); and an antibody comprising the H chain and the L chain described above in (5-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (6-1) can include an antibody comprising the H chain and L chain V regions described above in (6-2) and can specifically include: the single chain antibody described above in (6-3); and an antibody comprising the H chain and the L chain described above in (6-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (7-1) can include an antibody comprising the H chain and L chain V regions described above in (7-2) and can specifically include: the single chain antibody described above in (7-3); and an antibody comprising the H chain and the L chain described above in (7-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (8-1) can include an antibody comprising the H chain and L chain V regions described above in (8-2) and can specifically include: the single chain antibody described above in (8-3); and an antibody comprising the H chain and the L chain described above in (8-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (9-1) can include an antibody comprising the H chain and L chain V regions described above in (9-2) and can specifically include: the single chain antibody described above in (9-3); and an antibody comprising the H chain and the L chain described above in (9-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (10-1)

can include an antibody comprising the H chain and L chain V regions described above in (10-2) and can specifically include: the single chain antibody described above in (10-3); and an antibody comprising the H chain and the L chain described above in (10-4). Examples of the antibody comprising the H chain and L chain CDR1 to CDR3 described above in (11-1) can include an antibody comprising the H chain and L chain V regions described above in (11-2) and can specifically include: the single chain antibody described above in (11-3); and an antibody comprising the H chain and the L chain described above in (11-4). The heavy chain variable region and the light chain variable region in the single chain antibody are usually bound via a peptide linker.

[0027] The present CAR can comprise the present single chain antibody, a transmembrane region fused with the C terminus of the present single chain antibody, and an immunocompetent cell activation signal transduction region fused with the C terminus of the transmembrane region. In this context, the fusion between the present single chain antibody and the transmembrane region, or between the transmembrane region and the immunocompetent cell activation signal transduction region may be mediated by a peptide linker or an IgG4 hinge region.

[0028] Examples of the length of the peptide linker in the present antibody can include 1 to 100 amino acid residues, preferably 10 to 50 amino acid residues. Examples of the

peptide linker in the present antibody can specifically include a consecutive linkage of 3 amino acid sequences each consisting of 1 to 4 glycine residues and 1 serine residue.

[0029] The transmembrane region can be any peptide that can penetrate a cell membrane. Examples thereof can include a transmembrane region derived from CD8, a T cell receptor α or β chain, CD3ζ, CD28, CD3ε, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, ICOS, CD154, EGFR (epidermal growth factor receptor), or GITR and can specifically include a human CD8 transmembrane region consisting of amino acid residues 1 to 83 of the amino acid sequence represented by SEQ ID NO: 185. Alternatively, the transmembrane region may be derived from a peptide that can penetrate cell membrane by the truncation of C-terminal 1 to 10 amino acid residues, preferably 6 or 7 amino acid residues. Examples thereof can include engineered form 1 of the human CD8 transmembrane region consisting of amino acid residues 1 to 77 of the amino acid sequence represented by SEQ ID NO: 186, and engineered form 2 of the human CD8 transmembrane region consisting of amino acid residues 1 to 76 of the amino acid sequence represented by SEQ ID NO: 187.

[0030] The immunocompetent cell activation signal transduction region can be any region capable of transducing a signal into immunocompetent cells upon binding of the present single chain antibody to human GPC3. The immunocompetent cell activation signal

transduction region preferably comprises at least one or more members selected from polypeptides of the intracellular regions of CD28, 4-1BB (CD137), GITR, CD27,OX40, HVEM, CD3ζ, and Fc receptor-associated γ chain, and more preferably comprises three polypeptides of the intracellular regions of CD28, 4-1BB, and CD3ζ. Examples of such a polypeptide of the intracellular region of CD28 can specifically include a polypeptide of the intracellular region of human CD28 consisting of amino acid residues 85 to 124 of the amino acid sequence represented by SEQ ID NO: 185. Examples of the "polypeptide of the intracellular region of 4-1BB" can specifically include a polypeptide of the intracellular region of human 4-1BB consisting of amino acid residues 125 to 170 of the amino acid sequence represented by SEQ ID NO: 185. Examples of the polypeptide of the intracellular region of CD3ζ can specifically include a polypeptide of the intracellular region of human CD3ζ consisting of amino acid residues 172 to 283 of the amino acid sequence represented by SEQ ID NO: 185.

[0031] Arginine (Arg) at position 84 of the amino acid sequence represented by SEQ ID NO: 185, arginine at position 78 of the amino acid sequence represented by SEQ ID NO: 186, and arginine at position 77 of the amino acid sequence represented by SEQ ID NO: 187 are a common sequence between the polypeptide of the transmembrane region derived from human CD8 and the polypeptide of the intracellular region of human CD28. Leucine (Leu) at position 171 of the amino acid sequence represented by SEQ ID NO: 185,

leucine at position 165 of the amino acid sequence represented by SEQ ID NO: 186, and leucine at position 164 of the amino acid sequence represented by SEQ ID NO: 187 are a common sequence between the polypeptide of the intracellular region of human 4-1BB and the polypeptide of the intracellular region of human CD3ζ.

[0032] In the present specification, the "immunocompetent cell" means a cell responsible for immune functions in a living body. Examples of the immunocompetent cell can include: a lymphoid cell such as a T cell, a natural killer cell (NK cell), and a B cell; an antigen-presenting cell such as a monocyte, a macrophage, and a dendritic cell; and a granulocyte such as a neutrophil, an eosinophil, a basophil, and a mast cell. Specific examples thereof can preferably include a T cell derived from a mammal such as a human, a dog, a cat, a pig, or a mouse, preferably a human-derived T cell. The T cell can be obtained by isolation or purification from an immunocompetent cell infiltrating a body fluid such as blood or bone marrow fluid, a tissue of the spleen, the thymus, lymph node or the like, or a cancer tissue of primary tumor, metastatic tumor, cancerous ascites or the like. Alternatively, a T cell prepared from an ES cell or an iPS cell may be utilized. Examples of such a T cell can include an alpha-beta T cell, a gamma-delta T cell, a $CD8^+$ T cell, a $CD4^+$ T cell, a tumor-infiltrating T cell, a memory T cell, a naive T cell, and a NKT cell. The origin of the immunocompetent cell may be the same as or different from an administration subject. When the administration subject is a human, an autologous cell collected from a patient as

the administration subject may be used as the immunocompetent cell, or any of other cells collected from a person other than the administration subject may be used as the immunocompetent cell. Specifically, the donor and the recipient may be the same or different and is preferably the same.

[0033] Examples of the administration subject can preferably include a mammal and a mammalian cell. Examples of the mammal can more preferably include a human, a mouse, a dog, a rat, a guinea pig, a rabbit, a bird, sheep, a pig, cattle, a horse, a cat, a monkey, and a chimpanzee, particularly preferably a human.

[0034] The present CAR is preferably used for *ex vivo* expression on the cell surface of the immunocompetent cell collected from a cancer patient in cancer treatment. In the case of using a T cell as the immunocompetent cell, examples of the peptide consisting of the transmembrane region and the immunocompetent cell activation signal transduction region fused with the C terminus of the transmembrane region in the present CAR can specifically include a peptide consisting of the amino acid sequence represented by any of SEQ ID NOs: 185 to 187. Examples of the present CAR can specifically include CAR comprising single chain antibody selected from the group consisting of the single chain antibody described above in (1-3), the single chain antibody described above in (2-3), the single chain antibody described above in (1-3'-1), the single chain antibody described above in (1-

3'-2), the single chain antibody described above in (1-3'-3), the single chain antibody described above in (2-3'-1), the single chain antibody described above in (2-3'-2), the single chain antibody described above in (2-3'-3), and the single chain antibody described above in (2-3'-4), and a peptide consisting of the amino acid sequence represented by any of SEQ ID NOs: 185 to 187, fused with the C terminus of the single chain antibody.

[0035] Specifically, examples of the present CAR can include

CAR comprising the single chain antibody described above in (1-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (1-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (1-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (1-3'-1), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (1-3'-1), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (1-3'-1), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (1-3'-2), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (1-3'-2), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (1-3'-2), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (1-3'-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (1-3'-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (1-3'-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (2-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (2-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (2-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (2-3'-1), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (2-3'-1), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (2-3'-1), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (2-3'-2), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (2-3'-2), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (2-3'-2), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (2-3'-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (2-3'-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186,

CAR comprising the single chain antibody described above in (2-3'-3), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187,

CAR comprising the single chain antibody described above in (2-3'-4), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 185,

CAR comprising the single chain antibody described above in (2-3'-4), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 186, and

CAR comprising the single chain antibody described above in (2-3'-4), and a peptide consisting of the amino acid sequence represented by SEQ ID NO: 187.

[0036] The present immunocompetent cell can be any immunocompetent cell expressing CAR. Since CAR usually does not occur naturally, the immunocompetent cell expresses foreign CAR, not endogenous CAR. The present immunocompetent cell preferably further expresses IL-7 and/or CCL19. When the immunocompetent cell is a cell found to not express IL-7 and/or CCL19, for example, a T cell, or when the immunocompetent cell is a cell, other than a T cell, low expressing IL-7 and/or CCL19, the present immunocompetent cell preferably expresses foreign IL-7 and/or CCL19.

[0037] The present immunocompetent cell can be prepared by introducing the present vector comprising the present CAR gene, and a vector comprising IL-7 and/or CCL19 gene to an immunocompetent cell. The introduction method can be any method for introducing DNA to mammalian cells. Examples thereof can include a method such as electroporation (Cytotechnology, 3, 133 (1990)), calcium phosphate method (Japanese unexamined Patent Application Publication No. 2-227075), lipofection (Proc. Natl. Acad. Sci. U.S.A., 84, 7413 (1987)), and viral infection method. Examples of such a viral infection method can include a method which involves transfecting a packaging cell such as a GP2-293 cell (manufactured by Takara Bio Inc.), a Plat-GP cell (manufactured by Cosmo Bio Co., Ltd.), a

PG13 cell (ATCC CRL-10686), or a PA317 cell (ATCC CRL-9078) with a CAR expression vector (International Publication No. WO 2016/056228) and a packaging plasmid to prepare a recombinant virus, and infecting a T cell with the recombinant virus.

[0038] The present immunocompetent cell may be produced by incorporating a nucleotide encoding the present CAR and a nucleotide encoding IL-7 and/or CCL19 into the genome of a cell by use of a gene editing technique known in the art such that the nucleotides are expressible under the control of an appropriate promoter. Examples of the gene editing technique known in the art include a technique using endonuclease such as zinc finger nuclease, TALEN (transcription activator-like effector nuclease), or CRISPR (clustered regularly interspaced short palindromic repeat)-Cas system.

[0039] The present immunocompetent cell can be used in combination with an additional anticancer agent. Examples of the additional anticancer agent can include: an alkylating drug such as cyclophosphamide, bendamustine, ifosfamide, and dacarbazine; an antimetabolite such as pentostatin, fludarabine, cladribine, methotrexate, 5-fluorouracil, 6-mercaptopurine, and enocitabine; a molecular targeting drug such as rituximab, cetuximab, and trastuzumab; a kinase inhibitor such as imatinib, gefitinib, erlotinib, afatinib, dasatinib, sunitinib, and trametinib; a proteasome inhibitor such as bortezomib; a calcineurin inhibitory drug such as cyclosporin and tacrolimus; an anticancer antibiotic such as idarubicin and

doxorubicin mitomycin C; a vegetable alkaloid such as irinotecan and etoposide; a platinum-containing drug such as cisplatin, oxaliplatin, and carboplatin; a hormone therapeutic such as tamoxifen and bicalutamide; and an immunosuppressive drug such as interferon, nivolumab, and pembrolizumab.

[0040] Examples of the method for "using the present immunocompetent cell in combination with the additional anticancer agent" can include a method using treatment with the additional anticancer agent followed by use of the present immunocompetent cell, a method using the present immunocompetent cell and the additional anticancer agent at the same time, and a method using treatment with the present immunocompetent cell followed by use of the additional anticancer agent. Use of the present immunocompetent cell in combination with the additional anticancer agent can further improve a therapeutic effect on a cancer and can also reduce their respective adverse reactions by decreasing their respective numbers of administration or doses.

[0041] The present antibody gene is not particularly limited as long as the antibody gene (nucleotide) encodes the present antibody. Examples thereof can include

(1-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 111 (gene encoding the H chain CDR1 described above in (1-

1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 111 (gene encoding the H chain CDR2 described above in (1-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 324 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 111 (gene encoding the H chain CDR3 described above in (1-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 112 (gene encoding the L chain CDR1 described above in (1-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 112 (gene encoding the L chain CDR2 described above in (1-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 112 (gene encoding the L chain CDR3 described above in (1-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(2-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 115 (gene encoding the H chain CDR1 described above in (2-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 115 (gene encoding the H chain CDR2 described above in (2-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 321 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 115 (gene encoding the H chain CDR3 described above in (2-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 117 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 116 (gene encoding the L chain CDR1 described above in (2-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 163 to 183 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 116 (gene encoding the L chain CDR2 described above in (2-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 280 to 306 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 116 (gene encoding the L chain CDR3

described above in (2-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(3-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 119 (gene encoding the H chain CDR1 described above in (3-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 119 (gene encoding the H chain CDR2 described above in (3-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 315 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 119 (gene encoding the H chain CDR3 described above in (3-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 120 (gene encoding the L chain CDR1 described above in (3-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 120 (gene encoding the L chain CDR2 described above in (3-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene

consisting of nucleotide residues 265 to 288 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 120 (gene encoding the L chain CDR3 described above in (3-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(4-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 123 (gene encoding the H chain CDR1 described above in (4-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 123 (gene encoding the H chain CDR2 described above in (4-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 298 to 330 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 123 (gene encoding the H chain CDR3 described above in (4-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 124 (gene encoding the L chain CDR1 described above in (4-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by

SEQ ID NO: 124 (gene encoding the L chain CDR2 described above in (4-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 124 (gene encoding the L chain CDR3 described above in (4-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(5-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 127 (gene encoding the H chain CDR1 described above in (5-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 127 (gene encoding the H chain CDR2 described above in (5-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 298 to 321 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 127 (gene encoding the H chain CDR3 described above in (5-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 120 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 128 (gene encoding the L chain CDR1 described above in (5-1)), or a degenerate codon engineered

form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 166 to 186 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 128 (gene encoding the L chain CDR2 described above in (5-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 283 to 309 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 128 (gene encoding the L chain CDR3 described above in (5-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(6-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 131 (gene encoding the H chain CDR1 described above in (6-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 131 (gene encoding the H chain CDR2 described above in (6-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 318 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 131 (gene encoding the H chain CDR3 described above in (6-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 132 (gene encoding the L chain CDR1 described above in (6-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 132 (gene encoding the L chain CDR2 described above in (6-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 132 (gene encoding the L chain CDR3 described above in (6-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(7-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 135 (gene encoding the H chain CDR1 described above in (7-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 135 (gene encoding the H chain CDR2 described above in (7-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 315 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO:

135 (gene encoding the H chain CDR3 described above in (7-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 136 (gene encoding the L chain CDR1 described above in (7-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 136 (gene encoding the L chain CDR2 described above in (7-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 136 (gene encoding the L chain CDR3 described above in (7-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(8-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 139 (gene encoding the H chain CDR1 described above in (8-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 139 (gene encoding the H chain CDR2 described above in (8-1)), or a degenerate codon engineered form of the H chain

CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 315 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 139 (gene encoding the H chain CDR3 described above in (8-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 140 (gene encoding the L chain CDR1 described above in (8-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 140 (gene encoding the L chain CDR2 described above in (8-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 140 (gene encoding the L chain CDR3 described above in (8-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(9-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 143 (gene encoding the H chain CDR1 described above in (9-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting

of the nucleotide sequence represented by SEQ ID NO: 143 (gene encoding the H chain CDR2 described above in (9-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 298 to 330 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 143 (gene encoding the H chain CDR3 described above in (9-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 144 (gene encoding the L chain CDR1 described above in (9-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 144 (gene encoding the L chain CDR2 described above in (9-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 144 (gene encoding the L chain CDR3 described above in (9-1)), or a degenerate codon engineered form of the L chain CDR3 gene,

(10-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 147 (gene encoding the H chain CDR1 described above in (10-

1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 147 (gene encoding the H chain CDR2 described above in (10-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 327 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 147 (gene encoding the H chain CDR3 described above in (10-1)), or a degenerate codon engineered form of the H chain CDR3 gene; and

a L chain CDR1 gene consisting of nucleotide residues 70 to 102 of a L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 148 (gene encoding the L chain CDR1 described above in (10-1)), or a degenerate codon engineered form of the L chain CDR1 gene; a L chain CDR2 gene consisting of nucleotide residues 148 to 168 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 148 (gene encoding the L chain CDR2 described above in (10-1)), or a degenerate codon engineered form of the L chain CDR2 gene; and a L chain CDR3 gene consisting of nucleotide residues 265 to 291 of the L chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 148 (gene encoding the L chain CDR3 described above in (10-1)), or a degenerate codon engineered form of the L chain CDR3 gene, and

(11-1D) an antibody gene comprising: a H chain CDR1 gene consisting of nucleotide residues 91 to 105 of a H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 151 (gene encoding the H chain CDR1 described above in (11-1)), or a degenerate codon engineered form of the H chain CDR1 gene; a H chain CDR2 gene consisting of nucleotide residues 148 to 198 of the H chain V region gene consisting of the nucleotide sequence represented by SEQ ID NO: 151 (gene encoding the H chain CDR2 described above in (11-1)), or a degenerate codon engineered form of the H chain CDR2 gene; and a H chain CDR3 gene consisting of nucleotide residues 295 to 324 of the H chain V region consisting of the nucleotide sequence represented by SEQ ID NO: 151 (gene encoding the H chain CDR3 described above in (11-1)), or a degenerate codon engineered form of the H chain CDR3 gene.

[0042] Further examples of the present antibody gene can include

(1-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 111 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 7), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 112 (gene encoding a L chain

variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 8),

(2-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 115 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 17), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 116 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 18),

(3-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 119 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 27), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 120 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 28),

(4-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 123 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 37), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 124 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 38),

(5-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 127 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 47), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 128 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 48),

(6-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide

sequence represented by SEQ ID NO: 131 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 57), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 132 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 58),

(7-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 135 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 67), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 136 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 68),

(8-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 139 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to

the amino acid sequence represented by SEQ ID NO: 77), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 140 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 78),

(9-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 143 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 87), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 144 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 88),

(10-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 147 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 97), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity

to the nucleotide sequence represented by SEQ ID NO: 148 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 98), and

(11-2D) an antibody gene comprising a H chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 151 (gene encoding a H chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 107), and a L chain variable region gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 152 (gene encoding a L chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 108).

[0043] Particularly, examples of the present antibody gene can specifically include

(1-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 113 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 9), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 114 (gene

encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 10),

(2-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 117 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 19), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 118 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 20),

(3-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 121 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 29), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 122 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 30),

(4-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by

SEQ ID NO: 125 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 39), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 126 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 40),

(5-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 129 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 49), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 130 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 50),

(6-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 133 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 59), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 134 (gene

encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 60),

(7-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 137 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 69), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 138 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 70),

(8-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 141 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 79), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 142 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 80),

(9-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by

SEQ ID NO: 145 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 89), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 146 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 90),

(10-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 149 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 99), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 150 (gene encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 100), and

(11-4D) an antibody gene comprising a H chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 153 (gene encoding a H chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 109), and a L chain gene consisting of a nucleotide sequence having at least 80% or higher sequence identity to the nucleotide sequence represented by SEQ ID NO: 154 (gene

encoding a L chain consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 110).

[0044] The present CAR gene is not particularly limited as long as the gene (nucleotide) encodes the present CAR. Examples thereof can specifically include

(1-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (1-3), or a degenerate codon engineered form of the gene,

(2-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (2-3), or a degenerate codon engineered form of the gene,

(3-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (3-3), or a degenerate codon engineered form of the gene,

(4-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (4-3), or a degenerate codon engineered form of the gene,

(5-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (5-3), or a degenerate codon engineered form of the gene,

(6-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (6-3), or a degenerate codon engineered form of the gene,

(7-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (7-3), or a degenerate codon engineered form of the gene,

(8-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (8-3), or a degenerate codon engineered form of the gene,

(9-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (9-3), or a degenerate codon engineered form of the gene,

(10-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (10-3), or a degenerate codon engineered form of the gene,

(11-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (11-3), or a degenerate codon engineered form of the gene,

(1-3'-1D) a CAR gene comprising a gene encoding the single chain antibody described above in (1-3'-1), or a degenerate codon engineered form of the gene,

(1-3'-2D) a CAR gene comprising a gene encoding the single chain antibody described above in (1-3'-2), or a degenerate codon engineered form of the gene,

(1-3'-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (1-3'-3), or a degenerate codon engineered form of the gene,

(2-3'-1D) a CAR gene comprising a gene encoding the single chain antibody described above in (2-3'-1), or a degenerate codon engineered form of the gene,

(2-3'-2D) a CAR gene comprising a gene encoding the single chain antibody described above in (2-3'-2), or a degenerate codon engineered form of the gene,

(2-3'-3D) a CAR gene comprising a gene encoding the single chain antibody described above in (2-3'-3), or a degenerate codon engineered form of the gene, and

(2-3'-4D) a CAR gene comprising a gene encoding the single chain antibody described above in (2-3'-4), or a degenerate codon engineered form of the gene.

[0045]

In the present specification, the phrase "at least 80% or higher identity" means that the identity is 80% or higher, preferably 85% or higher, more preferably 88% or higher, further preferably 90% or higher, still further preferably 93% or higher, particularly preferably 95% or higher, particularly more preferably 98% or higher, most preferably 100%.

[0046] In the present specification, the term "identity" means the degree of similarity between polypeptide or polynucleotide sequences (this degree is determined by matching a query sequence to another sequence, preferably of the same type (nucleic acid or protein sequence)). Examples of a preferred computer program method for calculating and determining the "identity" include, but are not limited to, GCG BLAST (Basic Local Alignment Search Tool) (Altschul et al., J. Mol. Biol. 1990, 215: 403-410; Altschul et al., Nucleic Acids Res. 1997, 25: 3389-3402; and Devereux et al., Nucleic Acid Res. 1984, 12: 387), BLASTN 2.0 (Gish W., http://blast.wustl.edu,1996-2002), FASTA (Pearson and Lipman, Proc. Natl. Acad. Sci. USA 1988, 85: 2444-2448), and GCG GelMerge which determines and aligns a pair of the longest overlapping contigs (Wibur and Lipman, SIAM J. Appl. Math. 1984, 44: 557-567; and Needleman and Wunsch, J. Mol. Biol. 1970, 48: 443-453).

[0047] In the present specification, the "amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: X" is, in other words, an "amino acid sequence derived from the amino acid sequence represented by SEQ ID NO: X by the deletion, substitution, insertion, and/or addition of 0, 1 or several amino acid residues" and has functions equivalent to those of the amino acid sequence represented by SEQ ID NO: X. In this context, the "amino acid sequence derived by the deletion, substitution, insertion, and/or addition of 1 or several amino acid residues" means an amino acid sequence in which amino acid residues have been deleted, substituted, inserted, and/or added, for example, within the range of 1 to 30 residues, preferably within the range of 1 to 20 residues, more preferably within the range of 1 to 15 residues, further preferably within the range of 1 to 10 residues, further preferably within the range of 1 to 5 residues, further preferably within the range of 1 to 3 residues, further preferably within the range of 1 or 2 residues. The mutation treatment of these amino acid residues can be performed by an arbitrary method known to those skilled in the art such as chemical synthesis, a gene engineering approach, or mutagenesis.

[0048] The promoter in the present vector can be any region that starts the transcription of mRNA encoded by the present antibody gene located downstream of the promoter. The promoter usually comprises a transcription start site (TSS).

[0049] The type of the promoter or the vector in the present vector can be appropriately selected according to the type of a host cell (or a host organism) to which the present vector is introduced.

[0050] The host cell can express the present antibody by the transcription of the present antibody gene, or can express the present CAR by the transcription of mRNA of the present CAR gene. In the case of introducing a "vector comprising the present antibody gene" as the present vector, a yeast, a mammalian cell, an insect cell, or a plant cell given below can be used as the host cell. In the case of introducing a "vector comprising the present CAR gene" as the present vector, the immunocompetent cell described above can be used as the host cell.

[0051] In the case of using a yeast (e.g., *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*) as the host cell, examples of the present vector can include a vector such as YEP13 (ATCC37115), YEp24 (ATCC37051), and YCp50 (ATCC37419), and a vector derived from the vector. Examples of the promoter can include glycolysis gene (e.g., hexose kinase gene) promoter, PHO5 promoter, PGK promoter, GAP promoter, ADH promoter, gal1 promoter, gal10 promoter, heat shock protein promoter, MFα1 promoter, and CUP1 promoter.

[0052] In the case of using a mammalian cell (e.g., a human-derived Namalwa cell, a monkey-derived COS cell, a Chinese hamster ovary-derived CHO cell, and a human- or mouse-derived T cell) as the host cell and using a vector comprising the antibody gene as the present vector, examples of the present vector can include a vector such as pcDNAI, pcDM8 (manufactured by Funakoshi Co., Ltd.), pAGE107 (Japanese unexamined Patent Application Publication No. 3-22979; and Cytotechnology, 3, 133,(1990)), pAS3-3 (Japanese unexamined Patent Application Publication No. 2-227075), pCDM8 (Nature, 329, 840, (1987)), pcDNAI/Amp (manufactured by Invitrogen Corp.), pREP4 (manufactured by Invitrogen Corp.), pAGE103 (J. Biochemistry, 101, 1307 (1987)), and pAGE210, and a vector derived from the vector. On the other hand, in the case of using a mammalian cell (e.g., the human-derived immunocompetent cell described above) as the host cell and using a vector comprising the CAR gene as the present vector, examples of the present vector can include a retrovirus vector such as a pMSGV vector (Tamada k et al., Clin Cancer Res 18: 6436-6445 (2002)) and a pMSCV vector (manufactured by Takara Bio Inc.), and a vector derived from the vector.

[0053] Examples of the promoter in the present vector can include cytomegalovirus (CMV) IE (immediate early) gene promoter, SV40 early promoter, retrovirus promoter,

metallothionein promoter, heat shock promoter, SRα promoter, NFAT promoter, and HIF promoter.

[0054] In the case of using an insect cell (e.g., a Sf9 cell and a Sf21 cell which are *Spodoptera frugiperda* ovarian cells, and a High5 cell which is a *Trichoplusia ni* ovarian cell) as the host cell, examples of the present vector can include a transfer vector for use in recombinant baculovirus preparation methods, specifically, a vector such as pVL1392, pVL1393, and pBlueBacIII (all manufactured by Invitrogen Corp.), and a vector derived from the vector. Examples of the promoter can include polyhedrin promoter and p10 promoter.

[0055] In the case of using a plant cell (e.g., tobacco, potato, tomato, carrot, soybean, rapeseed, alfalfa, rice, wheat, and barley cells) as the host cell, examples of the expression vector can include a vector such as Ti plasmid and tobacco mosaic virus vector, and a vector derived from the vector. Examples of the promoter can include cauliflower mosaic virus (CaMV) 35S promoter and rice actin 1 promoter.

[0056] The present vector preferably further comprises the nucleotide sequences of an enhancer region and a ribosome binding site (RBS) for further enhancing gene expression efficiency, and further comprises a drug resistance gene (e.g., spectinomycin resistance gene, chloramphenicol resistance gene, tetracycline resistance gene, kanamycin resistance

gene, ampicillin resistance gene, puromycin resistance gene, hygromycin resistance gene, blasticidin resistance gene, and geneticin resistance gene) appropriate for the type of the host cell for screening for the present host cell. The enhancer region is usually arranged upstream of the promoter, and RBS is usually arranged between the promoter and the present gene. The nucleotide sequence of the present antibody gene to be incorporated into the present vector may be subjected to the optimization of a codon sequence according to the host cell for expression. The present vector can be prepared by a method known in the art using a gene recombination technique.

[0057] The present host cell can be obtained by introducing the present vector to the host cell (transfecting the host cell therewith) by a method appropriate for the type of the host cell.

[0058] In the case of using the yeast described above as the host cell, the method for introducing the present vector to the yeast can be any method for introducing DNA to the yeast. Examples thereof can include a method such as electroporation (Methods Enzymol., 194, 182 (1990)), spheroplast method (Proc. Natl. Acad. Sci. U.S.A, 84, 1929 (1978)), and lithium acetate method (J. Bacteriology, 153, 163 (1983)).

[0059] In the case of using the mammalian cell described above as the host cell, the method for introducing the present vector to the mammalian cell can be any method for introducing DNA to the mammalian cell. Examples thereof can include a method such as electroporation (Cytotechnology, 3, 133 (1990)), calcium phosphate method (Japanese unexamined Patent Application Publication No. 2-227075), lipofection (Proc. Natl. Acad. Sci. U.S.A., 84, 7413 (1987)), and viral infection method, as mentioned above. Examples of such a viral infection method can include a method which involves transfecting a packaging cell such as a GP2-293 cell (manufactured by Takara Bio Inc.), a Plat-GP cell (manufactured by Cosmo Bio Co., Ltd.), a PG13 cell (ATCC CRL-10686), or a PA317 cell (ATCC CRL-9078) with a CAR expression vector (International Publication No. WO 2016/056228) and a packaging plasmid to prepare a recombinant virus, and infecting a T cell with the recombinant virus, as mentioned above.

[0060] In the case of using the insect cell described above as the host cell, examples of the method for introducing the present vector to the insect cell can include a method which involves cotransfecting the insect cell with the present vector (transfer vector) and baculovirus-derived genomic DNA to prepare a recombinant baculovirus, according to a method described in "Current Protocols in Molecular Biology", "Baculovirus Expression Vectors, A Laboratory Manual, W.H. Freeman and Company, New York (1992)", "Bio/Technology, 6, 47 (1988)", etc. Examples of such a cotransfection method can

include a method such as calcium phosphate method (Japanese unexamined Patent Application Publication No. 2-227075) and lipofection (Proc. Natl. Acad. Sci. U.S.A., 84, 7413 (1987).

[0061] In the case of using the plant cell described above as the host cell, examples of the method for introducing the present vector to the plant cell can include a method such as a method using *Agrobacterium* (Japanese unexamined Patent Application Publication Nos. 59-140885 and 60-70080), electroporation (Japanese unexamined Patent Application Publication No. 60-251887), and a method using a particle gun (gene gun) (Japanese Patent Nos. 2606856 and 2517813).

[0062] The present antibody can be obtained by culturing the present host cell obtained by the method mentioned above in a culture solution appropriate for the host cell.

[0063] A transgenic animal, such as a mouse, cattle, a goat, sheep, a chicken, or a pig, in which the present antibody gene (the present vector) has been incorporated is prepared by use of a transgenic animal preparation technique, and an antibody derived from the present antibody gene can also be produced in a large amount from the blood, milk, or the like of the transgenic animal.

[0064] Nonhuman animals (e.g., mice and rats) are immunized with a substance comprising a human-derived GPC3 polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155 (GPC3 polypeptide antigen). A phage library of scFv genes is prepared by a phage display method. The present scFv can be obtained by a biopanning method using the GPC3 polypeptide antigen and/or a cell line expressing the GPC3 polypeptide antigen (preferably a cell line expressing no endogenous GPC3), and further, preferably, a competitor C-terminal polypeptide of GPC3 consisting of the amino acid sequence represented by SEQ ID NO: 159. From the nonhuman animals thus immunized with the antigen, antibody-producing hybridomas are prepared by use of a cell fusion technique. A culture supernatant containing the present antibody can also be obtained through screening by ELISA using a plate in which the antigen has been immobilized on a solid phase. The present antibody can be separated and purified from the culture supernatant by use of an antibody purification technique known in the art.

[0065] The present detection method can be any method comprising the step of detecting GPC3 localized on a cell membrane (anchored on a cell membrane) in a sample (e.g., blood, a tissue, and urine) using the present antibody. Specific examples of the detection method can include immunofluorescent staining, Western blotting, and ELISA using the present antibody.

[0066] The present kit for detection is a kit comprising the present antibody or a labeled form thereof and is limited by the purpose of "detecting GPC3". The kit usually comprises components generally used in this kind of kit, for example, a carrier, a pH buffering agent, and a stabilizer as well as an attached document such as a manual and an instruction for detecting GPC3.

[0067] The organism species of GPC3 to be detected in the present detection method or the present kit for detection may be a nonhuman animal such as a mouse or a rat and is usually a human.

[0068] Examples of the labeling material for the labeled form of the present antibody can include: an enzyme such as peroxidase (e.g., horseradish peroxidase [HRP]), alkaline phosphatase, β-D-galactosidase, glucose oxidase, glucose-6-phosphate dehydrogenase, alcohol dehydrogenase, malate dehydrogenase, penicillinase, catalase, apo-glucose oxidase, urease, luciferase and acetylcholinesterase; a fluorescent material such as fluorescein isothiocyanate, phycobiliprotein, rare earth metal chelates, dansyl chloride and tetramethylrhodamine isothiocyanate; a fluorescence protein such as green fluorescence protein (GFP), cyan fluorescence protein (CFP), blue fluorescence protein (BFP), yellow fluorescence protein (YFP), red fluorescence protein (RFP) and luciferase; a radioisotope such as ^{3}H, ^{14}C, ^{125}I and ^{131}I; biotin; avidin; and a chemiluminescence material.

[0069] References, such as scientific literatures, patents, and patent applications, cited herein are incorporated herein by reference in their entirety to the same extent as if each individual reference was specifically described. The present application claims the priority based on Japanese Patent Application No. 2017-001732 (filed on January 10, 2017), the contents of which are incorporated herein by reference in their entirety.

[0070] Hereinafter, the present invention will be described more specifically with reference to Examples. However, the technical scope of the present invention is not limited by these examples.

[0071] Example 1

1. Preparation of novel anti-GPC3 antibody recognizing N-terminal polypeptide of human GPC3

[Summary]

SKG/Jcl mice were used as animals to be immunized for preparing an anti-human GPC3 antibody, and full-length human GPC3 protein was used as an immunizing antigen. The SKG/Jcl mice were autoimmune disease model mice that spontaneously develop rheumatoid arthritis and are known to produce antibodies in response even to self-components depending on aging or a rearing environment. Meanwhile, GPC3 is highly homologous between humans and mice and is usually less likely to cause antibody

production even by the immunization of normal mice. Therefore, the SKG/Jcl mice were used as animals to be immunized. A scFv phage library was prepared from cDNA derived from B cells of the mice immunized with GPC3, and an anti-human GPC3 antibody was isolated by the application of the phage display method.

[0072] Although the antiserum of immunized mice contains many types of antibodies, it is necessary to select mice producing antibodies having specificity for the N-terminal polypeptide of GPC3 by excluding mice producing antibodies low specific for GPC3 or antibodies recognizing the C-terminal polypeptide of GPC3. Accordingly, mouse individuals that exhibited the production of an antibody specifically binding to the N-terminal polypeptide of GPC3 were selected by use of ELISA and FCM. Specifically, cDNA was synthesized by reverse transcription reaction from total RNA of the B cells derived from the immunized mice, and antibody genes were amplified to prepare an antibody gene library. A scFv phage library was constructed from the antibody gene library, and *E. coli* was infected with the library so that *E. coli* expressed scFv, followed by biopanning using recombinant GPC3, the GPC3-expressing cell line, and the C-terminal polypeptide of GPC3 to enrich phages expressing the target scFv, i.e., an antibody against the N-terminal polypeptide of GPC3. In order to further analyze the obtained scFv for binding specificity for GPC3 in cells, i.e., GPC3 localized on (bound to) a cell membrane (membrane-bound GPC3) via a GPI (glycosylphosphatidylinositol) anchor, verification was made by use of cell

based-ELISA and FCM. Furthermore, the nucleotide sequences of H chain and L chain variable regions of clones having binding specificity were sequenced, and the nucleotide sequences of the anti-GPC3 antibodies produced by the B cells derived from the immunized mice were determined on the basis of these sequences. Finally, the mammalian display method which involved expressing the N-terminal polypeptide fragment and the C-terminal polypeptide fragment of GPC3 on cell surface was used to confirm that the epitope for the scFv was the N-terminal polypeptide fragment of GPC3. Hereinafter, detailed methods and results will be shown.

1-1 Material and method

[Cell culture]

[0073] A JHH7 cell line, a HepG2 cell line, and a SK-Hep-1 cell line forced to express full-length human GPC3 (hereinafter, also referred to as a "GPC3-expressing cell line") were used as human GPC3-expressing cells to perform the biopanning and screening of an anti-GPC3 antibody. The JHH7 cell line is a GPC3-expressing cell line derived from hepatocellular carcinoma, and the cells constitutively express GPC3 bound to a cell membrane (membrane-bound GPC3) via a GPI (glycosylphosphatidylinositol) anchor. On the other hand, the HepG2 cell line is a GPC3-expressing cell line derived from hepatocellular carcinoma, as in the JHH7 cell line, but is a cell line in which the expression of secretory GPC3 that is not bound to a cell membrane is dominant over membrane-bound

GPC3. The Sk-Hep-1 cell line is a hepatocellular carcinoma-derived cell line expressing no GPC3. Hence, a cell line expressing only membrane-bound full-length GPC3 or membrane-bound GPC3 having a partial length deficient in a portion of exons can be prepared by forced expression.

[0074] The culture of 4 types of cell lines (JHH7 cell line, HepG2 cell line, GPC3-expressing cell line, and human embryonic kidney epithelium-derived 293T cell line) was performed under conditions of 37°C and 5% CO_2 in a DMEM culture solution (manufactured by Sigma-Aldrich Co. LLC) containing 10% FBS (manufactured by Gibco/Thermo Fisher Scientific Inc.) and 1% penicillin-streptomycin (manufactured by Gibco/Thermo Fisher Scientific Inc.) (hereinafter, simply referred to as a "DMEM culture solution"). The culture of a CHO-K1 cell line was performed under conditions of 37°C and 5% CO_2 in a Ham's F12 culture solution (manufactured by Sigma-Aldrich Co. LLC) containing 10% FBS (manufactured by Gibco/Thermo Fisher Scientific Inc.).

[Immunizing antigen]

[0075] C-terminally 6 × His-tagged recombinant GPC3 (manufactured by R & D Systems Inc.) was adjusted to 0.1 mg/mL with PBS and mixed with an artificial adjuvant TiterMax Gold (manufactured by TiterMax USA, Inc.) or CFA (Freund's Adjuvant Complete) (F5881, manufactured by Sigma-Aldrich Co. LLC) in equal amounts to prepare an emulsion, which

was then used as an initial immunizing antigen. Recombinant GPC3 was adjusted to a concentration from 10 to 100 μg/mL with PBS and used as the second or later immunizing antigens.

[Preparation of GPC3-expressing cell line]

[0076] A gene encoding full-length human GPC3 consisting of the amino acid sequence represented by SEQ ID NO: 157 (full-length human GPC3 gene consisting of the nucleotide sequence represented by SEQ ID NO: 160) was inserted to a pcDNA3.1 vector (manufactured by Thermo Fisher Scientific Inc.) to prepare a GPC3 expression vector. A SK-Hep-1 cell line was transfected with the GPC3 expression vector according to a standard method and then cultured in a DMEM culture solution containing G418 (manufactured by Roche Diagnostics K.K.) to establish a SK-Hep-1 cell line stably expressing full-length GPC3 (GPC3-expressing cell line).

[Immunization of mouse]

[0077] SKG/Jcl mice (CLEA Japan, Inc., 8-week-old female, SPF) were used as animals to be immunized, and immunized through footpads with recombinant GPC3 a total of 4 times on 1-week intervals. On 5 weeks from the start of immunization, blood was collected, and serum was prepared according to a standard method and used as a specimen for the confirmation of an antibody titer.

[Serum antibody titer of antiserum using ELISA]

[0078] In order to confirm the response of the immunized mice to produce an anti-GPC3 antibody, a serum antibody titer was measured by use of antigen-immobilized ELISA. 0.5 or 2 μg/mL recombinant GPC3 was added at 50 μL/well to a 96-well microplate (manufactured by Nalge Nunc International), and the plate was incubated at room temperature for 1 hour or at 4°C for 12 hours. Then, 2% Block ACE (manufactured by DS Pharma Biomedical Co., Ltd.) was added at 200 μL/well to perform blocking treatment. The serum derived from the GPC3-immunized mice was serially diluted from 100-fold to 16500-fold with 0.1% Block ACE/PBS solution. Each diluted serum sample was added at 50 μL/well, and the plate was incubated at room temperature for 2 hours to perform antigen-antibody reaction treatment. After washing of the wells with a Tween 20-containing PBS (PBST) solution, goat anti-mouse IgG (manufactured by Jackson ImmunoResearch Laboratories Inc.) conjugated with 2 μg/mL peroxidase was added thereto, and the plate was incubated at room temperature for 2 hours to perform secondary antibody reaction treatment. After washing of the well five times with a PBST solution, moisture was removed, and a TMB substrate (manufactured by Thermo Fisher Scientific Inc.) was then added at 50 μL/well to perform color reaction. 15 minutes later, the color reaction was terminated by the addition of 0.18 M sulfuric acid at 50 μL/well, followed by the measurement of absorbance at 450 nm and 540 nm using a plate reader (manufactured by

Bio-Rad Laboratories, Inc.). Quantification was performed using a corrected value obtained by subtracting the measurement value of 540 nm from the measurement value of 450 nm.

[Specificity of antibody in antiserum using FCM]

[0079] In order to further confirm the specific binding activity of the antiserum against membrane-bound GPC3 as to the immunized mice, the mouse serum diluted 100-fold and 5×10^5 cells of the GPC3-expressing cell line were mixed and incubated for 30 minutes on ice. A FACS buffer (1% BSA/PBS solution) was added thereto, and the mixture was centrifuged to remove a supernatant. Then, 100 µL of 1 µg/mL goat anti-mouse IgG (H + L) Alexa Fluor 488 (manufactured by Thermo Fisher Scientific Inc.) was added as a secondary antibody, and the mixture was incubated for 30 minutes on ice to perform secondary antibody reaction treatment. The detection of Alexa Fluor 488 and the measurement of a fluorescence level were performed using a flow cytometer (FACSCanto) (manufactured by BD Biosciences).

[Preparation of scFv phage library]

[0080] B cells-derived total RNA was extracted according to a standard method as to the mice shown to produce an antibody binding to membrane-bound GPC3 by the method described above in the section [Flow cytometer]. RT-PCR with the total RNA as a

template was performed according to a standard method to prepare cDNA. Antibody H chain and L chain variable region genes were amplified by PCR. A nucleotide sequence encoding a fusion protein of scFv having the H chain and L chain variable regions linked via a flexible linker, and coat protein g3p (cp3) of fibrous bacteriophage M13 was inserted to the multicloning site of a pTZ19R phagemid vector to prepare a scFv expression vector. The scFv library size was calculated from the transformation efficiency of an *E. coli* DH12S strain (manufactured by Invitrogen Corp.). The transformed DH12S strain was infected with a helper phage M13KO7 (manufactured by Invitrogen Corp.) to prepare a phage library expressing scFv.

[Biopanning and cloning of phage scFv]

[0081] The biopanning of phage scFv using a combination of recombinant GPC3 immobilized on Dynabeads His-Tag Isolation & Pulldown magnetic beads (manufactured by VERITAS Corp.) via 6 × His tag, and the GPC3-expressing cell line as a bait was performed according to the method described in a document such as "J Mol Biol. 1991 Dec 5; 222 (3): 581-97", "J Med Virol. 2007 Jun; 79 (6): 852-62", "Proc Natl Acad Sci U S A. 2008 May 20; 105 (20): 7287-92", or "JOURNAL OF VIROLOGY, Apr. 2004, p. 3325-3332 Vol. 78, No. 7". In each round (step) of biopanning consisting of 5 types of series (A to E series) (see Figure 1), an aliquot of polyclonal phage antibodies was sampled. In order to confirm the binding specificity of scFv, antigen-immobilized ELISA was performed according to the method

described above in the section [Serum antibody titer of antiserum using ELISA] (method using the culture supernatant of *E. coli* containing a phage instead of the serum), while cell-based ELISA was performed according to the method described below in the section [Screening of scFv by cell-based ELISA]. Each step of this biopanning was devised so as not to select a scFv phage binding to the same portion as the C-terminal epitope of GPC3 recognized by existing antibodies, by binding in advance the existing anti-GPC3 antibodies GC33 (manufactured by Chugai Pharmaceutical Co., Ltd.) and GC199 (manufactured by Chugai Pharmaceutical Co., Ltd.) to the bait. Specifically, this competition method enables selective panning of a novel antibody recognizing a GPC3 epitope different from that for the existing anti-GPC3 antibodies. *E. coli* DH12S was transformed with the phages enriched by biopanning and inoculated to an LB agarose agar medium to separate single colonies. The *E. coli* was further cultured in a small-scale LB liquid medium, followed by the extraction and purification of plasmids. The purified plasmids were subjected to DNA sequencing to determine the nucleotide sequences of scFv H chain and L chain variable regions.

[Screening of scFv by FCM]

[0082] 100 μL of the culture supernatant in which scFv phages were secreted was added to a GPC3-expressing cell line (5×10^5 cells per sample) and mixed therewith, and the mixture was then incubated for 30 minutes on ice. A FACS buffer (1% BSA/PBS solution)

was added thereto, and the mixture was centrifuged and washed. Then, 1 μg/mL anti-mouse antibody-Alexa 488 (manufactured by Thermo Fisher Scientific Inc.) was added thereto as a secondary antibody, and the mixture was incubated for 30 minutes on ice. Then, the fluorescent staining of the cells was measured using a flow cytometer (FACSCanto, manufactured by BD Biosciences).

[Screening of scFv by cell-based ELISA]

[0083] After removal of a DMEM culture solution from a 96-well microplate in which 2 × 10^5 GPC3-expressing cells were attached per well, 2% BSA-PBS solution was added for the purpose of preventing the nonspecific binding of scFv to the cells or the plate, and the plate was incubated for 30 minutes on ice. Then, 100 μL of the culture supernatant of *E. coli* in which scFv phages were secreted was added to each well, and the plate was incubated for 45 minutes on ice. Then, 5 μg/mL rabbit anti-cp3 antibody (manufactured by Medical & Biological Laboratories Co., Ltd.) against cp3 fused on the C-terminal side of scFv was added at 100 μL per well, and the plate was further incubated for 45 minutes on ice. A HRP-labeled anti-rabbit IgG antibody (manufactured by Medical & Biological Laboratories Co., Ltd.) diluted 5000-fold was added at 100 μL per well as a tertiary antibody for anti-cp3 antibody detection, and the plate was incubated for 45 minutes on ice. Then, o-phenylenediamine (OPD) and hydrogen peroxide were added as substrates of HRP for color development. Quantification was performed using a numeric value obtained by

subtracting absorbance at 620 nm as a background from absorbance at 492 nm. When cell-based ELISA was carried out using an antibody already converted to an IgG type antibody, not scFv, a HRP-labeled anti-mouse IgG antibody (manufactured by Medical & Biological Laboratories Co., Ltd.) diluted 2000-fold was used as a secondary antibody for the detection of the IgG type antibody instead of the anti-cp3 antibody and the HRP-labeled anti-rabbit IgG antibody among the conditions described above.

[Determination of variable region gene sequences of scFv]

[0084] The variable region gene sequences of phage scFv binding to membrane-bound GPC3 were decoded in a sequencer (CEQ2000XL, manufactured by Beckman Coulter, Inc.) using a T7 primer (primer consisting of the nucleotide sequence represented by SEQ ID NO: 176), which is a universal primer, and a cp3R primer (primer consisting of the nucleotide sequence represented by SEQ ID NO: 177) as a forward primer for H chain V region (V_H) decoding and a reverse primer for L chain V region (V_L) decoding, respectively.

[Preparation of cell line for use in antibody epitope mapping]

[0085] In order to identify an epitope for the cloned scFv, the mammalian display method was applied. A gene consisting of human GPC3 exons 1 to 7 and encoding a GPC3 N-terminal fragment (polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155), and a gene consisting of human GPC3 exons 8 and 9 and encoding a GPC3

C-terminal fragment (polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 156) were amplified by PCR and each inserted to the multicloning site (MSC) of a pDisplay expression vector (manufactured by Thermo Fisher Scientific Inc.). The pDisplay expression vector is an expression vector capable of fusing a transmembrane domain of platelet-derived growth factor receptor (PDGFR) to the C terminus of the target protein and displaying the fusion product on the cell surface of arbitrary mammalian cells. Also, the pDisplay expression vector is constituted so as to add a HA tag to the N terminus of the target protein and to add a myc tag to the C terminus of the PDGFR. The pDisplay expression vector for expressing the GPC3 N-terminal fragment or the GPC3 C-terminal fragment was gene-transferred to a SK-Hep-1 cell line or a 293T cell line, and a cell line expressing the GPC3 N-terminal fragment or the GPC3 C-terminal fragment on the cell surface (GPC3 N-terminal fragment-expressing cell line and GPC3 C-terminal fragment-expressing cell line) was isolated and used in the epitope mapping of scFv.

[Antibody epitope mapping by FCM]

[0086] The GPC3 N-terminal fragment-expressing cell line, the GPC3 C-terminal fragment-expressing cell line, and the GPC3-expressing cell line (5×10^5 cells each per sample) were each mixed with 100 μL of the culture supernatant in which scFv phages were secreted, and the mixture was incubated for 30 minutes on ice. A FACS buffer (1% BSA/PBS solution) was added thereto, and the mixture was centrifuged and washed.

Then, 1 μg/mL anti-mouse antibody-Alexa 488 (manufactured by Thermo Fisher Scientific Inc.) was added thereto as a secondary antibody, and the mixture was incubated for 30 minutes on ice. Then, the fluorescent staining of the cells was measured using a flow cytometer (FACSCanto, manufactured by BD Biosciences).

[Construction of recombinant IgG expression vector]

[0087] In order to convert scFv to IgG, an expression vector of Mammalian PowerExpress system (manufactured by Toyobo Co., Ltd.) was used. A nucleotide sequence encoding a fusion protein of the H chain variable region of scFv and a mouse IgG2a H chain-derived constant region was inserted to MSC of a pEH1.1 vector (pEH1.1-H). Also, a nucleotide sequence encoding a fusion protein of the L chain variable region of scFv and a mouse IgG2a L chain-derived constant region was inserted to MSC of a pELX2.2 vector (pEH2.2-L). Then, a polynucleotide fragment from EF1α promoter to the L chain gene was excised from pEH2.2-L with restriction enzymes (BglII and SalI) and ligated with pEH1.1-H treated with restriction enzymes (BglII and SalI) to construct a vector for coexpressing the antibody H chain and L chain.

[Expression of recombinant IgG]

[0088] 32.6 μg of the antibody H chain and L chain coexpression vector prepared by the method described above in [Construction of recombinant IgG expression vector] was

diluted with 1.6 mL of opti-MEM (manufactured by Gibco/Thermo Fisher Scientific Inc.) and mixed with 65 μL of Transficient Transfection Reagent (manufactured by Medical & Biological Laboratories Co., Ltd.) diluted with 1.6 mL of opti-MEM, and the mixture was incubated at room temperature for 10 minutes. Then, the mixture was mixed with CHO-K1 cells (1×10^7 cells) suspended in 10 mL of a DMEM culture solution, followed by culture. 4 hours later, a serum-free medium (Free Style expression CHO media [manufactured by Gibco/Thermo Fisher Scientific Inc.]) was added thereto, and the mixture was further cultured for 4 to 6 days to recover a culture supernatant containing a recombinant antibody.

[Affinity purification of antibody]

[0089] An empty column (manufactured by Bio-Rad Laboratories, Inc.) was packed with Protein G Sepharose 4 Fast Flow (manufactured by GE Healthcare Japan Corp.) or Bipo Resin Protein L (manufactured by Protein Express) at 1 mL bed volume. Then, the column resin was washed with PBS in an amount of 10 times the bed volume. The culture supernatant filtered through a 0.22 micron filter was added to the column so that the antibody was entrapped to protein G or protein L within the column. Then, the column was washed with PBS in an amount of 10 times the bed volume to wash off nonspecifically adsorbed contaminants. The antibody was eluted using a 100 mM glycine-HCl (pH 2.7) solution, and pH of the eluate was neutralized with 1 M Tris-HCl (pH 8.5). Absorbance at 280 nm was measured with an absorbance meter nanoDrop (manufactured by Thermo

Fisher Scientific Inc.), and the antibody concentration was calculated. Expression vectors were also designed and prepared by the same method as above as to the GC33 antibody and the GC199 antibody used as competitive antibodies.

1-2 Results

[Antiserum evaluation of immunized mouse]

[0090] Blood was collected from SKG/Jcl mice immunized four times with recombinant GPC3, and the production of an antibody against GPC3 in serum was confirmed. As a result, an antibody having binding activity against GPC3 was detected by experiments of ELIS on recombinant GPC3 and FCM on GPC3-expressing cells. Two mice having a particularly high antibody titer (individual Nos. 1413 #2 and 1413 #3) among the mice were used as sources for the preparation of an antibody library.

[Construction of phage library]

[0091] The number of members in a scFv library estimated by calculation from transformation efficiency was 5.8×10^7 for mouse 1413 #2 and 4.3×10^8 for mouse 1413 #3. The immunoglobulin library prepared in this Example was a library prepared from the mice found to produce antibodies in response to the target antigen by immunization with the antigen GPC3. Therefore, a feature of this library is the high possibility of containing the target antibody gene even if the library size is small. Another advantageous feature

thereof is that the library contains an antibody that forms a correct conformation *in vivo*, as compared with a random synthetic antibody library.

[Classification of clone by sequence analysis of monoclonal scFv]

[0092] The DNA sequence analysis of picked up monoclonal scFv was conducted to perform clone classification excluding overlap. As a result, candidate clones were identified as 7 types from D series of the mouse 1413 #2 library, 5 types from E series thereof, 3 types from D series of the mouse 1413 #3 library, and 9 types from E series thereof. The nucleotide sequences of heavy chain and light chain variable regions of these candidate clones were analyzed to exclude overlapping identical clones. As a result, a total of 18 types of scFv clones, i.e., 9 types of scFv clones derived from the mouse 1413 #2 library, and 9 types of scFv clones derived from the mouse 1413 #3 library, were identified.

[Epitope mapping analysis of anti-GPC3 scFv clone]

[0093] 18 types of scFv clones identified according to the method described above in the section [Classification of clone by sequence analysis of monoclonal scFv] were used to analyze binding to each GPC3 by FCM using 3 types of cell lines (GPC3 N-terminal fragment-expressing cell line, GPC3 C-terminal fragment-expressing cell line, and GPC3-expressing cell line). As a result, among the 18 types of scFv clones, 14 types (TF1413-

02d028, 02d030, 02d039, 02e004, 02e014, 02e030, 02e040, 03e001, 03e004, 03e005, 03e015, 03e019, 03e027, and 03e034) bound to full-length GPC3 and the GPC3 N-terminal fragment (polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155), but did not bind to the GPC3 C-terminal fragment (polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 156) (see Figure 2). On the other hand, the existing anti-GPC3 antibodies GC33 (manufactured by Chugai Pharmaceutical Co., Ltd.) and GC199 (manufactured by Chugai Pharmaceutical Co., Ltd.) bound to full-length GPC3 and the GPC3 C-terminal fragment, but did not bind to the GPC3 N-terminal fragment.

From these results, the 14 types of novel scFv clones described above recognizing a GPC3 N-terminal epitope different from a GPC3 C-terminal epitope for the existing anti-GPC3 antibodies (GC33 and GC199) were identified.

[0094] Among the 14 types of scFv clones thus identified, top 11 scFv clones (TF1413-02d028, 02d039, 02e004, 02e014, 02e030, 02e040, 03e001, 03e004, 03e005, 03e015, and 03e034) having particularly high binding strength were selected. Table 1 shows the correspondence of SEQ ID NOs to the H chain and L chain V regions of these 11 types of scFv clones. Table 2 shows the correspondence of SEQ ID NOs to the H chain CDR1 to CDR3 of these 11 types of scFv clones. Table 3 shows the correspondence of SEQ ID NOs to the L chain CDR1 to CDR3 of these 11 types of scFv clones.

[0095]

[Table 1]

scFv clone name and V region		SEQ ID NO
TF1413-02d028	H chain V region	7
TF1413-02d039	H chain V region	17
TF1413-02e004	H chain V region	27
TF1413-02e014	H chain V region	37
TF1413-02e030	H chain V region	47
TF1413-02e040	H chain V region	57
TF1413-03e001	H chain V region	67
TF1413-03e004	H chain V region	77
TF1413-03e005	H chain V region	87
TF1413-03e015	H chain V region	97
TF1413-03e034	H chain V region	107
TF1413-02d028	L chain V region	8
TF1413-02d039	L chain V region	18
TF1413-02e004	L chain V region	28
TF1413-02e014	L chain V region	38
TF1413-02e030	L chain V region	48
TF1413-02e040	L chain V region	58
TF1413-03e001	L chain V region	68
TF1413-03e004	L chain V region	78
TF1413-03e005	L chain V region	88
TF1413-03e015	L chain V region	98
TF1413-03e034	L chain V region	108

[0096]

[Table 2]

Clone name and CDR		SEQ ID NO
TF1413-02d028	H chain CDR1	1
	H chain CDR2	2
	H chain CDR3	3
TF1413-02d039	H chain CDR1	11
	H chain CDR2	12
	H chain CDR3	13
TF1413-02e004	H chain CDR1	21
	H chain CDR2	22
	H chain CDR3	23
TF1413-02e014	H chain CDR1	31
	H chain CDR2	32
	H chain CDR3	33
TF1413-02e030	H chain CDR1	41
	H chain CDR2	42
	H chain CDR3	43
TF1413-02e040	H chain CDR1	51
	H chain CDR2	52
	H chain CDR3	53
TF1413-03e001	H chain CDR1	61
	H chain CDR2	62
	H chain CDR3	63
TF1413-03e004	H chain CDR1	71
	H chain CDR2	72
	H chain CDR3	73
TF1413-03e005	H chain CDR1	81
	H chain CDR2	82
	H chain CDR3	83
TF1413-03e015	H chain CDR1	91
	H chain CDR2	92
	H chain CDR3	93
TF1413-03e034	H chain CDR1	101

	H chain CDR2	102
	H chain CDR3	103

[0097]

[Table 3]

Clone name and CDR		SEQ ID NO
TF1413-02d028	L chain CDR1	4
	L chain CDR2	5
	L chain CDR3	6
TF1413-02d039	L chain CDR1	14
	L chain CDR2	15
	L chain CDR3	16
TF1413-02e004	L chain CDR1	24
	L chain CDR2	25
	L chain CDR3	26
TF1413-02e014	L chain CDR1	34
	L chain CDR2	35
	L chain CDR3	36
TF1413-02e030	L chain CDR1	44
	L chain CDR2	45
	L chain CDR3	46
TF1413-02e040	L chain CDR1	54
	L chain CDR2	55
	L chain CDR3	56
TF1413-03e001	L chain CDR1	64
	L chain CDR2	65
	L chain CDR3	66
TF1413-03e004	L chain CDR1	74
	L chain CDR2	75
	L chain CDR3	76
TF1413-03e005	L chain CDR1	84
	L chain CDR2	85
	L chain CDR3	86
TF1413-03e015	L chain CDR1	94
	L chain CDR2	95
	L chain CDR3	96
TF1413-03e034	L chain CDR1	104

	L chain CDR2	105
	L chain CDR3	106

[Conversion of anti-GPC3 scFv antibody to IgG and its ability to bind]

[0098] The H chain and L chain variable regions of the 11 types of scFv clones selected as described above were bound to mouse IgG constant regions, and full-length recombinant antibodies were expressed using a vector for recombinant IgG expression and affinity-purified. The ability of these IgG antibodies to bind to the GPC3 N-terminal fragment was analyzed using the GPC3 N-terminal fragment-expressing cell line. As a result, 9 types of IgG clones (TF1413-02d028, 02d039, 02e004, 02e014, 02e030, 02e040, 03e004, 03e005, and 03e034) maintained binding activity against the GPC3 N-terminal fragment, whereas the remaining two types of IgG clones (TF1413-03e001 and 03e015) lacked binding activity against the GPC3 N-terminal fragment (see Figure 3). The 9 types of IgG clones described above did not bind to the GPC3 C-terminal fragment (see Figure 3).

These results indicate that among the 11 types of scFv clones, 9 types (TF1413-02d028, 02d039, 02e004, 02e014, 02e030, 02e040, 03e004, 03e005, and 03e034) are convertible to IgG type. Table 4 shows the correspondence of SEQ ID NOs to the H chains and the L chains of the 11 types of IgG clones.

[0099]

[Table 4]

IgG clone name and region		SEQ ID NO
TF1413-02d028	H chain	9
TF1413-02d039	H chain	19
TF1413-02e004	H chain	29
TF1413-02e014	H chain	39
TF1413-02e030	H chain	49
TF1413-02e040	H chain	59
TF1413-03e001	H chain	69
TF1413-03e004	H chain	79
TF1413-03e005	H chain	89
TF1413-03e015	H chain	99
TF1413-03e034	H chain	109
TF1413-02d028	L chain	10
TF1413-02d039	L chain	20
TF1413-02e004	L chain	30
TF1413-02e014	L chain	40
TF1413-02e030	L chain	50
TF1413-02e040	L chain	60
TF1413-03e001	L chain	70
TF1413-03e004	L chain	80
TF1413-03e005	L chain	90
TF1413-03e015	L chain	100
TF1413-03e034	L chain	110

Example 2

[0100]

2. Binding activity of novel anti-GPC3 antibody against GPC3 treated with EDTA (ethylenediaminetetraacetic acid), trypsin or collagenase

[Preparation of cell treated with EDTA or trypsin]

A SK-Hep-1 cell line forced to express GPC3 was cultured in two T-75 flasks. The culture supernatant of each flask was aspirated, and the flask was washed with 3 mL of PBS. Then, 3 mL of 0.02% EDTA/PBS solution (hereinafter, simply referred to as "EDTA") or 0.05% trypsin solution (hereinafter, simply referred to as "trypsin") was added to each flask. Each flask was incubated at 37°C for 5 minutes (EDTA) or 2 minutes and 30 seconds (trypsin) to dissociate the cells from the flask. Then, 7 mL of a DMEM culture solution was added to each flask. After pipetting, the cell suspension was recovered into each 50 mL conical tube. Each flask was further washed with 10 mL of a DMEM culture solution. Then, the recovered washes were also recovered into the 50 mL conical tube containing each cell suspension, followed by centrifugation (1,500 rpm, 4°C, 4 min). After aspiration of the supernatant from each conical tube, 10 mL of a DMEM culture solution was added to the pellet, and the number of cells dissociated with EDTA or trypsin was counted.

[0101] The cells treated with EDTA or trypsin were adjusted to 2×10^5 cells/tube and subjected to FACS (EC800) analysis. The FACS analysis employed 3 types of antibodies (fluorescently APC-labeled anti-mouse IgG antibody [5 μg/tube; manufactured by BioLegend, Inc.], GC33 antibody [1.0 μg/tube; manufactured by Medical & Biological Laboratories Co., Ltd. Life Science], and scFv clone [TF1413-02d028] antibody described above [1.0 μg/tube]).

[Preparation of cell treated with collagenase]

[0102] 1×10^6 cells dissociated with EDTA as described above were placed in a 50 mL conical tube and centrifuged (1,500 rpm, 4°C, 4 min), and the supernatant was aspirated to prepare a cell mass (pellet). 5 mL of a collagenase P solution was added to the pellet, and the mixture was incubated at 37°C for 30 minutes to prepare a cell suspension. Then, the cell suspension was passed through a 100 μm cell strainer while washed with 30 mL of a DMEM culture solution. The cell suspension was passed again through a 100 μm cell strainer and centrifuged (300 g, 4°C, 10 min), and the supernatant was aspirated. The pellet was washed by the addition of 20 mL of PBS and then centrifuged (300 g, 4°C, 5 min), and the supernatant was aspirated. The cells were suspended by the addition of 5 mL of a DMEM culture solution. Then, the number of cells was counted, and 2×10^5 cells/tube were analyzed by FACS (EC800). The FACS analysis employed 3 types of antibodies (fluorescently APC-labeled anti-mouse IgG antibody [5 μg/tube; manufactured by BioLegend, Inc.], GC33 antibody [1.0 μg/tube; manufactured by Medical & Biological Laboratories Co., Ltd. Life Science], and scFv clone [TF1413-02d028] antibody described above [1.0 μg/tube]), as in the cells treated with EDTA or trypsin. The results are shown in Figure 4. In Figure 4, the right peak on the abscissa represents that the GC33 antibody or the scFv clone [TF1413-02d028] antibody bound to the GPC3 protein.

[Results]

[0103] As shown in Figure 4, the binding activity of the antibody of the present invention (TF1413-02d028) against the GPC3 protein treated with trypsin or collagenase was markedly decreased. These results indicate that the antibody of the present invention specifically recognizes the conformation of the GPC3 protein, suggesting that the antibody of the present invention has high specificity *in vivo*.

Example 3

[0104]

3. Development of GPC3 CAR-T cell using novel anti-GPC3 antibody

[Summary]

GPC3 is a cell surface molecule, the expression of which is not observed in human adult tissues except for placenta, but is observed in tissues of various cancers such as hepatocellular carcinoma, melanoma, ovarian clear cell adenocarcinoma, and lung squamous cell carcinoma. Thus, GPC3 is capable of serving as a target molecule in CAR-T cell therapy exploiting a chimeric antigen receptor (CAR). Accordingly, GPC3 CAR-T cells were prepared using 11 types of scFv clones prepared in Example 1 and analyzed for cancer cytotoxic activity and the ability to produce interferon γ (IFN-γ).

[Preparation of GPC3 CAR vector]

[0105] scFv having a V_H-linker-V_L sequence was designed as to 11 types of scFv clones (TF1413-02d028, 02d039, 02e004, 02e014, 02e030, 02e040, 03e001, 03e004, 03e005, 03e015, and 03e034) prepared in Example 1, on the basis of their respective amino acid sequences of V_H and V_L (see Table 5). The linker used consisted of 15 amino acid residues with 3 repeats of a polypeptide "GGGGS". A human immunoglobulin H chain-derived signal sequence consisting of the amino acid sequence represented by SEQ ID NO: 188 was added to the N terminus of V_H.

[0106]

[Table 5-1]

SEQ ID NO: 165: TF1413-02d028 -derived scFv
QVQLKESGPELEKPGASVKISCKASGYSFTGYNMNWVKQSNGKSLEWIGNIDPYYGGTSYNQKF KGKATLTVDKSSSTAYMQLKSLTSEDSAVYYCARGDYRAYYFDYWGQGTTLTVSGGGGSGGGGS GGGGSDIQMTQSPKFMSTSVGDRVSITCKASQNVRTAVAWYQQKPGQSPKALIYLASNRHTGVP DRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWNYPLTFGAGTKLELKR
SEQ ID NO: 166: TF1413-02d039 -derived scFv
EVKLVESGGGLVKPGGSLKLSCAASGFAFSSYDMSWVRQTPEKRLEWVAYISSGGGSTYYPDTVK GRFTISRDNAKNTLYLQMSSLKSEDTAMYYCARRGLRRAMDYWGQGTSVTVSGGGGSGGGGSG GGGSDVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGAGTKLELKR
SEQ ID NO: 167: TF1413-02e004 -derived scFv
QVQLQQSGAELVKPGAPVKLSCKASGYTFTSYWMNWVKQRPGRGLEWIGRIDPSDSETHYNQK FKDEATLTVDKSSSTAYIQLSSLTSEDSAVYYCARGYYAMDYWGQGTSVTVSGGGGSGGGGSGG GGSDIVLTQSPKFMSTSVGDRVSITCKASQDVSTAVAWYQQKPGQSPKLLIYSASYRYTGVPDRFT GSGSGTDFTFTISSVQAEDLAVYYCQQHYSTPTFGGGTKLEIKR
SEQ ID NO: 168: TF1413-02e014 -derived scFv
QVQLKQSGAELVRSGASVKLSCTASGFNIKDYYMHWVKQRPEQGLEWIGWIDPENGDTEYAPKF QGKATMTADTSSNTAYLQLSSLTSEDTAVYYCNAGYYDYDGYAMDYWGQGTSVTVSGGGGSGG GGSGGGGSDIVLTQSPKFMSTSVGDRVSITCKASQDVGTAVAWYQQKPGQSPKLLIYWASTRHTG VPDRFTGSGSGTDFTLTISNVQSEDLADYFCQQYSSYPLTFGGGTKLEIKR
SEQ ID NO: 169: TF1413-02e030 -derived scFv
EVQLQQSGAELVRPGALVKLSCKASGFNIKDYYMHWVKQRPEQGLEWIGWIDPENGNTIYDPKF QGKASITADTSSNTAYLQLSSLTSEDTAVYYCAISTMITTLDYWGQGTTLTVSGGGGSGGGGSGG GGSDIQMTQSPSSLAMSVGQKVTMSCKSSQSLLNSSNQKNYLAWYQQKPGQSPKLLVYFASTRE SGVPDRFIGSGSGTDFTLTISSVQAEDLADYFCQQHYSTPLTFGAGTKLELKR
SEQ ID NO: 170: TF1413-02e040 -derived scFv
EVMLVESGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTSYNQN FKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCARGYYGRFDYWGQGTTLTVSGGGGSGGGGSG GGGSDILLTQSPKFMSTSVGDRVSITCKASQNVRTAVAWYQQKPGQSPKALIYLASNRHTGVPDR FTGSGSGTDFTLTISNVQSEDLADYFCLQHWNYPLTFGAGTKLELKR

[0107]

[Table 5-2]

SEQ ID NO: 171: TF1413-03e001-derived scFv
QVQLKQSGPELVKPGASVKISCKASGYSFTGYYMHWVKQSHVKSLEWIGRINPYNGATSYNQNF KDKASLTVDKSSSTAYMELHSLTSEDSAVYYCARNYGYFDYWGQGTTLTVSGGGGSGGGGSGG GGSDIKMTQSPKFMSTSVGDRVSVTCEASQNVDNNVVWYQQKPGQSPKALIYSASYRYSGVPDR FTGSGSGTDFTLTISNVQSEDLAEYFCQQYNSYPLTFGAGTKLEIKR
SEQ ID NO: 172: TF1413-03e004-derived scFv
QVQLKQSGAELVKPGAPVKLSCKASGYTFTSYWMNWVKQRPGRGLEWIGRIDPSDSETHYNQK FKDKATLTVDKSSSTAYIQLSSLTSEDSAVYYCARGYYGSNYWGQGTTLTVSGGGGSGGGGSGGG GSDIKMTQSPKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKALIYSASYRYSGVPDRF TGSGSGTDFTLTISNVQSEDLAEYFCQQYNSYPLTFGAGTKLELKR
SEQ ID NO: 173: TF1413-03e005-derived scFv
QVQLKESGAELVRSGASVKLSCTASGFNIKDYYMHWVKQRPEQGLEWIGWIDPENGDTEYAPKF QGKATMTADTSSNTAYLQLSSLTSEDTAVYYCNAFYYDYDGYAMDYWGQGTSVTVSGGGGSGG GGSGGGGSDVVMTQTPSSLSASLGERVSLTCRASQEISGYLSWLQQKPDGTIKRLIYAASTLDSG VPKRFSGSRSGSDYSLTISSLESEDFADYYCLQYASYPLTFGAGTKLELKR
SEQ ID NO: 174: TF1413-03e015-derived scFv
EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTSYNQK FKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCARGDYYPPYAMDYWGQGTSVTVSGGGGSGGG GSGGGGSDIVMSQSPKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKPLIYSASYRYSG VPDRFTGSGSGTDFTLTISNVQSEDLAEYFCQQYNRYPLTFGVGTKLEIKR
SEQ ID NO: 175: TF1413-03e034-derived scFv
EVQLQQSGPELEKPGASVKISCKASGYSFTGYNMNWVKQSNGKSLEWIGNIDPYYGGTSYNQKF KGKATLTVDKSSSTAYMQLKSLTSEDSAVYYCARGNYGYYAMDYWGQGTSVTVSGGGGSGGGG SGGGGSDIVMSQSPKFMSTSVGDRVSITCKASQNVRTAVAWYQQKPGQSPKALIYLASNRHTGV PDRFTGSGSGTDFTLTISNVQSEDLADYFCLQHWNYPLTFGAGTKLELKR

In the tables, the linker is boxed in a double line, V_H is underlined with a single line, and V_L is underlined with a double line.

[0108] A nucleotide sequence encoding each anti-GPC3 scFv of Table 5 was synthesized by optimization for human codons and inserted to a CAR expression vector. The CAR gene used had a gene encoding a fusion peptide (peptide consisting of the amino acid sequence represented by SEQ ID NO: 185) consisting of a human CD8-derived

transmembrane region and a human CD28/4-1BB/CD3 zeta-derived immunocompetent cell activation signal transduction region, a 2A self-cleaving sequence, human IL-7 gene, a 2A self-cleaving sequence, human CCL19 gene, a 2A self-cleaving sequence, and HSV-TK gene, downstream of the scFv gene, and the whole was incorporated into a MSGV1 retrovirus vector (see International Publication No. WO 2016/056228).

[Preparation of GPC3 CAR-T cell]

[0109] The GPC3 CAR vectors derived from the 11 types of scFv clones described above were each transiently introduced to GP2 packaging cells to prepare retrovirus vectors. T cells were infected with these vectors for gene transfer to induce GPC3 CAR-T cells. The ratio of GPC3 CAR-expressing cells to the gene-transferred T cells varied from 5.3 to 39.2%. Accordingly, the following function assay was carried out using GPC3 CAR-T cells derived from 5 types of scFv clones (TF1413-02d028, TF1413-02d039, TF1413-02e014, TF1413-02e030, and TF1413-03e005) that exhibited 25% or more of the ratio.

[Damaging activity of GPC3 CAR-T cell against GPC3-expressing cell line]

[0110] In order to study the damaging activity of the GPC3 CAR-T cells against cancer cells, coculture assay was carried out using the GPC3 CAR-T cells and a GPC3-expressing cell line, i.e., a hepatocellular carcinoma-derived cell line Sk-HEP-1 caused to express GPC3 (Sk-HEP-1 GPC3 cell line), or a cell line expressing no GPC3 (Sk-HEP-1 mock cell

line). The GPC3 CAR-T cells were mixed with the target cancer cells (Sk-HEP-1 GPC3 cell line or Sk-HEP-1 mock cell line) at a ratio of 1:1 (1×10^5 cells/well) and cultured in a 24-well plate. 48 hours later, the cells were recovered, stained with an anti-CD45 antibody, and analyzed by FCM with CD45-positive cells as GPC3 CAR-T cells and CD45-negative cells as residual cancer cells [Sk-HEP-1 GPC3 cells]. As a result, all the GPC3 CAR-T cells derived from the 5 types of scFv clones described above almost completely damaged the Sk-HEP-1 GPC3 cells, but did not exhibit damaging activity against the Sk-HEP-1 mock cells (see Figures 5 and 6). In the case of using cells uninfected with the virus vector (non-gene-transferred cells ["Non infection" in Figures 5 and 6]) as a negative control for the GPC3 CAR-T cells, these cells exhibited damaging activity neither against the Sk-HEP-1 GPC3 cells nor against the Sk-HEP-1 mock cells.

[0111] From these results, the GPC3CAR-T cells derived from the selected 5 types of anti-GPC3 scFv clones (TF1413-02d028, TF1413-02d039, TF1413-02e014, TF1413-02e030, and TF1413-03e005) were shown to specifically exert cytotoxic activity against cancer cells expressing GPC3.

[Ability of GPC3 CAR-T cell to produce IFN-γ by recognizing GPC3-expressing cell]

[0112] In addition to the damaging activity against GPC3-expressing (positive) cancer cells, the ability of the GPC3 CAR-T cells to produce IFN-γ was analyzed. The GPC3

CAR-T cells were mixed with the target cancer cells (Sk-HEP-1 GPC3 cell line or Sk-HEP-1 mock cell line) at a ratio of 1:1 (1×10^5 cells/well) and cultured for 48 hours in a 24-well plate, and the concentration of IFN-γ produced into the culture supernatant was measured by ELISA. As a result, all the GPC3 CAR-T cells derived from the 5 types of scFv clones described above exhibited the ability to produce IFN-γ in a manner dependent on the expression of GPC3. Particularly, the GPC3 CAR-T cells derived from clone TF1413-02d028 exhibited the highest ability to produce IFN-γ (see Figure 7).

Example 4

[0113]

4. Preparation of humanized antibody

scFv humanized antibodies were designed on the basis of two types of scFv clones (TF1413-02d028 and 02d039) prepared in Example 1 (see Table 6). The linker used consisted of 15 amino acid residues with 3 repeats of a polypeptide "GGGGS". A human immunoglobulin H chain-derived signal sequence consisting of the amino acid sequence represented by SEQ ID NO: 188 was added to the N terminus of V_H.

[0114]

[Table 6-1]

SEQ ID NO: 178: #5 VH1-15-VL1 (TF1413-02d028-derived scFv humanized antibody 1)
QVQLVQSGAEVKKPGASVKVSCKASGYSFTGYNMNWVRQAPGQGLEWIGNIDPYYGGTSYNQK FKGRATLTVDTSTSTAYMELRSLRSDDTAVYYCARGDYRAYYFDYWGQGTTVTVSSGGGGSGGG GSGGGGSDIQMTQSPSSLSASVGDRVTITCKASQNVRTAVAWYQQKPGKAPKALIYLASNRHTGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCLQHWNYPLTFGGGTKVEIK
SEQ ID NO: 179: #5 VH2-15-VL1 (TF1413-02d028-derived scFv humanized antibody 2)
QVQLVQSGAEVKKPGASVKVSCKASGYSFTGYNMNWVRQAPGQGLEWIGNIDPYYGGTSYNQK FKGRVTLTVDTSTSTAYMELRSLRSDDTAVYYCARGDYRAYYFDYWGQGTTVTVSSGGGGSGGG GSGGGGSDIQMTQSPSSLSASVGDRVTITCKASQNVRTAVAWYQQKPGKAPKALIYLASNRHTGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCLQHWNYPLTFGGGTKVEIK
SEQ ID NO: 180: #5 VH3-15-VL1 (TF1413-02d028-derived scFv humanized antibody 3)
QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYNMNWVRQAPGQGLEWIGNIDPYYGGTSYNQK FKGRVTLTVDTSTSTAYMELRSLRSDDTAVYYCARGDYRAYYFDYWGQGTTVTVSSGGGGSGGG GSGGGGSDIQMTQSPSSLSASVGDRVTITCKASQNVRTAVAWYQQKPGKAPKALIYLASNRHTGV PSRFSGSGSGTDFTLTISSLQ PEDFATYYCLQHWNYPLTFGGGTKVEIK
SEQ ID NO: 181: #6 VH1-15-VL1 (TF1413-02d039-derived scFv humanized antibody 1)
EVQLVESGGGLVQPGGSLRLSCAASGFAFSSYDMSWVRQAPGKGLEWVAYISSGGGSTYYPDTVK GRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRGLRRAMDYWGQGTMVTVSSGGGGSGGGGS GGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPLTFGGGTKVEIK
SEQ ID NO: 182: #6 VH1-15-VL2 (TF1413-02d039-derived scFv humanized antibody 2)
EVQLVESGGGLVQPGGSLRLSCAASGFAFSSYDMSWVRQAPGKGLEWVAYISSGGGSTYYPDTVK GRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRGLRRAMDYWGQGTMVTVSSGGGGSGGGGS GGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLVHSSGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCSQSTHVPLTFGGGTKVEIK
SEQ ID NO: 183: #6 VH2-15-VL1 (TF1413-02d039-derived scFv humanized antibody 3)
EVQLVESGGGLVQPGGSLRLSCAASGFAFSSYDMSWVRQAPGKRLEWVAYISSGGGSTYYPDTVK GRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRGLRRAMDYWGQGTMVTVSSGGGGSGGGGS GGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCSQSTHVPLTFGGGTKVEIK

[0115]

[Table 6-2]

SEQ ID NO: 184: #6 VH2-15-VL2 (TF1413-02d039-derived scFv humanized antibody 4)
EVQLVESGGGLVQPGGSLRLSCAASGFAFSSYDMSWVRQAPGKRLEWVAYISSGGGSTYYPDTVK GRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARRGLRRAMDYWGQGTMVTVSSGGGGSGGGGS GGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLVHSSGNTYLHWYLQKPGQSPQLLIYKVSNRF SGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCSQSTHVPLTFGGGTKVEIK

In the tables, the linker is boxed in a double line, V_H is underlined with a single line, and V_L is underlined with a double line.

[0115a] In the claims which follow and in the description of the invention, except where the context requires otherwise due to express language or necessary implication, the word “comprise” or variations such as “comprises” or “comprising” is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

Industrial Applicability

[0116]

The present invention contributes to the field of cancer immunotherapy.

Claims

1. A chimeric antigen receptor (CAR), comprising a single chain antibody, a transmembrane region fused with a carboxyl terminus of the single chain antibody, and an immunocompetent cell activation signal transduction region fused with a carboxyl terminus of the transmembrane region,

wherein the single chain antibody is a single chain Fv specifically binding to a human GPC3 (glypican-3)-derived polypeptide consisting of the amino acid sequence represented by SEQ ID NO: 155, and:

comprises a heavy chain complementarity determining region (CDR) 1 consisting of the amino acid sequence represented by SEQ ID NO: 1, a heavy chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 2, and a heavy chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 3, and

a light chain CDR1 consisting of the amino acid sequence represented by SEQ ID NO: 4, a light chain CDR2 consisting of the amino acid sequence represented by SEQ ID NO: 5, and a light chain CDR3 consisting of the amino acid sequence represented by SEQ ID NO: 6.

2. The CAR according to claim 1, wherein the single chain antibody:

comprises a heavy chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ

ID NO: 7, and a light chain variable region consisting of an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 8.

3. The CAR according to claim 1 or 2, wherein the single chain antibody:

comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 165.

4. The CAR according to claim 1 or 2, wherein the single chain antibody:

comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 178; or

comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 179; or

comprises an amino acid sequence having at least 80% or higher sequence identity to the amino acid sequence represented by SEQ ID NO: 180.

5. The CAR according to any one of claims 1 to 4, wherein the CAR comprises the amino acid sequence represented by any one of SEQ ID NOs: 185 to 187.

6. An immunocompetent cell expressing the chimeric antigen receptor (CAR) according to any one of claims 1 to 5.

7. The immunocompetent cell according to claim 6, further expressing interleukin 7 (IL-7) and chemokine ligand 19 (CCL19).

8. A chimeric antigen receptor (CAR) gene encoding the CAR according to any one of claims 1 to 5.

9. A vector comprising a promoter and the CAR gene according to claim 8 operably linked downstream of the promoter.

10. A host cell in which the vector according to claim 9 has been introduced.

11. Use of the immunocompetent cell according to claim 6 or 7 in the manufacture of a medicine for treating a human GPC3 expressing condition or disease treatable by cancer immunotherapy.

12. A method for treating a human GPC3 expressing condition or disease treatable by cancer immunotherapy, comprising administering the immunocompetent cell according to claim 6 or 7 to a subject in need thereof.

13. A medicine when used for treating a human GPC3 expressing condition or disease treatable by cancer immunotherapy, comprising the immunocompetent cell according to claim 6 or 7.

[Fig. 1]

A series

Round name	Antigen/support	Competition operation
a1st	Recombinant-bound beads	Competition using G33 & G199
a2nd	Recombinant-bound beads	Competition using G33 & G199
a3rd	Recombinant-bound beads	Competition using G33 & G199
a4th	GPC3-expressing cell	Competition using G33 & G199
a5th (only for 03)	GPC3-expressing cell	No competition

B series

Round name	Antigen/support	Competition operation
b3rd	GPC3-expressing cell	Competition using G33 & G199

E series

Round name	Antigen/support	Competition operation
e4th	Recombinant-bound beads	No competition

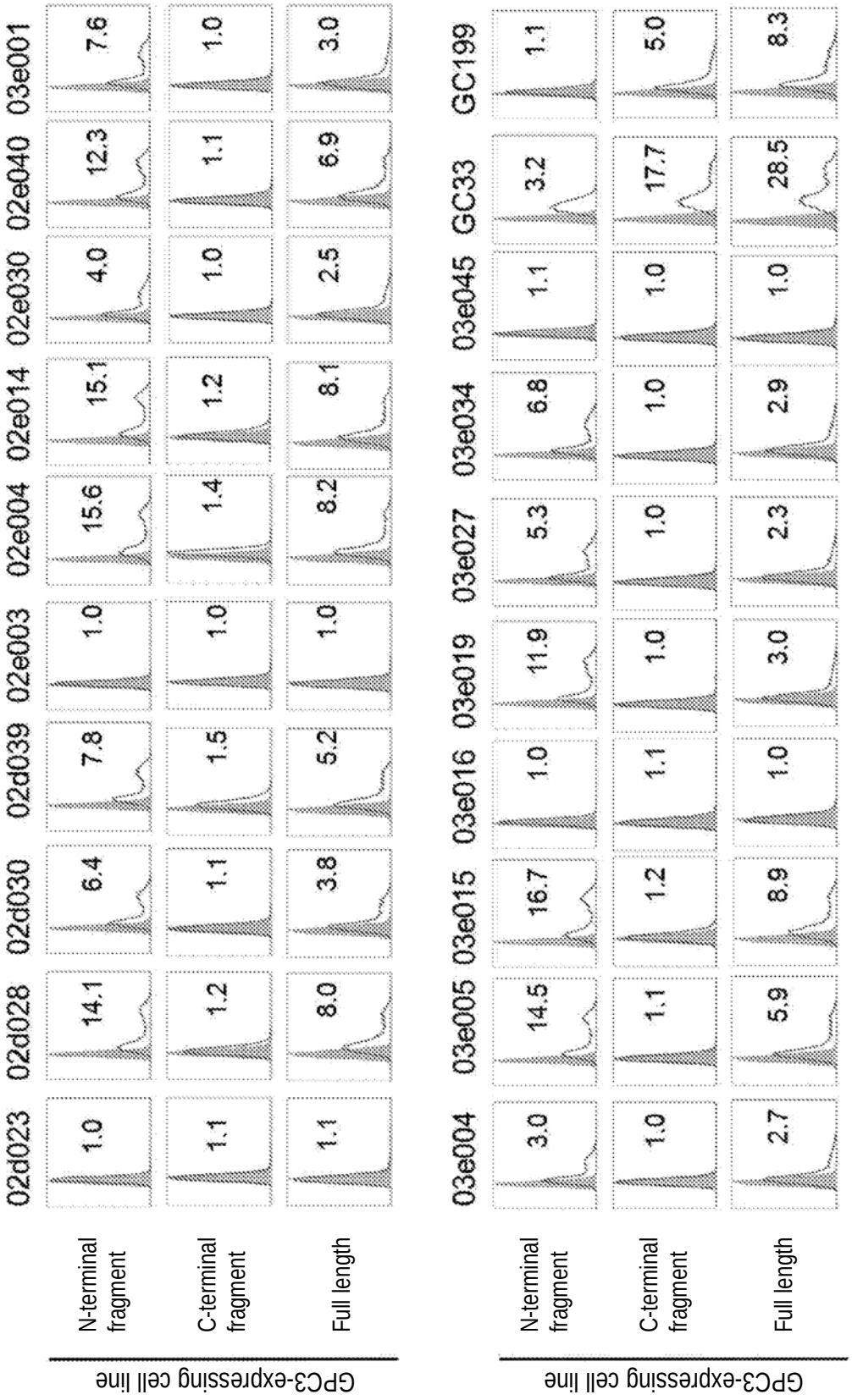
C series

Round name	Antigen/support	Competition operation
c1st	GPC3-expressing cell	No competition
c2nd	GPC3-expressing cell	No competition
c3rd	Recombinant-bound beads	No competition
c4th	Recombinant-bound beads	No competition

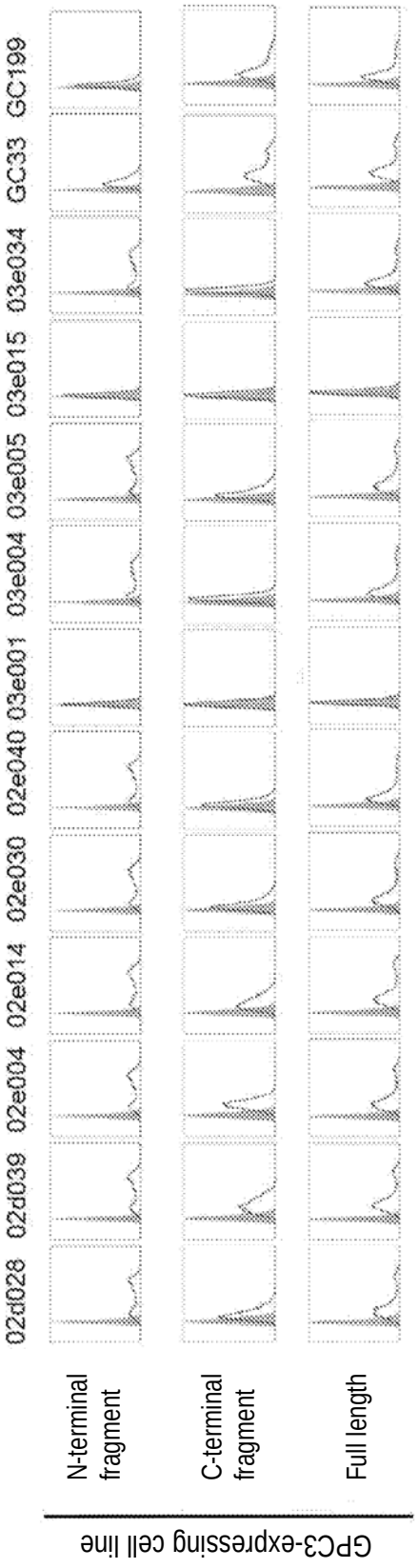
D series

Round name	Antigen/support	Competition operation
d1st	Recombinant-bound beads	No competition
d2nd	Recombinant-bound beads	No competition
d3rd	Recombinant-bound beads	No competition
d4th	GPC3-expressing cell	No competition
d5th	GPC3-expressing cell	No competition

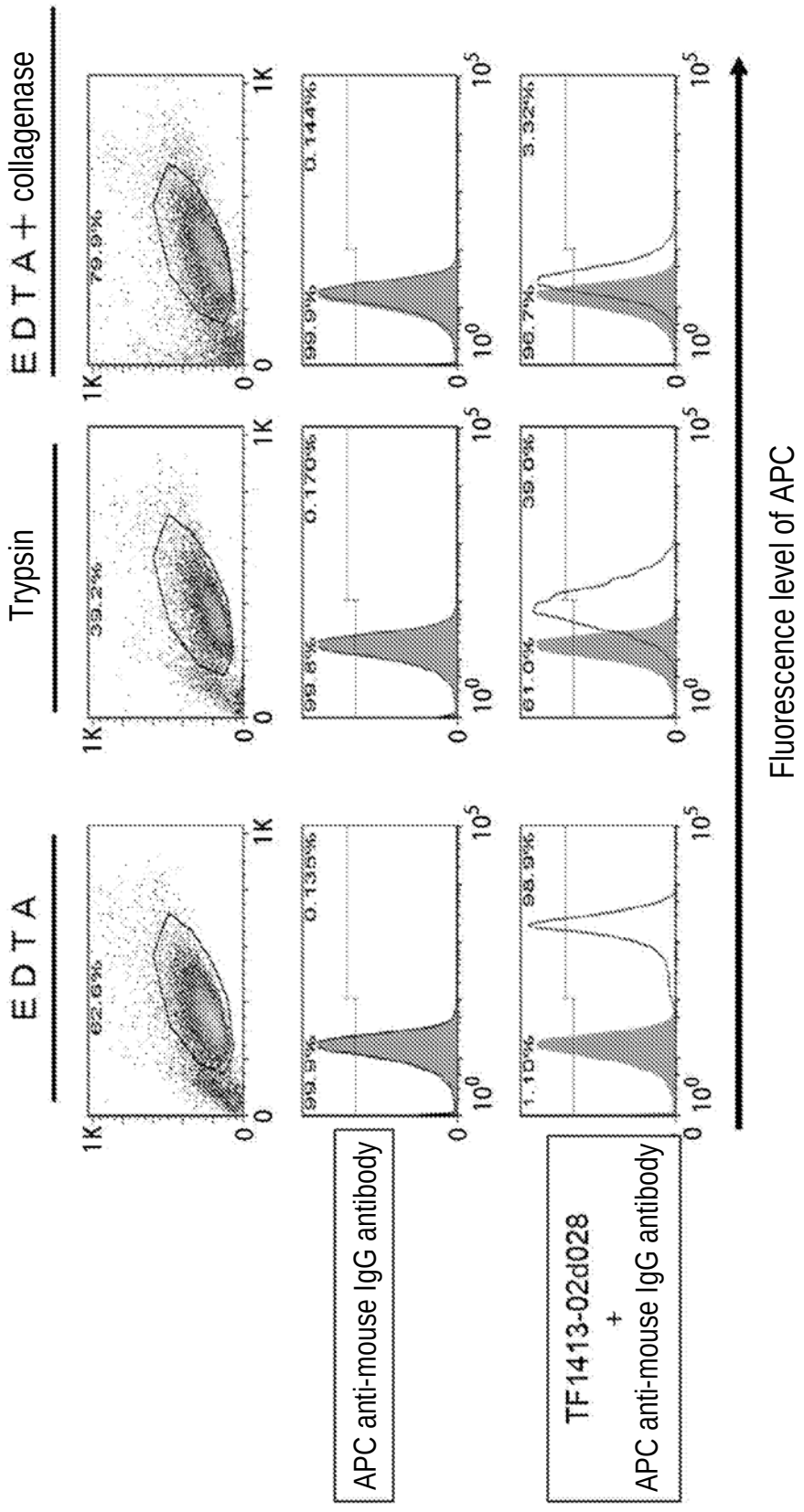
[Fig. 2]


GPC3-expressing cell line
02d023
02d028
02d030
02d039
02e003
02e004
02e014
02e030
02e040
03e001
N-terminal fragment
1.0
14.1
6.4
7.8
1.0
15.6
15.1
4.0
12.3
7.6
C-terminal fragment
1.1
1.2
1.1
1.5
1.0
1.4
1.2
1.0
1.1
1.0
Full length
1.1
8.0
3.8
5.2
1.0
8.2
8.1
2.5
6.9
3.0
GPC3-expressing cell line
03e004
03e005
03e015
03e016
03e019
03e027
03e034
03e045
GC33
GC199
N-terminal fragment
3.0
14.5
16.7
1.0
11.9
5.3
6.8
1.1
3.2
1.1
C-terminal fragment
1.0
1.1
1.2
1.1
1.0
1.0
1.0
1.0
17.7
5.0
Full length
2.7
5.9
8.9
1.0
3.0
2.3
2.9
1.0
28.5
8.3

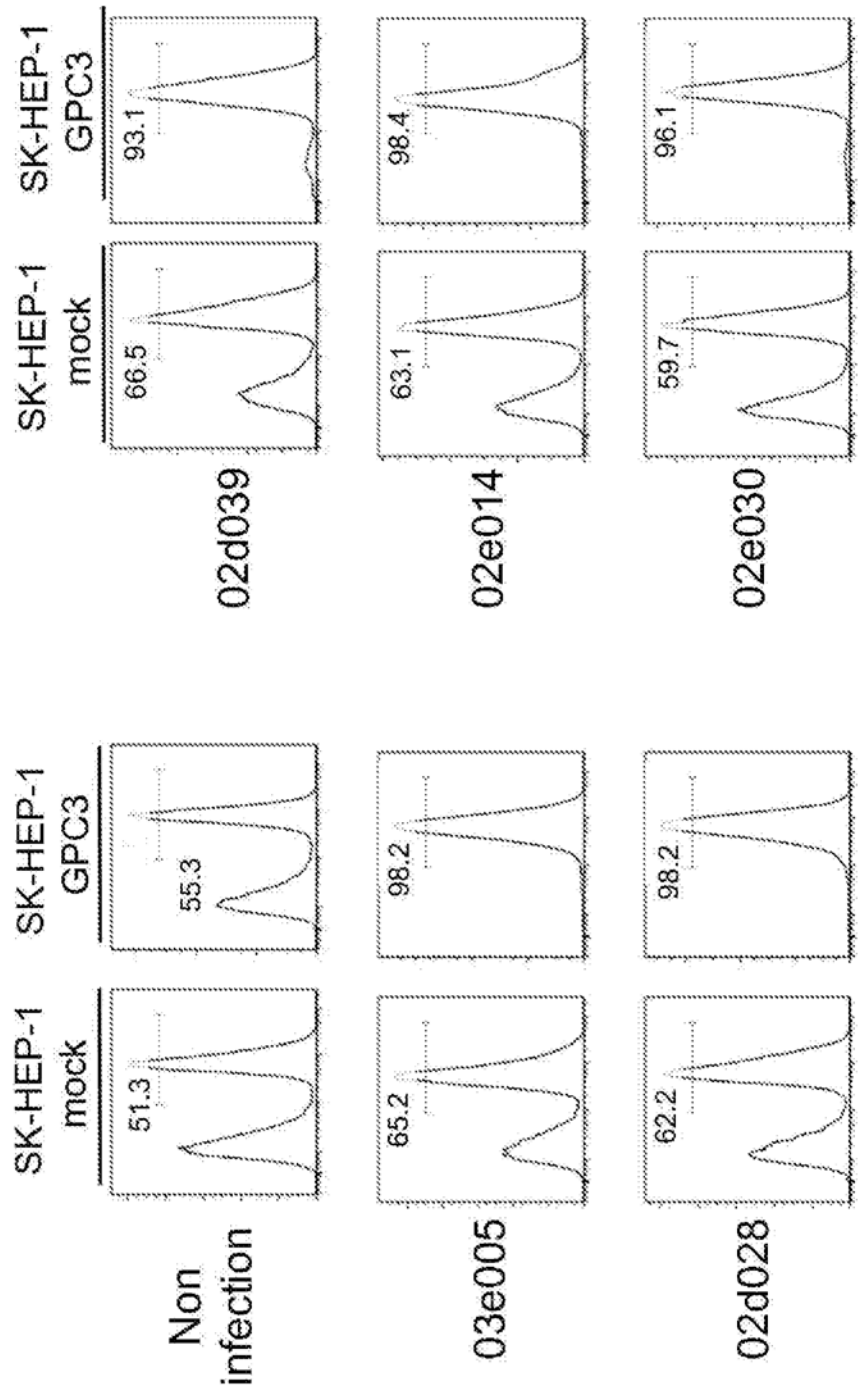
[Fig. 3]


02d028
02d039
02e004
02e014
02e030
02e040
03e001
03e004
03e005
03e015
03e034
GC33
GC199
N-terminal fragment
C-terminal fragment
Full length
GPC3-expressing cell line

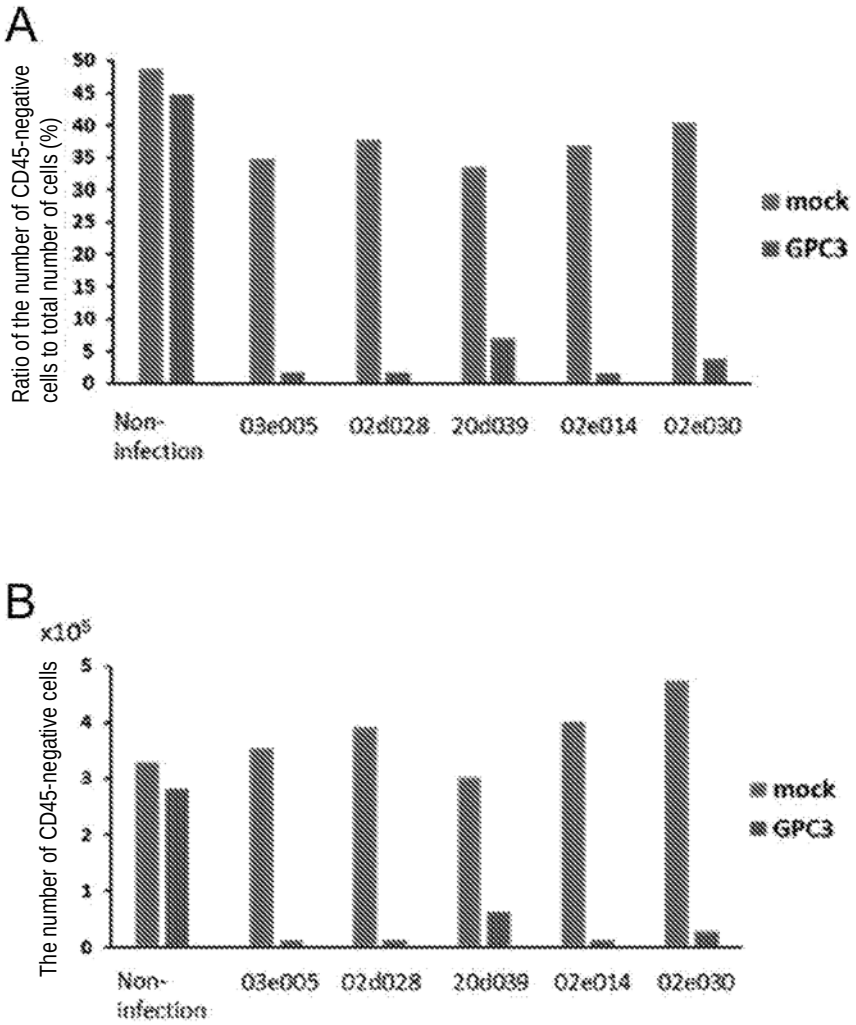
[Fig. 4]


EDTA
Trypsin
EDTA + collagenase
APC anti-mouse IgG antibody
TF1413-02d028
+
APC anti-mouse IgG antibody
Fluorescence level of APC

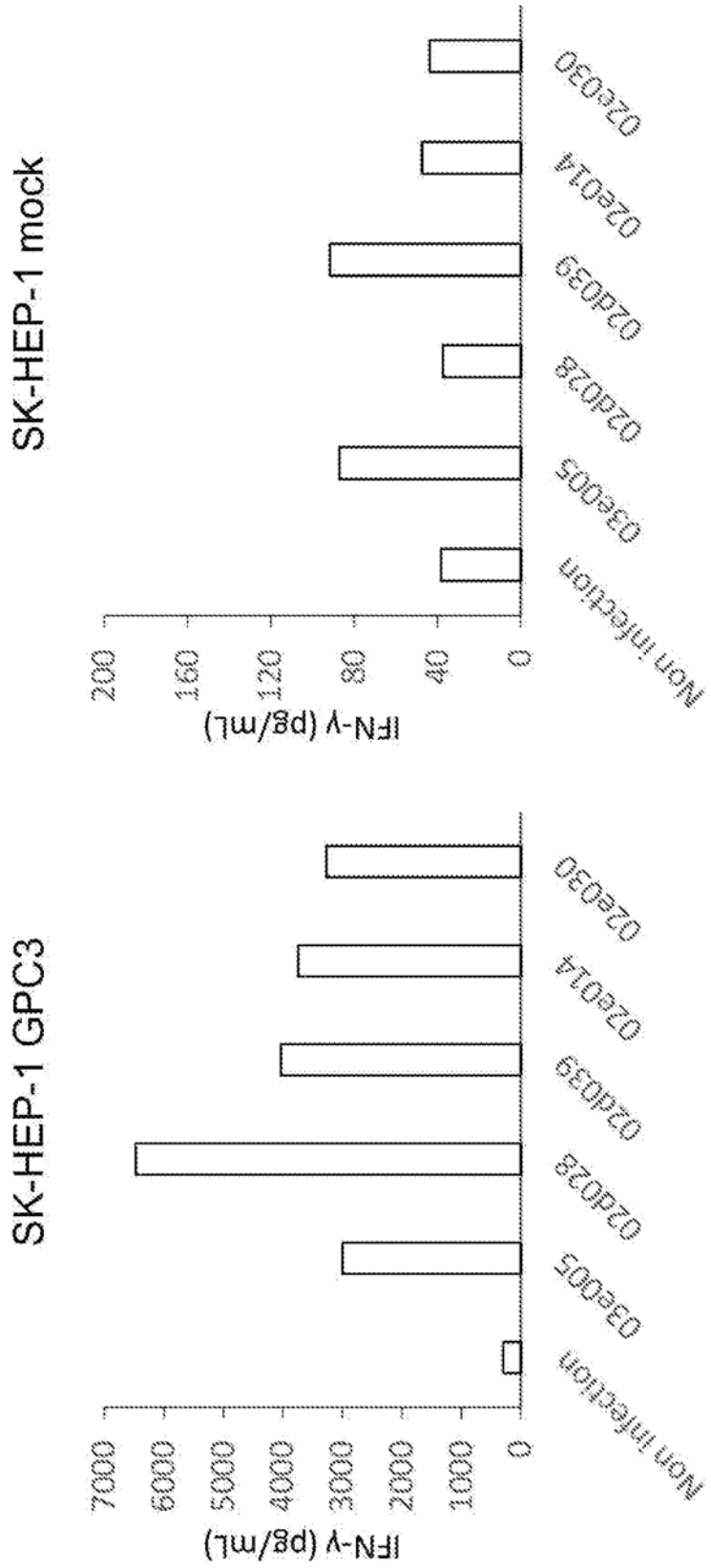
[Fig. 5]


SK-HEP-1 mock
SK-HEP-1 GPC3
Non infection
51.3
55.3
03e005
65.2
98.2
02d028
62.2
98.2
02d039
66.5
93.1
02e014
63.1
98.4
02e030
59.7
96.1

[Fig. 6]


A
Ratio of the number of CD45-negative cells to total number of cells (%)
50
45
40
35
30
25
20
15
10
5
0
mock
GPC3
Non-infection
03e005
02d028
20d039
02e014
02e030
B
x10^5
The number of CD45-negative cells
5
4
3
2
1
0
mock
GPC3
Non-infection
03e005
02d028
20d039
02e014
02e030

[Fig. 7]


SK-HEP-1 mock
IFN-γ (pg/mL)
0
40
80
120
160
200
Non infection
03ec005
02d028
02d039
02e014
02e030
SK-HEP-1 GPC3
IFN-γ (pg/mL)
0
1000
2000
3000
4000
5000
6000
7000
Non infection
03ec005
02d028
02d039
02e014
02e030

SEQUENCE LISTING

<110> YAMAGUCHI UNIVERSITY
NATIONAL CANCER CENTER

<120> Anti-GPC3 antibody

<130> FH29-004WO

<150> JP 2017-1732
<151> 2017-01-10

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<220>
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<223> Inventor: TAMADA, Koji; SAKODA, Yukimi; NAKATSURA, Tetsuya; SAITO, Keigo

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Gly Tyr Asn Met Asn
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Gly

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Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr
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Leu Ala Ser Asn Arg His Thr
1 5

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Leu Gln His Trp Asn Tyr Pro Leu Thr
1 5

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

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

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

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

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

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

Ala Arg Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser
115

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Asp Ile Gln Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
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Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Thr Ala
20 25 30

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

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

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

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Leu
85 90 95

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

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1               5                  10                  15


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


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


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


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


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


Ala Arg Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125


Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140


Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160
```

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

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
    210                 215                 220

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
                245                 250                 255

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
            260                 265                 270

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
        275                 280                 285

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
    290                 295                 300

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305                 310                 315                 320

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg
                325                 330                 335

Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val
            340                 345                 350
```

```
Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
        355                 360                 365

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380

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

Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
                405                 410                 415

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
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Lys
```

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Asp Ile Gln Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
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Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Thr Ala
            20                  25                  30

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

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

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

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

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

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
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Ser Tyr Asp Met Ser
1 5

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Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro Asp Thr Val Lys
1 5 10 15

Gly

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<212> PRT
<213> Artificial

<220>
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<400> 13

Arg Gly Leu Arg Arg Ala Met Asp Tyr
1 5

<210> 14
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<212> PRT
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Arg Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
1   5   10   15

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<212> PRT
<213> Artificial

<220>
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Lys Val Ser Asn Arg Phe Ser
1   5

<210> 16
<211> 9
<212> PRT
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<220>
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Ser Gln Ser Thr His Val Pro Leu Thr
1   5

<210> 17
<211> 117
<212> PRT
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<400> 17

```
Glu Val Lys 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 Ala Phe Ser Ser Tyr
            20                  25                  30


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


Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro 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 Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


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


Ser Val Thr Val Ser
        115


<210>  18
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<212>  PRT
<213>  Artificial

<220>
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Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                  10                  15


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

```
Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

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

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

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

Thr His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110

Arg
```

<210> 19
<211> 448
<212> PRT
<213> Artificial

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<223> TF1413-02d039 H Chain

<400> 19

```
Glu Val Lys 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 Ala Phe Ser Ser Tyr
            20                  25                  30

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

```
Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro 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 Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

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

Ser Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro
        115                 120                 125

Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly
    130                 135                 140

Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn
145                 150                 155                 160

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

Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr
            180                 185                 190

Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser
        195                 200                 205

Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro
    210                 215                 220

Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser
225                 230                 235                 240
```

```
Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu
                245                 250                 255

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

Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala
        275                 280                 285

Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val
    290                 295                 300

Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe
305                 310                 315                 320

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

Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu
            340                 345                 350

Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys
        355                 360                 365

Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn
    370                 375                 380

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

Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys
                405                 410                 415

Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly
            420                 425                 430
```

Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
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<223> TF1413-02d039 L Chain

<400> 20

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

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

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

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

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

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

Thr His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100   105   110

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
        115   120   125

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
    130   135   140

```
Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
145                 150                 155                 160


Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
                165                 170                 175


Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
            180                 185                 190


Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
        195                 200                 205


Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215


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Ser Tyr Trp Met Asn
1               5


<210>  22
<211>  17
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e004 H Chain CDR 2

<400>  22

Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe Lys
1               5                   10                  15
```

Asp

<210> 23
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<212> PRT
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<220>
<223> TF1413-02e004 H Chain CDR 3

<400> 23

Gly Tyr Tyr Ala Met Asp Tyr
1 5

<210> 24
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<212> PRT
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<223> TF1413-02e004 L Chain CDR 1

<400> 24

Lys Ala Ser Gln Asp Val Ser Thr Ala Val Ala
1 5 10

<210> 25
<211> 7
<212> PRT
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<223> TF1413-02e004 L Chain CDR 2

<400> 25

Ser Ala Ser Tyr Arg Tyr Thr
1 5

<210> 26
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<212> PRT
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<220>
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<400> 26

Gln Gln His Tyr Ser Thr Pro Thr
1 5

<210> 27
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<212> PRT
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Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

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

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

Gly Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Glu Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

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

Thr Val Ser
115

<210> 28
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Asp Ile Val Leu Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
20 25 30

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65 70 75 80

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

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

<210> 29
<211> 446

<212> PRT
<213> Artificial

<220>
<223> TF1413-02e004 H Chain

<400> 29

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


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


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


Gly Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Asp Glu Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80


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


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


Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala
        115                 120                 125


Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu
    130                 135                 140


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

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

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

Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys
        195                 200                 205

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
    210                 215                 220

Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
                245                 250                 255

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

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
        275                 280                 285

Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala
    290                 295                 300

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

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

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
            340                 345                 350
```

```
Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val
        355                 360                 365


Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
    370                 375                 380


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


Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp
                405                 410                 415


Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His
            420                 425                 430


Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        435                 440                 445


<210>  30
<211>  213
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e004 L Chain

<400>  30

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


Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Thr Ala
            20                  25                  30


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


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

```
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala
65                  70                  75                  80

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

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

Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly
        115                 120                 125

Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn
    130                 135                 140

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

Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser
                165                 170                 175

Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr
            180                 185                 190

Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
        195                 200                 205

Asn Arg Asn Glu Cys
    210
```

<210> 31
<211> 5
<212> PRT
<213> Artificial

<220>

<223> TF1413-02e014 H Chain CDR 1

<400> 31

Asp Tyr Tyr Met His
1   5

<210> 32
<211> 17
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 H Chain CDR 2

<400> 32

Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe Gln
1   5   10   15

Gly

<210> 33
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 H Chain CDR 3

<400> 33

Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr
1   5   10

<210> 34
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 L Chain CDR 1

<400> 34

Lys Ala Ser Gln Asp Val Gly Thr Ala Val Ala
1 5 10

<210> 35
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 L Chain CDR 2

<400> 35

Trp Ala Ser Thr Arg His Thr
1 5

<210> 36
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 L Chain CDR 3

<400> 36

Gln Gln Tyr Ser Ser Tyr Pro Leu Thr
1 5

<210> 37
<211> 120
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 H Chain V Region

<400> 37

Gln Val Gln Leu Lys Gln Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1 5 10 15

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

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

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

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65   70   75   80

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

Asn Ala Gly Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly
            100   105   110

Gln Gly Thr Ser Val Thr Val Ser
        115   120

<210> 38
<211> 108
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 L Chain V Region

<400> 38

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

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20   25   30

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

```
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

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

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

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

<210> 39
<211> 451
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 H Chain

<400> 39

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

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

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

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

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80
```

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

Asn Ala Gly Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Lys Thr Ala Pro Ser
        115                 120                 125

Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val
    130                 135                 140

Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu
145                 150                 155                 160

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

Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr
            180                 185                 190

Ser Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro
        195                 200                 205

Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr
    210                 215                 220

Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly
225                 230                 235                 240

Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met
                245                 250                 255

Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu
            260                 265                 270
```

```
Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val
        275                 280                 285

His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu
    290                 295                 300

Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly
305                 310                 315                 320

Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile
                325                 330                 335

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

Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr
        355                 360                 365

Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu
    370                 375                 380

Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val
                405                 410                 415

Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val
            420                 425                 430

His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr
        435                 440                 445

Pro Gly Lys
    450
```

<210> 40
<211> 214
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 L Chain

<400> 40

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


Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30


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


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


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


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


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


Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125


Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140


Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160
```

```
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175


Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190


Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205


Phe Asn Arg Asn Glu Cys
    210


<210>  41
<211>  5
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e030 H Chain CDR 1

<400>  41

Asp Tyr Tyr Met His
1               5


<210>  42
<211>  17
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e030 H Chain CDR 2

<400>  42

Trp Ile Asp Pro Glu Asn Gly Asn Thr Ile Tyr Asp Pro Lys Phe Gln
1               5                   10                  15


Gly
```

<210> 43
<211> 8
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 H Chain CDR 3

<400> 43

Thr Met Ile Thr Thr Leu Asp Tyr
1 5

<210> 44
<211> 17
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 L Chain CDR 1

<400> 44

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 45
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 L Chain CDR 2

<400> 45

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 46
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 L Chain CDR 3

<400> 46

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 47
<211> 117
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 H Chain V Region

<400> 47

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

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

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

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

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

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

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

Thr Leu Thr Val Ser
115

<210> 48
<211> 114
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 L Chain V Region

<400> 48

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

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

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

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys Arg

<210> 49
<211> 448
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 H Chain

<400> 49

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


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


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


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


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


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


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


Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro
        115                 120                 125


Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly
    130                 135                 140
```

```
Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp Asn
145                 150                 155                 160


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


Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr
            180                 185                 190


Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser
        195                 200                 205


Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro
    210                 215                 220


Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser
225                 230                 235                 240


Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu
                245                 250                 255


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


Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala
        275                 280                 285


Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val
    290                 295                 300


Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe
305                 310                 315                 320


Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr
                325                 330                 335
```

Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu
340 345 350

Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys
355 360 365

Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn
370 375 380

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

Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys
405 410 415

Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly
420 425 430

Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
435 440 445

<210> 50
<211> 220
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e030 L Chain

<400> 50

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

```
Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

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

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser
        115                 120                 125

Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn
    130                 135                 140

Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu
145                 150                 155                 160

Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp
                165                 170                 175

Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr
            180                 185                 190

Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr
        195                 200                 205

Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215                 220
```

<210> 51
<211> 5

<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 H Chain CDR 1

<400> 51

Gly Tyr Thr Met Asn
1 5

<210> 52
<211> 17
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 H Chain CDR 2

<400> 52

Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Asn Phe Lys
1 5 10 15

Gly

<210> 53
<211> 8
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 H Chain CDR 3

<400> 53

Gly Tyr Tyr Gly Arg Phe Asp Tyr
1 5

<210> 54
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 L Chain CDR 1

<400> 54

Lys Ala Ser Gln Asn Val Arg Thr Ala Val Ala
1   5   10

<210> 55
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 L Chain CDR 2

<400> 55

Leu Ala Ser Asn Arg His Thr
1   5

<210> 56
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 L Chain CDR 3

<400> 56

Leu Gln His Trp Asn Tyr Pro Leu Thr
1   5

<210> 57
<211> 116
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 H Chain V Region

<400> 57

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


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


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


Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Asn Phe
    50                  55                  60


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


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


Ala Arg Gly Tyr Tyr Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110


Leu Thr Val Ser
        115


<210>  58
<211>  108
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e040 L Chain V Region

<400>  58

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


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

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

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

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

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Leu
                85                  90                  95

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


<210>  59
<211>  447
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e040 H Chain

<400>  59

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

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

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

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Asn Phe
    50                  55                  60
```

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


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


Ala Arg Gly Tyr Tyr Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110


Leu Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu
        115                 120                 125


Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys
    130                 135                 140


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


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


Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp
            180                 185                 190


Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr
        195                 200                 205


Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys
    210                 215                 220


Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240


Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser
                245                 250                 255
```

```
Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp
            260                 265                 270

Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln
        275                 280                 285

Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser
    290                 295                 300

Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys
305                 310                 315                 320

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

Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro
            340                 345                 350

Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met
        355                 360                 365

Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn
    370                 375                 380

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

Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn
                405                 410                 415

Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu
            420                 425                 430

His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        435                 440                 445
```

<210> 60
<211> 214
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 L Chain

<400> 60

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


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


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


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


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


Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Leu
                85                  90                  95


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110


Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125


Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140


Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160
```

```
Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175


Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190


Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205


Phe Asn Arg Asn Glu Cys
    210


<210>  61
<211>  5
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e001 H Chain CDR 1

<400>  61

Gly Tyr Tyr Met His
1               5


<210>  62
<211>  17
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e001 H Chain CDR 2

<400>  62

Arg Ile Asn Pro Tyr Asn Gly Ala Thr Ser Tyr Asn Gln Asn Phe Lys
1               5                   10                  15


Asp
```

<210> 63
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 H Chain CDR 3

<400> 63

Asn Tyr Gly Tyr Phe Asp Tyr
1   5

<210> 64
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 L Chain CDR 1

<400> 64

Glu Ala Ser Gln Asn Val Asp Asn Asn Val Val
1   5   10

<210> 65
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 L Chain CDR 2

<400> 65

Ser Ala Ser Tyr Arg Tyr Ser
1   5

<210> 66
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 L Chain CDR 3

<400> 66

Gln Gln Tyr Asn Ser Tyr Pro Leu Thr
1   5

<210> 67
<211> 115
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 H Chain V Region

<400> 67

Gln Val Gln Leu Lys 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 Gly Tyr
            20   25   30

Tyr Met His Trp Val Lys Gln Ser His Val Lys Ser Leu Glu Trp Ile
        35   40   45

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

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

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

Ala Arg Asn Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
            100   105   110

Thr Val Ser
        115

<210> 68
<211> 108
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 L Chain V Region

<400> 68

Asp Ile Lys Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1   5   10   15

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

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

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

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

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85   90   95

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

<210> 69
<211> 446
<212> PRT
<213> Artificial

<220>

<223> TF1413-03e001 H Chain

<400> 69

```
Gln Val Gln Leu Lys 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 Gly Tyr
            20                  25                  30


Tyr Met His Trp Val Lys Gln Ser His Val Lys Ser Leu Glu Trp Ile
        35                  40                  45


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


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


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


Ala Arg Asn Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
            100                 105                 110


Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala
        115                 120                 125


Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu
    130                 135                 140


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


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

```
Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser Thr Trp Pro
            180                 185                 190

Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys
        195                 200                 205

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
    210                 215                 220

Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
                245                 250                 255

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

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
        275                 280                 285

Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala
    290                 295                 300

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

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

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
            340                 345                 350

Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val
        355                 360                 365
```

```
Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
    370                 375                 380

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

Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp
                405                 410                 415

Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His
            420                 425                 430

Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
        435                 440                 445
```

<210> 70
<211> 214
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e001 L Chain

<400> 70

```
Asp Ile Lys Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15

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

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

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

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

```
Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95

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

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

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

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
```

<210> 71
<211> 5
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 H Chain CDR 1

<400> 71

Ser Tyr Trp Met Asn
1 5

<210> 72
<211> 17
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 H Chain CDR 2

<400> 72

Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe Lys
1 5 10 15

Asp

<210> 73
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 H Chain CDR 3

<400> 73

Gly Tyr Tyr Gly Ser Asn Tyr
1 5

<210> 74
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 L Chain CDR 1

<400> 74

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
1 5 10

<210> 75
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 L Chain CDR 2

<400> 75

Ser Ala Ser Tyr Arg Tyr Ser
1 5

<210> 76
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 L Chain CDR 3

<400> 76

Gln Gln Tyr Asn Ser Tyr Pro Leu Thr
1 5

<210> 77
<211> 115
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 H Chain V Region

<400> 77

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

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

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

Gly Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Tyr Tyr Gly Ser Asn Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser
115

<210> 78
<211> 108
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 L Chain V Region

<400> 78

Asp Ile Lys Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

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

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

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


Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95


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


<210>  79
<211>  403
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e004 H Chain

<400>  79

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


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


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


Gly Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60


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


Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95
```

```
Ala Arg Gly Tyr Tyr Gly Ser Asn Tyr Trp Gly Gln Gly Thr Thr Leu
            100                 105                 110

Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala
        115                 120                 125

Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu Gly Cys Leu
    130                 135                 140

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

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

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

Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys
        195                 200                 205

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
    210                 215                 220

Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
                245                 250                 255

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

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
        275                 280                 285
```

```
Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala
    290                 295                 300

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
305                 310                 315                 320

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

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
            340                 345                 350

Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val
        355                 360                 365

Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
    370                 375                 380

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

Gly Ser Tyr
```

<210> 80
<211> 214
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 L Chain

<400> 80

```
Asp Ile Lys Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15

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

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

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

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

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

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

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
```

<210> 81
<211> 5
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 H Chain CDR 1

<400> 81

Asp Tyr Tyr Met His
1   5

<210> 82
<211> 17
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 H Chain CDR 2

<400> 82

Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Pro Lys Phe Gln
1   5   10   15

Gly

<210> 83
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 H Chain CDR 3

<400> 83

Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr
1   5   10

<210> 84
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 L Chain CDR 1

<400> 84

Arg Ala Ser Gln Glu Ile Ser Gly Tyr Leu Ser
1 5 10

<210> 85
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 L Chain CDR 2

<400> 85

Ala Ala Ser Thr Leu Asp Ser
1 5

<210> 86
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 L Chain CDR 3

<400> 86

Leu Gln Tyr Ala Ser Tyr Pro Leu Thr
1 5

<210> 87
<211> 120
<212> PRT
<213> Artificial

<220>

<223> TF1413-03e005 H Chain V Region

<400> 87

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


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


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


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


Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80


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


Asn Ala Phe Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Ser Val Thr Val Ser
        115                 120
```

<210> 88
<211> 108
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e005 L Chain V Region

<400> 88

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

```
Glu Arg Val Ser Leu Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
            20                  25                  30

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

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

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

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

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


<210>  89
<211>  451
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e005 H Chain

<400>  89

Gln Val Gln Leu Lys Glu Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1               5                   10                  15

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

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

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

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

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

Asn Ala Phe Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Ser Val Thr Val Ser Arg Ala Lys Thr Thr Ala Pro Ser
        115                 120                 125

Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val
    130                 135                 140

Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu
145                 150                 155                 160

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

Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr
            180                 185                 190

Ser Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro
        195                 200                 205

Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr
    210                 215                 220

Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly
225                 230                 235                 240
```

```
Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met
                245                 250                 255

Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu
            260                 265                 270

Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val
        275                 280                 285

His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu
    290                 295                 300

Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly
305                 310                 315                 320

Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile
                325                 330                 335

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

Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr
        355                 360                 365

Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu
    370                 375                 380

Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro
385                 390                 395                 400

Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val
                405                 410                 415

Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val
            420                 425                 430
```

```
His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr
        435                 440                 445


Pro Gly Lys
    450


<210>  90
<211>  214
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e005 L Chain

<400>  90

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


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


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


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


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


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


Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110


Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125
```

```
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140


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


Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175


Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190


Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205


Phe Asn Arg Asn Glu Cys
    210


<210>  91
<211>  5
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e015 H Chain CDR 1

<400>  91

Gly Tyr Thr Met Asn
1               5


<210>  92
<211>  17
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e015 H Chain CDR 2
```

<400> 92

Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 93
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 H Chain CDR 3

<400> 93

Gly Asp Tyr Tyr Pro Pro Tyr Ala Met Asp Tyr
1 5 10

<210> 94
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 L Chain CDR 1

<400> 94

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala
1 5 10

<210> 95
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 L Chain CDR 2

<400> 95

Ser Ala Ser Tyr Arg Tyr Ser
1 5

<210> 96
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 L Chain CDR 3

<400> 96

Gln Gln Tyr Asn Arg Tyr Pro Leu Thr
1 5

<210> 97
<211> 119
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 H Chain V Region

<400> 97

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

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

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

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Asp Tyr Tyr Pro Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser
115

<210> 98
<211> 108
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 L Chain V Region

<400> 98

Asp Ile Val Met Ser Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

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

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

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

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Arg Tyr Pro Leu
85 90 95

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

<210> 99
<211> 450
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 H Chain

<400> 99

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


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


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


Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60


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


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


Ala Arg Gly Asp Tyr Tyr Pro Pro Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110


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


Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr
    130                 135                 140
```

```
Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr
145                 150                 155                 160


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


Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser
            180                 185                 190


Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205


Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile
    210                 215                 220


Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly
225                 230                 235                 240


Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
                245                 250                 255


Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp
            260                 265                 270


Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
        275                 280                 285


Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg
    290                 295                 300


Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
305                 310                 315                 320


Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu
                325                 330                 335
```

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

Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
355 360 365

Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
370 375 380

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

Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
405 410 415

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
420 425 430

Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
435 440 445

Gly Lys
450

<210> 100
<211> 214
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 L Chain

<400> 100

Asp Ile Val Met Ser Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

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

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

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

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Arg Tyr Pro Leu
                85                  90                  95

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

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

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

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
```

<210> 101
<211> 5
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 H Chain CDR 1

<400> 101

Gly Tyr Asn Met Asn
1   5

<210> 102
<211> 17
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 H Chain CDR 2

<400> 102

Asn Ile Asp Pro Tyr Tyr Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys
1   5   10   15

Gly

<210> 103
<211> 10
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 H Chain CDR 3

<400> 103

Gly Asn Tyr Gly Tyr Tyr Ala Met Asp Tyr
1   5   10

<210> 104
<211> 11
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 L Chain CDR 1

<400> 104

Lys Ala Ser Gln Asn Val Arg Thr Ala Val Ala
1 5 10

<210> 105
<211> 7
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 L Chain CDR 2

<400> 105

Leu Ala Ser Asn Arg His Thr
1 5

<210> 106
<211> 9
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 L Chain CDR 3

<400> 106

Leu Gln His Trp Asn Tyr Pro Leu Thr
1 5

<210> 107
<211> 118
<212> PRT
<213> Artificial

<220>

<223> TF1413-03e034 H Chain V Region

<400> 107

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


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


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


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


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


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


Ala Arg Gly Asn Tyr Gly Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Ser Val Thr Val Ser
        115
```

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

<220>
<223> TF1413-03e034 L Chain V Region

<400> 108

```
Asp Ile Val Met Ser Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15
```

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

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

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

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

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Leu
                85                  90                  95

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


<210>  109
<211>  449
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e034 H Chain

<400>  109

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

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

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

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

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

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

Ala Arg Gly Asn Tyr Gly Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Val Cys Gly Asp Thr Thr Gly Ser Ser Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr Trp
145                 150                 155                 160

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

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser Ser
            180                 185                 190

Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys
    210                 215                 220

Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro
225                 230                 235                 240
```

```
Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser
                245                 250                 255

Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp
            260                 265                 270

Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr
        275                 280                 285

Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val
    290                 295                 300

Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu
305                 310                 315                 320

Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg
                325                 330                 335

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

Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr
        355                 360                 365

Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr
    370                 375                 380

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

Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys
                405                 410                 415

Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu
            420                 425                 430
```

Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly
435 440 445

Lys

<210> 110
<211> 214
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e034 L Chain

<400> 110

Asp Ile Val Met Ser Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

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

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

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

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

Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
100 105 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
115 120 125

```
Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

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

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
```

<210> 111
<211> 354
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d028 H Chain V Region Gene

<400> 111

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caggtgcagc tgaaggagtc aggacctgag ctggagaagc ctggtgcttc agtgaagata     60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgaactgggt gaagcagagc    120

aatggaaaga gccttgagtg gattggaaat attgatcctt actatggtgg tactagctac    180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac    240

atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagaggagac    300

tatagggcgt actactttga ctactggggc caaggcacca ctctcacagt ctcg          354
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<210> 112
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d028 L Chain V Region Gene

<400> 112
gacattcaga tgacccagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt actgctgtag cctggtatca acagaaacca 120

gggcagtctc ctaaagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcaatct 240

gaagacctgg cagattattt ctgtctgcaa cattggaatt atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa acgg 324

<210> 113
<211> 1347
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d028 H Chain Gene

<400> 113
caggtgcagc tgaaggagtc aggacctgag ctggagaagc ctggtgcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgaactgggt gaagcagagc 120

aatggaaaga gccttgagtg gattggaaat attgatcctt actatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagaggagac 300

tatagggcgt actactttga ctactggggc caaggcacca ctctcacagt ctcgagcgcc 360

aaaacaacag ccccatcggt ctatccactg gcccctgtgt gtggagatac aactggctcc 420

tcggtgactc taggatgcct ggtcaagggt tatttccctg agccagtgac cttgacctgg 480

aactctggat ccctgtccag tggtgtgcac accttcccag ctgtcctgca gtctgacctc 540

tacaccctca gcagctcagt gactgtaacc tcgagcacct ggcccagcca gtccatcacc 600

tgcaatgtgg cccacccggc aagcagcacc aaggtggaca agaaaattga gccccgggga 660

cccacaatca agccctgtcc tccatgcaaa tgcccagcac ctaacctctt gggtggacca 720

tccgtcttca tcttccctcc aaagatcaag gatgtactca tgatctccct gagccccata 780

gtcacatgtg tggtggtgga tgtgagcgag gatgacccag atgtccagat cagctggttt 840

gtgaacaacg tggaagtaca cacagctcag acacaaaccc atagagagga ttacaacagt 900

actctccggg tggtcagtgc cctccccatc cagcaccagg actggatgag tggcaaggag 960

ttcaaatgca aggtcaacaa caaagacctc ccagcgccca tcgagagaac catctcaaaa 1020

cccaaagggt cagtaagagc tccacaggta tatgtcttgc ctccaccaga agaagagatg 1080

actaagaaac aggtcactct gacctgcatg gtcacagact tcatgcctga agacatttac 1140

gtggagtgga ccaacaacgg gaaaacagag ctaaactaca agaacactga accagtcctg 1200

gactctgatg gttcttactt catgtacagc aagctgagag tggaaaagaa gaactgggtg 1260

gaaagaaata gctactcctg ttcagtggtc cacgagggtc tgcacaatca ccacacgact 1320

aagagcttct cccggactcc gggtaaa 1347

<210> 114
<211> 642
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d028 H Chain Gene

<400> 114
gacattcaga tgacccagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt actgctgtag cctggtatca acagaaacca 120

gggcagtctc ctaaagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcaatct 240

gaagacctgg cagattattt ctgtctgcaa cattggaatt atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 115
<211> 351
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d039 H Chain V Region Gene

<400> 115
gaagtgaagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cgctttcagt agctatgaca tgtcttgggt tcgccagact 120

ccggagaaga ggctggagtg ggtcgcatac attagtagtg gtggtggtag cacctactat 180

ccagacactg tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgc aagaagagga 300

ttacgacgag ctatggacta ctggggtcaa ggaacctcag tcaccgtctc g 351

<210> 116
<211> 339
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d039 L Chain V Region Gene

<400> 116
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaacgg 339

<210> 117
<211> 1344
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d039 H Chain Gene

<400> 117
gaagtgaagc tggtggagtc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cgctttcagt agctatgaca tgtcttgggt tcgccagact 120

ccggagaaga ggctggagtg ggtcgcatac attagtagtg gtggtggtag cacctactat 180

ccagacactg tgaagggccg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgc aagaagagga 300

ttacgacgag ctatggacta ctggggtcaa ggaacctcag tcaccgtctc gagcgccaaa 360

acaacagccc catcggtcta tccactggcc cctgtgtgtg gagatacaac tggctcctcg 420

gtgactctag gatgcctggt caagggttat ttccctgagc cagtgacctt gacctggaac 480

tctggatccc tgtccagtgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac 540

accctcagca gctcagtgac tgtaacctcg agcacctggc ccagccagtc catcacctgc 600

aatgtggccc acccggcaag cagcaccaag gtggacaaga aaattgagcc ccggggaccc 660

acaatcaagc cctgtcctcc atgcaaatgc ccagcaccta acctcttggg tggaccatcc 720

gtcttcatct tccctccaaa gatcaaggat gtactcatga tctccctgag ccccatagtc 780

acatgtgtgg tggtggatgt gagcgaggat gacccagatg tccagatcag ctggtttgtg 840

aacaacgtgg aagtacacac agctcagaca caaacccata gagaggatta caacagtact 900

ctccgggtgg tcagtgccct ccccatccag caccaggact ggatgagtgg caaggagttc 960

aaatgcaagg tcaacaacaa agacctccca gcgcccatcg agagaaccat ctcaaaaccc 1020

aaagggtcag taagagctcc acaggtatat gtcttgcctc caccagaaga agagatgact 1080

aagaaacagg tcactctgac ctgcatggtc acagacttca tgcctgaaga catttacgtg 1140

gagtggacca acaacgggaa aacagagcta aactacaaga acactgaacc agtcctggac 1200

tctgatggtt cttacttcat gtacagcaag ctgagagtgg aaaagaagaa ctgggtggaa 1260

agaaatagct actcctgttc agtggtccac gagggtctgc acaatcacca cacgactaag 1320

agcttctccc ggactccggg taaa 1344

<210> 118
<211> 657
<212> DNA
<213> Artificial

<220>
<223> TF1413-02d039 L Chain Gene

<400> 118
gatgttgtga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc 60

atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acatgttccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaacggg ctgatgctgc accaactgta 360

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 420

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 480

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 540

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 600

gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgt 657

<210> 119
<211> 345
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e004 H Chain V Region Gene

<400> 119
caggtccagc tgcagcagtc tggggctgag cttgtgaagc ctggggctcc agtgaagctg 60

tcctgcaagg cttctggcta caccttcacc agctactgga tgaactgggt gaagcagagg 120

cctggacgag gcctcgagtg gattggaagg attgatcctt ccgatagtga aactcactac 180

aatcaaaagt tcaaggacga ggccacactg actgtagaca aatcctccag cacagcctac 240

atccaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagagggtac 300

tatgctatgg actactgggg tcaaggaacc tcagtcaccg tctcg 345

<210> 120
<211> 321
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e004 L Chain V Region Gene

<400> 120
gacattgtgc tgacccaatc tcccaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgagt actgctgtag cctggtatca acagaaacca 120

ggacaatctc ctaaactact gatttactca gcatcctacc ggtacactgg agtccctgat 180

cgcttcactg gcagtggatc tgggacggat ttcactttca ccatcagcag tgtgcaggct 240

gaagacctgg cagtttatta ctgtcagcaa cattatagta ctccgacgtt cggtggaggc 300

accaagctgg aaatcaaacg g 321

<210> 121
<211> 1338

<212> DNA
<213> Artificial

<220>
<223> TF1413-02e004 H Chain Gene

<400> 121
caggtccagc tgcagcagtc tggggctgag cttgtgaagc ctggggctcc agtgaagctg 60

tcctgcaagg cttctggcta caccttcacc agctactgga tgaactgggt gaagcagagg 120

cctggacgag gcctcgagtg gattggaagg attgatcctt ccgatagtga aactcactac 180

aatcaaaagt tcaaggacga ggccacactg actgtagaca aatcctccag cacagcctac 240

atccaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagagggtac 300

tatgctatgg actactgggg tcaaggaacc tcagtcaccg tctcgagcgc caaaacaaca 360

gccccatcgg tctatccact ggcccctgtg tgtggagata caactggctc ctcggtgact 420

ctaggatgcc tggtcaaggg ttatttccct gagccagtga ccttgacctg gaactctgga 480

tccctgtcca gtggtgtgca caccttccca gctgtcctgc agtctgacct ctacaccctc 540

agcagctcag tgactgtaac ctcgagcacc tggcccagcc agtccatcac ctgcaatgtg 600

gcccacccgg caagcagcac caaggtggac aagaaaattg agccccgggg acccacaatc 660

aagccctgtc ctccatgcaa atgcccagca cctaacctct tgggtggacc atccgtcttc 720

atcttccctc caaagatcaa ggatgtactc atgatctccc tgagccccat agtcacatgt 780

gtggtggtgg atgtgagcga ggatgaccca gatgtccaga tcagctggtt tgtgaacaac 840

gtggaagtac acacagctca gacacaaacc catagagagg attacaacag tactctccgg 900

gtggtcagtg ccctccccat ccagcaccag gactggatga gtggcaagga gttcaaatgc 960

aaggtcaaca acaaagacct cccagcgccc atcgagagaa ccatctcaaa acccaaaggg 1020

tcagtaagag ctccacaggt atatgtcttg cctccaccag aagaagagat gactaagaaa 1080

caggtcactc tgacctgcat ggtcacagac ttcatgcctg aagacattta cgtggagtgg 1140

accaacaacg ggaaaacaga gctaaactac aagaacactg aaccagtcct ggactctgat 1200

ggttcttact tcatgtacag caagctgaga gtggaaaaga agaactgggt ggaaagaaat 1260

agctactcct gttcagtggt ccacgagggt ctgcacaatc accacacgac taagagcttc 1320

tcccggactc cgggtaaa 1338

<210> 122
<211> 639
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e004 L Chain Gene

<400> 122
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atcacctgca aggccagtca ggatgtgagt actgctgtag cctggtatca acagaaacca 120

ggacaatctc ctaaactact gatttactca gcatcctacc ggtacactgg agtccctgat 180

cgcttcactg gcagtggatc tgggacggat ttcactttca ccatcagcag tgtgcaggct 240

gaagacctgg cagtttatta ctgtcagcaa cattatagta ctccgacgtt cggtggaggc 300

accaagctgg aaatcaaacg ggctgatgct gcaccaactg tatccatctt cccaccatcc 360

agtgagcagt taacatctgg aggtgcctca gtcgtgtgct tcttgaacaa cttctacccc 420

aaagacatca atgtcaagtg gaagattgat ggcagtgaac gacaaaatgg cgtcctgaac 480

agttggactg atcaggacag caaagacagc acctacagca tgagcagcac cctcacgttg 540

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acttcaccca ttgtcaagag cttcaacagg aatgagtgt 639

<210> 123
<211> 360
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e014 H Chain V Region Gene

<400> 123
caggtgcagc tgaagcagtc aggggcagag cttgtgaggt caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gactactata tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtga tactgaatat 180

gccccgaagt tccagggcaa ggccactatg actgcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtaa tgcaggctac 300

tatgattacg acggctatgc tatggactac tggggtcaag gaacctcagt caccgtctcg 360

<210> 124
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e014 L Chain V Region Gene

<400> 124
gacattgtgc tgacacagtc tcccaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca ggatgtgggt actgctgtag cctggtatca acagaaacca 120

gggcaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccccgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 240

gaagacttgg cagattattt ctgtcagcaa tatagcagct atcctctgac gttcggtgga 300

ggcaccaagc tggaaatcaa acgg 324

<210> 125
<211> 1353
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e014 H Chain Gene

<400> 125
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tcctgcacag cttctggctt caacattaaa gactactata tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtga tactgaatat 180

gccccgaagt tccagggcaa ggccactatg actgcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtaa tgcaggctac 300

tatgattacg acggctatgc tatggactac tggggtcaag gaacctcagt caccgtctcg 360

agcgccaaaa aaacagcccc atcggtctat ccactggccc ctgtgtgtgg agatacaact 420

ggctcctcgg tgactctagg atgcctggtc aagggttatt tccctgagcc agtgaccttg 480

acctggaact ctggatccct gtccagtggt gtgcacacct tcccagctgt cctgcagtct 540

gacctctaca ccctcagcag ctcagtgact gtaacctcga gcacctggcc cagccagtcc 600

atcacctgca atgtggccca cccggcaagc agtaccaagg tggacaagaa aattgagccc 660

cggggaccca caatcaagcc ctgtcctcca tgcaaatgcc cagcacctaa cctcttgggt 720

ggaccatccg tcttcatctt ccctccaaag atcaaggatg tactcatgat ctccctgagc 780

cccatagtca catgtgtggt ggtggatgtg agcgaggatg acccagatgt ccagatcagc 840

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aacagtactc tccgggtggt cagtgccctc cccatccagc accaggactg gatgagtggc 960

aaggagttca aatgcaaggt caacaacaaa gacctcccag cgcccatcga gagaaccatc 1020

tcaaaaccca aagggtcagt aagagctcca caggtatatg tcttgcctcc accagaagaa 1080

gagatgacta agaaacaggt cactctgacc tgcatggtca cagacttcat gcctgaagac 1140

atttacgtgg agtggaccaa caacgggaaa acagagctaa actacaagaa cactgaacca 1200

gtcctggact ctgatggttc ttacttcatg tacagcaagc tgagagtgga aaagaagaac 1260

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acgactaaga gcttctcccg gactccgggt aaa 1353

<210> 126
<211> 642
<212> DNA
<213> Artificial

<220>

<223> TF1413-02e014 L Chain Gene

<400> 126
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atcacctgca aggccagtca ggatgtgggt actgctgtag cctggtatca acagaaacca 120

gggcaatctc ctaaactact gatttactgg gcatccaccc ggcacactgg agtccccgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcagtct 240

gaagacttgg cagattattt ctgtcagcaa tatagcagct atcctctgac gttcggtgga 300

ggcaccaagc tggaaatcaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 127
<211> 351
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e030 H Chain V Region Gene

<400> 127
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tcctgcaaag cttctggctt caacattaaa gactactata tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtaa cactatatat 180

gacccgaagt tccagggcaa ggccagtata acagcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtgc tatatctact 300

atgattacga cccttgacta ctggggccaa ggcaccactc tcacagtctc g 351

<210> 128
<211> 342
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e030 L Chain V Region Gene

<400> 128
gacatccaga tgacccagtc tccatcctcc ctggctatgt cagtagggca gaaggtcact 60

atgagctgca agtccagtca gagcctttta aatagtagca atcaaaagaa ctatttggcc 120

tggtaccagc agaaaccagg acagtctcct aaacttctgg tatactttgc atccactagg 180

gaatctgggg tccctgatcg cttcataggc agtggatctg ggacagattt cactcttacc 240

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ccgctcacgt tcggtgctgg gaccaagctg gagctgaaac gg 342

<210> 129
<211> 1344
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e030 H Chain Gene

<400> 129
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tcctgcaaag cttctggctt caacattaaa gactactata tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtaa cactatatat 180

gacccgaagt tccagggcaa ggccagtata acagcagaca catcctccaa cacagcctac 240

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gtgactctag gatgcctggt caagggttat ttccctgagc cagtgacctt gacctggaac 480

tctggatccc tgtccagtgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac 540

accctcagca gctcagtgac tgtaacctcg agcacctggc ccagccagtc catcacctgc 600

aatgtggccc acccggcaag cagcaccaag gtggacaaga aaattgagcc ccggggaccc 660

acaatcaagc cctgtcctcc atgcaaatgc ccagcaccta acctcttggg tggaccatcc 720

gtcttcatct tccctccaaa gatcaaggat gtactcatga tctccctgag ccccatagtc 780

acatgtgtgg tggtggatgt gagcgaggat gacccagatg tccagatcag ctggtttgtg 840

aacaacgtgg aagtacacac agctcagaca caaacccata gagaggatta caacagtact 900

ctccgggtgg tcagtgccct ccccatccag caccaggact ggatgagtgg caaggagttc 960

aaatgcaagg tcaacaacaa agacctccca gcgcccatcg agagaaccat ctcaaaaccc 1020

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aagaaacagg tcactctgac ctgcatggtc acagacttca tgcctgaaga catttacgtg 1140

gagtggacca acaacgggaa aacagagcta aactacaaga acactgaacc agtcctggac 1200

tctgatggtt cttacttcat gtacagcaag ctgagagtgg aaaagaagaa ctgggtggaa 1260

agaaatagct actcctgttc agtggtccac gagggtctgc acaatcacca cacgactaag 1320

agcttctccc ggactccggg taaa 1344

<210> 130
<211> 660
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e030 L Chain Gene

<400> 130
gacatccaga tgacccagtc tccatcctcc ctggctatgt cagtagggca gaaggtcact 60

atgagctgca agtccagtca gagcctttta aatagtagca atcaaaagaa ctatttggcc 120

tggtaccagc agaaaccagg acagtctcct aaacttctgg tatactttgc atccactagg 180

gaatctgggg tccctgatcg cttcataggc agtggatctg ggacagattt cactcttacc 240

atcagcagtg tgcaggctga agacctggca gattacttct gtcagcaaca ttatagcact 300

ccgctcacgt tcggtgctgg gaccaagctg gagctgaaac gggctgatgc tgcaccaact 360

gtatccatct tcccaccatc cagtgagcag ttaacatctg gaggtgcctc agtcgtgtgc 420

ttcttgaaca acttctaccc caaagacatc aatgtcaagt ggaagattga tggcagtgaa 480

cgacaaaatg gcgtcctgaa cagttggact gatcaggaca gcaaagacag cacctacagc 540

atgagcagca ccctcacgtt gaccaaggac gagtatgaac gacataacag ctatacctgt 600

gaggccactc acaagacatc aacttcaccc attgtcaaga gcttcaacag gaatgagtgt 660

<210> 131
<211> 348
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e040 H Chain V Region Gene

<400> 131
gaagtgatgc tggtggagtc tggacctgag ctggtgaagc ctggagcttc aatgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acaatggtgg tactagctac 180

aaccagaatt ttaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgtgc aagagggtac 300

tacggtcgct ttgactactg gggccaaggc accactctca cagtctcg 348

<210> 132
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e040 L Chain V Region Gene

<400> 132
gacatcttgc tgactcagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt actgctgtag cctggtatca acagaaacca 120

gggcagtctc ctaaagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcaatct 240

gaagacctgg cagattattt ctgtctgcaa cattggaatt atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa acgg 324

<210> 133
<211> 1341
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e040 H Chain Gene

<400> 133
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tcctgcaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acaatggtgg tactagctac 180

aaccagaatt ttaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgtgc aagagggtac 300

tacggtcgct ttgactactg gggccaaggc accactctca cagtctcgag cgccaaaaca 360

acagccccat cggtctatcc actggcccct gtgtgtggag atacaactgg ctcctcggtg 420

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ggatccctgt ccagtggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacacc 540

ctcagcagct cagtgactgt aacctcgagc acctggccca gccagtccat cacctgcaat 600

gtggcccacc cggcaagcag caccaaggtg gacaagaaaa ttgagccccg gggacccaca 660

atcaagccct gtcctccatg caaatgccca gcacctaacc tcttgggtgg accatccgtc 720

ttcatcttcc ctccaaagat caaggatgta ctcatgatct ccctgagccc catagtcaca 780

tgtgtggtgg tggatgtgag cgaggatgac ccagatgtcc agatcagctg gtttgtgaac 840

aacgtggaag tacacacagc tcagacacaa acccatagag aggattacaa cagtactctc 900

cgggtggtca gtgccctccc catccagcac caggactgga tgagtggcaa ggagttcaaa 960

tgcaaggtca acaacaaaga cctcccagcg cccatcgaga gaaccatctc aaaacccaaa 1020

gggtcagtaa gagctccaca ggtatatgtc ttgcctccac cagaagaaga gatgactaag 1080

aaacaggtca ctctgacctg catggtcaca gacttcatgc ctgaagacat ttacgtggag 1140

tggaccaaca acgggaaaac agagctaaac tacaagaaca ctgaaccagt cctggactct 1200

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aatagctact cctgttcagt ggtccacgag ggtctgcaca atcaccacac gactaagagc 1320

ttctcccgga ctccgggtaa a 1341

<210> 134
<211> 642
<212> DNA
<213> Artificial

<220>
<223> TF1413-02e040 L Chain Gene

<400> 134
gacatcttgc tgactcagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt actgctgtag cctggtatca acagaaacca 120

gggcagtctc ctaaagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

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gaagacctgg cagattattt ctgtctgcaa cattggaatt atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 135
<211> 345
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e001 H Chain V Region Gene

<400> 135
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tcctgcaagg cttctggtta ctcattcact ggctactaca tgcactgggt gaagcaaagc 120

catgtaaaga gccttgagtg gattggacgt attaatcctt acaatggtgc tactagctac 180

aaccagaatt tcaaggacaa ggccagcttg actgtagata agtcctccag cacagcctac 240

atggagctcc acagcctgac atctgaggac tctgcagtct attactgtgc aagaaactac 300

ggctactttg actactgggg ccaaggcacc actctcacag tctcg 345

<210> 136
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e001 L Chain V Region Gene

<400> 136
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gtcacctgcg aggccagtca gaatgtggat aataatgtag tctggtatca acagaaacca 120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

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gggaccaagt tggaaataaa acgg 324

<210> 137
<211> 1338

<212> DNA
<213> Artificial

<220>
<223> TF1413-03e001 H Chain Gene

<400> 137
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tcctgcaagg cttctggtta ctcattcact ggctactaca tgcactgggt gaagcaaagc 120

catgtaaaga gccttgagtg gattggacgt attaatcctt acaatggtgc tactagctac 180

aaccagaatt tcaaggacaa ggccagcttg actgtagata agtcctccag cacagcctac 240

atggagctcc acagcctgac atctgaggac tctgcagtct attactgtgc aagaaactac 300

ggctactttg actactgggg ccaaggcacc actctcacag tctcgagcgc caaaacaaca 360

gccccatcgg tctatccact ggcccctgtg tgtggagata caactggctc ctcggtgact 420

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agcagctcag tgactgtaac ctcgagcacc tggcccagcc agtccatcac ctgcaatgtg 600

gcccacccgg caagcagcac caaggtggac aagaaaattg agccccgggg acccacaatc 660

aagccctgtc ctccatgcaa atgcccagca cctaacctct tgggtggacc atccgtcttc 720

atcttccctc caaagatcaa ggatgtactc atgatctccc tgagccccat agtcacatgt 780

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gtggaagtac acacagctca gacacaaacc catagagagg attacaacag tactctccgg 900

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aaggtcaaca acaaagacct cccagcgccc atcgagagaa ccatctcaaa acccaaaggg 1020

tcagtaagag ctccacaggt atatgtcttg cctccaccag aagaagagat gactaagaaa 1080

caggtcactc tgacctgcat ggtcacagac ttcatgcctg aagacattta cgtggagtgg 1140

accaacaacg ggaaaacaga gctaaactac aagaacactg aaccagtcct ggactctgat 1200

ggttcttact tcatgtacag caagctgaga gtggaaaaga agaactgggt ggaaagaaat 1260

agctactcct gttcagtggt ccacgagggt ctgcacaatc accacacgac taagagcttc 1320

tcccggactc cgggtaaa 1338

<210> 138
<211> 642
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e001 L Chain Gene

<400> 138
gacatcaaga tgacccagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgcg aggccagtca gaatgtggat aataatgtag tctggtatca acagaaacca 120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtcagcaa tataacagct atcctctcac gttcggtgct 300

gggaccaagt tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 139
<211> 345
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e004 H Chain V Region Gene

<400> 139
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tcctgcaagg cttctggcta caccttcacc agctactgga tgaactgggt gaagcagagg 120

cctggacgag gcctcgagtg gattggaagg attgatcctt ccgatagtga aactcactac 180

aatcaaaagt tcaaggacaa ggccacactg actgtagaca aatcctccag cacagcctac 240

atccaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagagggtac 300

tacggtagta actactgggg ccaaggcacc actctcacag tctcg 345

<210> 140
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e004 L Chain V Region Gene

<400> 140
gacatcaaga tgacccagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtatca acagaaacca 120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtcagcaa tataacagct atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa acgg 324

<210> 141
<211> 1338
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e004 H Chain Gene

<400> 141
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tcctgcaagg cttctggcta caccttcacc agctactgga tgaactgggt gaagcagagg 120

cctggacgag gcctcgagtg gattggaagg attgatcctt ccgatagtga aactcactac 180

aatcaaaagt tcaaggacaa ggccacactg actgtagaca aatcctccag cacagcctac 240

atccaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagagggtac 300

tacggtagta actactgggg ccaaggcacc actctcacag tctcgagcgc caaaacaaca 360

gccccatcgg tctatccact ggcccctgtg tgtggagata caactggctc ctcggtgact 420

ctaggatgcc tggtcaaggg ttatttccct gagccagtga ccttgacctg gaactctgga 480

tccctgtcca gtggtgtgca caccttccca gctgtcctgc agtctgacct ctacaccctc 540

agcagctcag tgactgtaac ctcgagcacc tggcccagcc agtccatcac ctgcaatgtg 600

gcccacccgg caagcagcac caaggtggac aagaaaattg agccccgggg acccacaatc 660

aagccctgtc ctccatgcaa atgcccagca cctaacctct tgggtggacc atccgtcttc 720

atcttccctc caaagatcaa ggatgtactc atgatctccc tgagccccat agtcacatgt 780

gtggtggtgg atgtgagcga ggatgaccca gatgtccaga tcagctggtt tgtgaacaac 840

gtggaagtac acacagctca gacacaaacc catagagagg attacaacag tactctccgg 900

gtggtcagtg ccctccccat ccagcaccag gactggatga gtggcaagga gttcaaatgc 960

aaggtcaaca acaaagacct cccagcgccc atcgagagaa ccatctcaaa acccaaaggg 1020

tcagtaagag ctccacaggt atatgtcttg cctccaccag aagaagagat gactaagaaa 1080

caggtcactc tgacctgcat ggtcacagac ttcatgcctg aagacattta cgtggagtgg 1140

accaacaacg ggaaaacaga gctaaactac aagaacactg aaccagtcct ggactctgat 1200

ggttcttact tcatgtacag caagctgaga gtggaaaaga agaactgggt ggaaagaaat 1260

agctactcct gttcagtggt ccacgagggt ctgcacaatc accacacgac taagagcttc 1320

tcccggactc cgggtaaa 1338

<210> 142
<211> 642
<212> DNA
<213> Artificial

<220>

<223> TF1413-03e004 L Chain Gene

<400> 142
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gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtatca acagaaacca 120

gggcaatctc ctaaagcact gatttactcg gcatcctacc ggtacagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtcagcaa tataacagct atcctctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggagcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 143
<211> 360
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e005 H Chain V Region Gene

<400> 143
caggtgcagc tgaaggagtc aggggcagag cttgtgaggt caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gactactata tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtga tactgaatat 180

gccccgaagt tccagggcaa ggccactatg actgcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtaa tgccttctac 300

tatgattacg acgggtatgc tatggactac tggggtcaag gaacctcagt caccgtctcg 360

<210> 144
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e005 L Chain V Region Gene

<400> 144
gatgttgtga tgacccaaac tccatcctcc ttatctgcct ctctgggaga aagagtcagt 60

ctcacttgtc gggcaagtca ggaaattagt ggttacttaa gctggcttca gcagaaacca 120

gatggaacta ttaaacgcct gatctacgcc gcatccactt tagattctgg tgtcccaaaa 180

aggttcagtg gcagtaggtc tgggtcagat tattctctca ccatcagcag ccttgagtct 240

gaagattttg cagactatta ctgtctacaa tatgctagtt atccgctcac gttcggtgct 300

gggaccaagc tggagctgaa acgg 324

<210> 145
<211> 1353
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e005 H Chain Gene

<400> 145
caggtgcagc tgaaggagtc aggggcagag cttgtgaggt caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gactactata tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtga tactgaatat 180

gccccgaagt tccagggcaa ggccactatg actgcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtaa tgccttctac 300

tatgattacg acgggtatgc tatggactac tggggtcaag gaacctcagt caccgtctcg 360

agggccaaaa caacagcccc atcggtctat ccactggccc ctgtgtgtgg agatacaact 420

ggctcctcgg tgactctagg atgcctggtc aagggttatt tccctgagcc agtgaccttg 480

acctggaact ctggatccct gtccagtggt gtgcacacct tcccagctgt cctgcagtct 540

gacctctaca ccctcagcag ctcagtgact gtaacctcga gcacctggcc cagccagtcc 600

atcacctgca atgtggccca cccggcaagc agcaccaagg tggacaagaa aattgagccc 660

cggggaccca caatcaagcc ctgtcctcca tgcaaatgcc cagcacctaa cctcttgggt 720

ggaccatccg tcttcatctt ccctccaaag atcaaggatg tactcatgat ctccctgagc 780

cccatagtca catgtgtggt ggtggatgtg agcgaggatg acccagatgt ccagatcagc 840

tggtttgtga acaacgtgga agtacacaca gctcagacac aaacccatag agaggattac 900

aacagtactc tccgggtggt cagtgccctc cccatccagc accaggactg gatgagtggc 960

aaggagttca aatgcaaggt caacaacaaa gacctcccag cgcccatcga gagaaccatc 1020

tcaaaaccca aagggtcagt aagagctcca caggtatatg tcttgcctcc accagaagaa 1080

gagatgacta agaaacaggt cactctgacc tgcatggtca cagacttcat gcctgaagac 1140

atttacgtgg agtggaccaa caacgggaaa acagagctaa actacaagaa cactgaacca 1200

gtcctggact ctgatggttc ttacttcatg tacagcaagc tgagagtgga aaagaagaac 1260

tgggtggaaa gaaatagcta ctcctgttca gtggtccacg agggtctgca caatcaccac 1320

acgactaaga gcttctcccg gactccgggt aaa 1353

<210> 146
<211> 642
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e005 L Chain Gene

<400> 146
gatgttgtga tgacccaaac tccatcctcc ttatctgcct ctctgggaga aagagtcagt 60

ctcacttgtc gggcaagtca ggaaattagt ggttacttaa gctggcttca gcagaaacca 120

gatggaacta ttaaacgcct gatctacgcc gcatccactt tagattctgg tgtcccaaaa 180

aggttcagtg gcagtaggtc tgggtcagat tattctctca ccatcagcag ccttgagtct 240

gaagattttg cagactatta ctgtctacaa tatgctagtt atccgctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 147
<211> 357
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e015 H Chain V Region Gene

<400> 147
gaggtccagc tgcagcagtc tggacctgag ctggtgaagc ctggagcttc aatgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acaatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgcgc aagaggggat 300

tactaccccc cctatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcg 357

<210> 148
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e015 L Chain V Region Gene

<400> 148
gacattgtga tgtcacagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtatca acagaaaccg 120

gggcaatctc ctaaaccact gatttattcg gcgtcctacc ggtatagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtcagcaa tataacagat atcctctcac gttcggtgtt 300

gggaccaagc tggaaatcaa acgg 324

<210> 149
<211> 1350
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e015 H Chain Gene

<400> 149
gaggtccagc tgcagcagtc tggacctgag ctggtgaagc ctggagcttc aatgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acaatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacatta actgtagaca agtcatccag cacagcctac 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgcgc aagaggggat 300

tactaccccc cctatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcgagc 360

gccaaaacaa cagccccatc ggtctatcca ctggcccctg tgtgtggaga tacaactggc 420

tcctcggtga ctctaggatg cctggtcaag ggttatttcc ctgagccagt gaccttgacc 480

tggaactctg gatccctgtc cagtggtgtg cacaccttcc cagctgtcct gcagtctgac 540

ctctacaccc tcagcagctc agtgactgta acctcgagca cctggcccag ccagtccatc 600

acctgcaatg tggcccaccc ggcaagcagc accaaggtgg acaagaaaat tgagccccgg 660

ggacccacaa tcaagccctg tcctccatgc aaatgcccag cacctaacct cttgggtgga 720

ccatccgtct tcatcttccc tccaaagatc aaggatgtac tcatgatctc cctgagcccc 780

atagtcacat gtgtggtggt ggatgtgagc gaggatgacc cagatgtcca gatcagctgg 840

tttgtgaaca acgtggaagt acacacagct cagacacaaa cccatagaga ggattacaac 900

agtactctcc gggtggtcag tgccctcccc atccagcacc aggactggat gagtggcaag 960

gagttcaaat gcaaggtcaa caacaaagac ctcccagcgc ccatcgagag aaccatctca 1020

aaacccaaag ggtcagtaag agctccacag gtatatgtct tgcctccacc agaagaagag 1080

atgactaaga aacaggtcac tctgacctgc atggtcacag acttcatgcc tgaagacatt 1140

tacgtggagt ggaccaacaa cgggaaaaca gagctaaact acaagaacac tgaaccagtc 1200

ctggactctg atggttctta cttcatgtac agcaagctga gagtggaaaa gaagaactgg 1260

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actaagagct tctcccggac tccgggtaaa 1350

<210> 150
<211> 642
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e015 L Chain Gene

<400> 150
gacattgtga tgtcacagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

gtcacctgca aggccagtca gaatgtgggt actaatgtag cctggtatca acagaaaccg 120

gggcaatctc ctaaaccact gatttattcg gcgtcctacc ggtatagtgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcagcaa tgtgcagtct 240

gaagacttgg cagagtattt ctgtcagcaa tataacagat atcctctcac gttcggtgtt 300

gggaccaagc tggaaatcaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 151
<211> 354
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e034 H Chain V Region Gene

<400> 151
gaggtccagc tgcagcagtc tggacctgag ctggagaagc ctggcgcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgaactgggt gaagcagagc 120

aatggaaaga gccttgagtg gattggaaat attgatcctt actatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagagggaac 300

tacgggtact atgctatgga ctactggggt caaggaacct cagtcaccgt ctcg 354

<210> 152
<211> 324
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e034 L Chain V Region Gene

<400> 152
gacattgtga tgtcacagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt actgctgtag cctggtatca acagaaacca 120

gggcagtctc ctaaagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcaatct 240

gaagacctgg cagattattt ctgtctgcaa cattggaatt atccgctcac gttcggtgct 300

gggaccaagc tggagctgaa acgg 324

<210> 153
<211> 1347

<212> DNA
<213> Artificial

<220>
<223> TF1413-03e034 H Chain Gene

<400> 153
gaggtccagc tgcagcagtc tggacctgag ctggagaagc ctggcgcttc agtgaagata 60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgaactgggt gaagcagagc 120

aatggaaaga gccttgagtg gattggaaat attgatcctt actatggtgg tactagctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca aatcctccag cacagcctac 240

atgcagctca agagcctgac atctgaggac tctgcagtct attactgtgc aagagggaac 300

tacgggtact atgctatgga ctactggggt caaggaacct cagtcaccgt ctcgagcgcc 360

aaaacaacag ccccatcggt ctatccactg gcccctgtgt gtggagatac aactggctcc 420

tcggtgactc taggatgcct ggtcaagggt tatttccctg agccagtgac cttgacctgg 480

aactctggat ccctgtccag tggtgtgcac accttcccag ctgtcctgca gtctgacctc 540

tacaccctca gcagctcagt gactgtaacc tcgagcacct ggcccagcca gtccatcacc 600

tgcaatgtgg cccacccggc aagcagcacc aaggtggaca agaaaattga gccccgggga 660

cccacaatca agccctgtcc tccatgcaaa tgcccagcac ctaacctctt gggtggacca 720

tccgtcttca tcttccctcc aaagatcaag gatgtactca tgatctccct gagccccata 780

gtcacatgtg tggtggtgga tgtgagcgag gatgacccag atgtccagat cagctggttt 840

gtgaacaacg tggaagtaca cacagctcag acacaaaccc atagagagga ttacaacagt 900

actctccggg tggtcagtgc cctccccatc cagcaccagg actggatgag tggcaaggag 960

ttcaaatgca aggtcaacaa caaagacctc ccagcgccca tcgagagaac catctcaaaa 1020

cccaaagggt cagtaagagc tccacaggta tatgtcttgc ctccaccaga agaagagatg 1080

actaagaaac aggtcactct gacctgcatg gtcacagact tcatgcctga agacatttac 1140

gtggagtgga ccaacaacgg gaaaacagag ctaaactaca agaacactga accagtcctg 1200

gactctgatg gttcttactt catgtacagc aagctgagag tggaaaagaa gaactgggtg 1260

gaaagaaata gctactcctg ttcagtggtc cacgagggtc tgcacaatca ccacacgact 1320

aagagcttct cccggactcc gggtaaa 1347

<210> 154
<211> 642
<212> DNA
<213> Artificial

<220>
<223> TF1413-03e034 L Chain Gene

<400> 154
gacattgtga tgtcacagtc tccaaaattc atgtccacat cagtaggaga cagggtcagc 60

atcacctgca aggccagtca gaatgttcgt actgctgtag cctggtatca acagaaacca 120

gggcagtctc ctaaagcact gatttacttg gcatccaacc ggcacactgg agtccctgat 180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccattagcaa tgtgcaatct 240

gaagacctgg cagattattt ctgtctgcaa cattggaatt atccgctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> 155
<211> 440
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<223> Human GPC3 N Terminal Fragment

<400> 155

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Asp Ala Thr Cys His Gln Val Arg Ser Phe Phe Gln Arg Leu Gln Pro
1               5                  10                  15

Gly Leu Lys Trp Val Pro Glu Thr Pro Val Pro Gly Ser Asp Leu Gln
            20                  25                  30

Val Cys Leu Pro Lys Gly Pro Thr Cys Cys Ser Arg Lys Met Glu Glu
        35                  40                  45

Lys Tyr Gln Leu Thr Ala Arg Leu Asn Met Glu Gln Leu Leu Gln Ser
    50                  55                  60

Ala Ser Met Glu Leu Lys Phe Leu Ile Ile Gln Asn Ala Ala Val Phe
65                  70                  75                  80

Gln Glu Ala Phe Glu Ile Val Val Arg His Ala Lys Asn Tyr Thr Asn
                85                  90                  95

Ala Met Phe Lys Asn Asn Tyr Pro Ser Leu Thr Pro Gln Ala Phe Glu
            100                 105                 110

Phe Val Gly Glu Phe Phe Thr Asp Val Ser Leu Tyr Ile Leu Gly Ser
        115                 120                 125

Asp Ile Asn Val Asp Asp Met Val Asn Glu Leu Phe Asp Ser Leu Phe
    130                 135                 140

Pro Val Ile Tyr Thr Gln Leu Met Asn Pro Gly Leu Pro Asp Ser Ala
145                 150                 155                 160

Leu Asp Ile Asn Glu Cys Leu Arg Gly Ala Arg Arg Asp Leu Lys Val
                165                 170                 175

Phe Gly Asn Phe Pro Lys Leu Ile Met Thr Gln Val Ser Lys Ser Leu
            180                 185                 190
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Gln Val Thr Arg Ile Phe Leu Gln Ala Leu Asn Leu Gly Ile Glu Val
        195                 200                 205

Ile Asn Thr Thr Asp His Leu Lys Phe Ser Lys Asp Cys Gly Arg Met
    210                 215                 220

Leu Thr Arg Met Trp Tyr Cys Ser Tyr Cys Gln Gly Leu Met Met Val
225                 230                 235                 240

Lys Pro Cys Gly Gly Tyr Cys Asn Val Val Met Gln Gly Cys Met Ala
                245                 250                 255

Gly Val Val Glu Ile Asp Lys Tyr Trp Arg Glu Tyr Ile Leu Ser Leu
            260                 265                 270

Glu Glu Leu Val Asn Gly Met Tyr Arg Ile Tyr Asp Met Glu Asn Val
        275                 280                 285

Leu Leu Gly Leu Phe Ser Thr Ile His Asp Ser Ile Gln Tyr Val Gln
    290                 295                 300

Lys Asn Ala Gly Lys Leu Thr Thr Thr Ile Gly Lys Leu Cys Ala His
305                 310                 315                 320

Ser Gln Gln Arg Gln Tyr Arg Ser Ala Tyr Tyr Pro Glu Asp Leu Phe
                325                 330                 335

Ile Asp Lys Lys Val Leu Lys Val Ala His Val Glu His Glu Glu Thr
            340                 345                 350

Leu Ser Ser Arg Arg Arg Glu Leu Ile Gln Lys Leu Lys Ser Phe Ile
        355                 360                 365

Ser Phe Tyr Ser Ala Leu Pro Gly Tyr Ile Cys Ser His Ser Pro Val
    370                 375                 380
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Ala Glu Asn Asp Thr Leu Cys Trp Asn Gly Gln Glu Leu Val Glu Arg
385                 390                 395                 400


Tyr Ser Gln Lys Ala Ala Arg Asn Gly Met Lys Asn Gln Phe Asn Leu
                405                 410                 415


His Glu Leu Lys Met Lys Gly Pro Glu Pro Val Val Ser Gln Ile Ile
            420                 425                 430


Asp Lys Leu Lys His Ile Asn Gln
        435                 440


<210>  156
<211>  109
<212>  PRT
<213>  Homo sapiens

<220>
<221>  MISC_FEATURE
<223>  Human GPC3 C Terminal Fragment


<400>  156

Leu Leu Arg Thr Met Ser Met Pro Lys Gly Arg Val Leu Asp Lys Asn
1               5                   10                  15


Leu Asp Glu Glu Gly Phe Glu Ser Gly Asp Cys Gly Asp Asp Glu Asp
            20                  25                  30


Glu Cys Ile Gly Gly Ser Gly Asp Gly Met Ile Lys Val Lys Asn Gln
        35                  40                  45


Leu Arg Phe Leu Ala Glu Leu Ala Tyr Asp Leu Asp Val Asp Asp Ala
    50                  55                  60


Pro Gly Asn Ser Gln Gln Ala Thr Pro Lys Asp Asn Glu Ile Ser Thr
65                  70                  75                  80
```

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Phe His Asn Leu Gly Asn Val His Ser Pro Leu Lys Leu Leu Thr Ser
                85                  90                  95


Met Ala Ile Ser Val Val Cys Phe Phe Phe Leu Val His
            100                 105


<210>  157
<211>  580
<212>  PRT
<213>  Homo sapiens

<220>
<221>  MISC_FEATURE
<223>  Human GPC3


<400>  157

Met Ala Gly Thr Val Arg Thr Ala Cys Leu Val Val Ala Met Leu Leu
1               5                   10                  15


Ser Leu Asp Phe Pro Gly Gln Ala Gln Pro Pro Pro Pro Pro Pro Asp
            20                  25                  30


Ala Thr Cys His Gln Val Arg Ser Phe Phe Gln Arg Leu Gln Pro Gly
        35                  40                  45


Leu Lys Trp Val Pro Glu Thr Pro Val Pro Gly Ser Asp Leu Gln Val
    50                  55                  60


Cys Leu Pro Lys Gly Pro Thr Cys Cys Ser Arg Lys Met Glu Glu Lys
65                  70                  75                  80


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


Ser Met Glu Leu Lys Phe Leu Ile Ile Gln Asn Ala Ala Val Phe Gln
            100                 105                 110
```

```
Glu Ala Phe Glu Ile Val Val Arg His Ala Lys Asn Tyr Thr Asn Ala
        115                 120                 125

Met Phe Lys Asn Asn Tyr Pro Ser Leu Thr Pro Gln Ala Phe Glu Phe
    130                 135                 140

Val Gly Glu Phe Phe Thr Asp Val Ser Leu Tyr Ile Leu Gly Ser Asp
145                 150                 155                 160

Ile Asn Val Asp Asp Met Val Asn Glu Leu Phe Asp Ser Leu Phe Pro
                165                 170                 175

Val Ile Tyr Thr Gln Leu Met Asn Pro Gly Leu Pro Asp Ser Ala Leu
            180                 185                 190

Asp Ile Asn Glu Cys Leu Arg Gly Ala Arg Arg Asp Leu Lys Val Phe
        195                 200                 205

Gly Asn Phe Pro Lys Leu Ile Met Thr Gln Val Ser Lys Ser Leu Gln
    210                 215                 220

Val Thr Arg Ile Phe Leu Gln Ala Leu Asn Leu Gly Ile Glu Val Ile
225                 230                 235                 240

Asn Thr Thr Asp His Leu Lys Phe Ser Lys Asp Cys Gly Arg Met Leu
                245                 250                 255

Thr Arg Met Trp Tyr Cys Ser Tyr Cys Gln Gly Leu Met Met Val Lys
            260                 265                 270

Pro Cys Gly Gly Tyr Cys Asn Val Val Met Gln Gly Cys Met Ala Gly
        275                 280                 285

Val Val Glu Ile Asp Lys Tyr Trp Arg Glu Tyr Ile Leu Ser Leu Glu
    290                 295                 300
```

```
Glu Leu Val Asn Gly Met Tyr Arg Ile Tyr Asp Met Glu Asn Val Leu
305                 310                 315                 320

Leu Gly Leu Phe Ser Thr Ile His Asp Ser Ile Gln Tyr Val Gln Lys
                325                 330                 335

Asn Ala Gly Lys Leu Thr Thr Thr Ile Gly Lys Leu Cys Ala His Ser
            340                 345                 350

Gln Gln Arg Gln Tyr Arg Ser Ala Tyr Tyr Pro Glu Asp Leu Phe Ile
        355                 360                 365

Asp Lys Lys Val Leu Lys Val Ala His Val Glu His Glu Glu Thr Leu
    370                 375                 380

Ser Ser Arg Arg Arg Glu Leu Ile Gln Lys Leu Lys Ser Phe Ile Ser
385                 390                 395                 400

Phe Tyr Ser Ala Leu Pro Gly Tyr Ile Cys Ser His Ser Pro Val Ala
                405                 410                 415

Glu Asn Asp Thr Leu Cys Trp Asn Gly Gln Glu Leu Val Glu Arg Tyr
            420                 425                 430

Ser Gln Lys Ala Ala Arg Asn Gly Met Lys Asn Gln Phe Asn Leu His
        435                 440                 445

Glu Leu Lys Met Lys Gly Pro Glu Pro Val Val Ser Gln Ile Ile Asp
    450                 455                 460

Lys Leu Lys His Ile Asn Gln Leu Leu Arg Thr Met Ser Met Pro Lys
465                 470                 475                 480

Gly Arg Val Leu Asp Lys Asn Leu Asp Glu Glu Gly Phe Glu Ser Gly
                485                 490                 495
```

Asp Cys Gly Asp Asp Glu Asp Glu Cys Ile Gly Gly Ser Gly Asp Gly
500 505 510

Met Ile Lys Val Lys Asn Gln Leu Arg Phe Leu Ala Glu Leu Ala Tyr
515 520 525

Asp Leu Asp Val Asp Asp Ala Pro Gly Asn Ser Gln Gln Ala Thr Pro
530 535 540

Lys Asp Asn Glu Ile Ser Thr Phe His Asn Leu Gly Asn Val His Ser
545 550 555 560

Pro Leu Lys Leu Leu Thr Ser Met Ala Ile Ser Val Val Cys Phe Phe
565 570 575

Phe Leu Val His
580

<210> 158
<211> 1320
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Human GPC3 N Terminal Fragment Gene

<400> 158
gacgccacct gtcaccaagt ccgctccttc ttccagagac tgcagcccgg actcaagtgg 60

gtgccagaaa ctcccgtgcc aggatcagat ttgcaagtat gtctccctaa gggcccaaca 120

tgctgctcaa gaaagatgga agaaaaatac caactaacag cacgattgaa catggaacag 180

ctgcttcagt ctgcaagtat ggagctcaag ttcttaatta ttcagaatgc tgcggttttc 240

caagaggcct ttgaaattgt tgttcgccat gccaagaact acaccaatgc catgttcaag 300

aacaactacc caagcctgac tccacaagct tttgagtttg tgggtgaatt tttcacagat 360

gtgtctctct acatcttggg ttctgacatc aatgtagatg acatggtcaa tgaattgttt 420

gacagcctgt ttccagtcat ctatacccag ctaatgaacc caggcctgcc tgattcagcc 480

ttggacatca atgagtgcct ccgaggagca agacgtgacc tgaaagtatt tgggaatttc 540

cccaagctta ttatgaccca ggtttccaag tcactgcaag tcactaggat cttccttcag 600

gctctgaatc ttggaattga agtgatcaac acaactgatc acctgaagtt cagtaaggac 660

tgtggccgaa tgctcaccag aatgtggtac tgctcttact gccagggact gatgatggtt 720

aaaccctgtg gcggttactg caatgtggtc atgcaaggct gtatggcagg tgtggtggag 780

attgacaagt actggagaga atacattctg tcccttgaag aacttgtgaa tggcatgtac 840

agaatctatg acatggagaa cgtactgctt ggtctctttt caacaatcca tgattctatc 900

cagtatgtcc agaagaatgc aggaaagctg accaccacta ttggcaagtt atgtgcccat 960

tctcaacaac gccaatatag atctgcttat tatcctgaag atctctttat tgacaagaaa 1020

gtattaaaag ttgctcatgt agaacatgaa gaaaccttat ccagccgaag aagggaacta 1080

attcagaagt tgaagtcttt catcagcttc tatagtgctt tgcctggcta catctgcagc 1140

catagccctg tggcggaaaa cgacaccctt tgctggaatg gacaagaact cgtggagaga 1200

tacagccaaa aggcagcaag gaatggaatg aaaaaccagt tcaatctcca tgagctgaaa 1260

atgaagggcc ctgagccagt ggtcagtcaa attattgaca aactgaagca cattaaccag 1320

<210> 159
<211> 327
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Human GPC3 C Terminal Fragment Gene

<400> 159
ctcctgagaa ccatgtctat gcccaaaggt agagttctgg ataaaaacct ggatgaggaa 60

gggtttgaaa gtggagactg cggtgatgat gaagatgagt gcattggagg ctctggtgat 120

ggaatgataa aagtgaagaa tcagctccgc ttccttgcag aactggccta tgatctggat 180

gtggatgatg cgcctggaaa cagtcagcag gcaactccga aggacaacga gataagcacc 240

tttcacaacc tcgggaacgt tcattccccg ctgaagcttc tcaccagcat ggccatctcg 300

gtggtgtgct tcttcttcct ggtgcac 327

<210> 160
<211> 1743
<212> DNA
<213> Homo sapiens

<400> 160
atggccggga ccgtgcgcac cgcgtgcttg gtggtggcga tgctgctcag cttggacttc 60

ccgggacagg cgcagccccc gccgccgccg ccggacgcca cctgtcacca agtccgctcc 120

ttcttccaga gactgcagcc cggactcaag tgggtgccag aaactcccgt gccaggatca 180

gatttgcaag tatgtctccc taagggccca acatgctgct caagaaagat ggaagaaaaa 240

taccaactaa cagcacgatt gaacatggaa cagctgcttc agtctgcaag tatggagctc 300

aagttcttaa ttattcagaa tgctgcggtt ttccaagagg cctttgaaat tgttgttcgc 360

catgccaaga actacaccaa tgccatgttc aagaacaact acccaagcct gactccacaa 420

gcttttgagt ttgtgggtga atttttcaca gatgtgtctc tctacatctt gggttctgac 480

atcaatgtag atgacatggt caatgaattg tttgacagcc tgtttccagt catctatacc 540

cagctaatga acccaggcct gcctgattca gccttggaca tcaatgagtg cctccgagga 600

gcaagacgtg acctgaaagt atttgggaat ttccccaagc ttattatgac ccaggtttcc 660

aagtcactgc aagtcactag gatcttcctt caggctctga atcttggaat tgaagtgatc 720

aacacaactg atcacctgaa gttcagtaag gactgtggcc gaatgctcac cagaatgtgg 780

tactgctctt actgccaggg actgatgatg gttaaaccct gtggcggtta ctgcaatgtg 840

gtcatgcaag gctgtatggc aggtgtggtg gagattgaca agtactggag agaatacatt 900

ctgtcccttg aagaacttgt gaatggcatg tacagaatct atgacatgga gaacgtactg 960

cttggtctct tttcaacaat ccatgattct atccagtatg tccagaagaa tgcaggaaag 1020

ctgaccacca ctattggcaa gttatgtgcc cattctcaac aacgccaata tagatctgct 1080

tattatcctg aagatctctt tattgacaag aaagtattaa aagttgctca tgtagaacat 1140

gaagaaacct tatccagccg aagaagggaa ctaattcaga agttgaagtc tttcatcagc 1200

ttctatagtg ctttgcctgg ctacatctgc agccatagcc ctgtggcgga aaacgacacc 1260

ctttgctgga atggacaaga actcgtggag agatacagcc aaaaggcagc aaggaatgga 1320

atgaaaaacc agttcaatct ccatgagctg aaaatgaagg gccctgagcc agtggtcagt 1380

caaattattg acaaactgaa gcacattaac cagctcctga gaaccatgtc tatgcccaaa 1440

ggtagagttc tggataaaaa cctggatgag gaagggtttg aaagtggaga ctgcggtgat 1500

gatgaagatg agtgcattgg aggctctggt gatggaatga taaaagtgaa gaatcagctc 1560

cgcttccttg cagaactggc ctatgatctg gatgtggatg atgcgcctgg aaacagtcag 1620

caggcaactc cgaaggacaa cgagataagc acctttcaca acctcgggaa cgttcattcc 1680

ccgctgaagc ttctcaccag catggccatc tcggtggtgt gcttcttctt cctggtgcac 1740

tga 1743

<210> 161
<211> 33
<212> DNA
<213> Artificial

<220>
<223> F-1 Primer

<400> 161
tccccccggg gacgccacct gtcaccaagt ccg 33

<210> 162
<211> 33
<212> DNA
<213> Artificial

<220>
<223> R-7 Primer

<400> 162
tccccgcggc tggttaatgt gcttcagttt gtc 33

<210> 163
<211> 28
<212> DNA
<213> Artificial

<220>
<223> F-8 Primer

<400> 163
tccccccggg ctcctgagaa ccatgtct 28

<210> 164
<211> 33
<212> DNA
<213> Artificial

<220>
<223> R-9 Primer

<400> 164
tccccgcggg tgcaccagga agaagaagca cac 33

<210> 165
<211> 241
<212> PRT
<213> Artificial

<220>
<223> TF1413-02d028 scFv

<400> 165

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

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

Asn Met Asn Trp Val Lys Gln Ser Asn Gly Lys Ser Leu Glu Trp Ile

```
        35                  40                  45

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

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

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

Ala Arg Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val 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 Lys Phe Met
    130                 135                 140

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln
145                 150                 155                 160

Asn Val Arg Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser
                165                 170                 175

Pro Lys Ala Leu Ile Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro
            180                 185                 190

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
        195                 200                 205

Ser Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His
    210                 215                 220

Trp Asn Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
```

225 230 235 240

Arg

<210> 166
<211> 245
<212> PRT
<213> Artificial

<220>
<223> TF1413-02d039 scFv

<400> 166

Glu Val Lys 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 Ala Phe Ser Ser Tyr
20 25 30

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

Ala Tyr Ile Ser Ser Gly Gly Gly Ser Thr Tyr Tyr Pro 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 Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

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

Ser Val Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

```
Gly Gly Gly Ser Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro
    130                 135                 140


Val Ser Leu Gly Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
145                 150                 155                 160


Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys
                165                 170                 175


Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe
            180                 185                 190


Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        195                 200                 205


Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe
    210                 215                 220


Cys Ser Gln Ser Thr His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys
225                 230                 235                 240


Leu Glu Leu Lys Arg
                245


<210>  167
<211>  237
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e004 scFv

<400>  167

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


Pro Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
```

```
            20                  25                  30

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

Gly Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
    50                  55                  60

Lys Asp Glu Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

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

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

Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Lys Phe Met Ser Thr Ser
    130                 135                 140

Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser
145                 150                 155                 160

Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu
                165                 170                 175

Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe
            180                 185                 190

Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val
        195                 200                 205

Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln His Tyr Ser Thr
```

210 215 220

Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
225 230 235

<210> 168
<211> 243
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e014 scFv

<400> 168

Gln Val Gln Leu Lys Gln Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1 5 10 15

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

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

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

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

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

Asn Ala Gly Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

```
Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Leu Thr Gln Ser Pro Lys
    130                 135                 140


Phe Met Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala
145                 150                 155                 160


Ser Gln Asp Val Gly Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175


Gln Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg His Thr Gly
            180                 185                 190


Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205


Thr Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Gln
    210                 215                 220


Gln Tyr Ser Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu
225                 230                 235                 240


Ile Lys Arg



<210>  169
<211>  246
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-02e030 scFv

<400>  169

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1               5                   10                  15


Leu Val Lys Leu Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Tyr
```

```
            20                  25                  30

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

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

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

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

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

Thr Leu Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ala
    130                 135                 140

Met Ser Val Gly Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
145                 150                 155                 160

Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
                165                 170                 175

Lys Pro Gly Gln Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg
            180                 185                 190

Glu Ser Gly Val Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205

Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr
```

210 215 220

Phe Cys Gln Gln His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr
225 230 235 240

Lys Leu Glu Leu Lys Arg
245

<210> 170
<211> 239
<212> PRT
<213> Artificial

<220>
<223> TF1413-02e040 scFv

<400> 170

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

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

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

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Asn Phe
50 55 60

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

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

Ala Arg Gly Tyr Tyr Gly Arg Phe Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

```
Leu Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125


Gly Gly Ser Asp Ile Leu Leu Thr Gln Ser Pro Lys Phe Met Ser Thr
    130                 135                 140


Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val
145                 150                 155                 160


Arg Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
                165                 170                 175


Ala Leu Ile Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro Asp Arg
            180                 185                 190


Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn
        195                 200                 205


Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His Trp Asn
    210                 215                 220


Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
225                 230                 235


<210>  171
<211>  238
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e001 scFv

<400>  171

Gln Val Gln Leu Lys 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 Gly Tyr
```

```
            20                  25                  30

Tyr Met His Trp Val Lys Gln Ser His Val Lys Ser Leu Glu Trp Ile
        35                  40                  45

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

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

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

Ala Arg Asn Tyr Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
            100                 105                 110

Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Asp Ile Lys Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser
    130                 135                 140

Val Gly Asp Arg Val Ser Val Thr Cys Glu Ala Ser Gln Asn Val Asp
145                 150                 155                 160

Asn Asn Val Val Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala
                165                 170                 175

Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe
            180                 185                 190

Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val
        195                 200                 205

Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr
```

210 215 220

Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys Arg
225 230 235

<210> 172
<211> 238
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e004 scFv

<400> 172

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

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

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

Gly Arg Ile Asp Pro Ser Asp Ser Glu Thr His Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Tyr Tyr Gly Ser Asn Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

```
Gly Ser Asp Ile Lys Met Thr Gln Ser Pro Lys Phe Met Ser Thr Ser
    130                 135                 140


Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly
145                 150                 155                 160


Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala
                165                 170                 175


Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe
            180                 185                 190


Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val
        195                 200                 205


Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr
    210                 215                 220


Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
225                 230                 235


<210>  173
<211>  243
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e005 scFv

<400>  173

Gln Val Gln Leu Lys Glu Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1               5                   10                  15


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


Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
```

```
        35                  40                  45

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

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

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

Asn Ala Phe Tyr Tyr Asp Tyr Asp Gly Tyr Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Ser Val Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Asp Val Val Met Thr Gln Thr Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Leu Gly Glu Arg Val Ser Leu Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Asp
                165                 170                 175

Gly Thr Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly
            180                 185                 190

Val Pro Lys Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Ser Leu
        195                 200                 205

Thr Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Leu
    210                 215                 220

Gln Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu
```

225 230 235 240

Leu Lys Arg

<210> 174
<211> 242
<212> PRT
<213> Artificial

<220>
<223> TF1413-03e015 scFv

<400> 174

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

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

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

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Asp Tyr Tyr Pro Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

```
Ser Gly Gly Gly Gly Ser Asp Ile Val Met Ser Gln Ser Pro Lys Phe
    130                 135                 140


Met Ser Thr Ser Val Gly Asp Arg Val Ser Val Thr Cys Lys Ala Ser
145                 150                 155                 160


Gln Asn Val Gly Thr Asn Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175


Ser Pro Lys Pro Leu Ile Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val
            180                 185                 190


Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205


Ile Ser Asn Val Gln Ser Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln
    210                 215                 220


Tyr Asn Arg Tyr Pro Leu Thr Phe Gly Val Gly Thr Lys Leu Glu Ile
225                 230                 235                 240


Lys Arg



<210>  175
<211>  241
<212>  PRT
<213>  Artificial

<220>
<223>  TF1413-03e034 scFv

<400>  175

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


Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
```

20 25 30

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

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

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

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

Ala Arg Gly Asn Tyr Gly Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Ser Val Thr Val Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Asp Ile Val Met Ser Gln Ser Pro Lys Phe Met
130 135 140

Ser Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln
145 150 155 160

Asn Val Arg Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser
165 170 175

Pro Lys Ala Leu Ile Tyr Leu Ala Ser Asn Arg His Thr Gly Val Pro
180 185 190

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
195 200 205

Ser Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln His

210 215 220

Trp Asn Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
225 230 235 240

Arg

<210> 176
<211> 20
<212> DNA
<213> Artificial

<220>
<223> T7 primer

<400> 176
taatacgact cactataggg 20

<210> 177
<211> 21
<212> DNA
<213> Artificial

<220>
<223> cp3R primer

<400> 177
gccagcattg acaggaggtt g 21

<210> 178
<211> 241
<212> PRT
<213> Artificial

<220>
<223> #5 VH1-15-VL1

<400> 178

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 Gly Tyr
            20                  25                  30

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

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

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

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

Ala Arg Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
    130                 135                 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
145                 150                 155                 160

Gln Asn Val Arg Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                165                 170                 175

Ala Pro Lys Ala Leu Ile Tyr Leu Ala Ser Asn Arg His Thr Gly Val
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205
```

```
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
    210                 215                 220


His Trp Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
225                 230                 235                 240


Lys



<210>  179
<211>  241
<212>  PRT
<213>  Artificial

<220>
<223>  #5 VH2-15-VL1

<400>  179

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 Gly Tyr
            20                  25                  30


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


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


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


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


Ala Arg Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
```

100 105 110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
130 135 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
145 150 155 160

Gln Asn Val Arg Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
165 170 175

Ala Pro Lys Ala Leu Ile Tyr Leu Ala Ser Asn Arg His Thr Gly Val
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
210 215 220

His Trp Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
225 230 235 240

Lys

<210> 180
<211> 241
<212> PRT
<213> Artificial

<220>
<223> #5 VH3-15-VL1

<400> 180

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

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

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

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

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

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

Ala Arg Gly Asp Tyr Arg Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
    130                 135                 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
145                 150                 155                 160

Gln Asn Val Arg Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                165                 170                 175

Ala Pro Lys Ala Leu Ile Tyr Leu Ala Ser Asn Arg His Thr Gly Val
            180                 185                 190
```

```
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205


Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
    210                 215                 220


His Trp Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
225                 230                 235                 240


Lys



<210>  181
<211>  245
<212>  PRT
<213>  Artificial

<220>
<223>  #6 VH1-15-VL1

<400>  181

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 Ala Phe Ser Ser Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg Gly Leu Arg Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Met 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 Val Met Thr Gln Ser Pro Leu Ser Leu
130 135 140

Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
145 150 155 160

Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln
165 170 175

Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
180 185 190

Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
195 200 205

Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
210 215 220

Tyr Cys Ser Gln Ser Thr His Val Pro Leu Thr Phe Gly Gly Gly Thr
225 230 235 240

Lys Val Glu Ile Lys
245

<210> 182
<211> 245
<212> PRT
<213> Artificial

<220>
<223> #6 VH1-15-VL2

<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 Ala Ala Ser Gly Phe Ala Phe Ser Ser Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg Gly Leu Arg Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Met 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 Val Met Thr Gln Ser Pro Leu Ser Leu
    130                 135                 140


Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
145                 150                 155                 160


Ser Leu Val His Ser Ser Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln
                165                 170                 175
```

```
Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190


Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205


Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
    210                 215                 220


Tyr Cys Ser Gln Ser Thr His Val Pro Leu Thr Phe Gly Gly Gly Thr
225                 230                 235                 240


Lys Val Glu Ile Lys
                245


<210>  183
<211>  245
<212>  PRT
<213>  Artificial

<220>
<223>  #6 VH2-15-VL1

<400>  183

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 Ala Phe Ser Ser Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg Gly Leu Arg Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Met 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 Val Met Thr Gln Ser Pro Leu Ser Leu
130 135 140

Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
145 150 155 160

Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln
165 170 175

Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
180 185 190

Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
195 200 205

Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
210 215 220

Tyr Cys Ser Gln Ser Thr His Val Pro Leu Thr Phe Gly Gly Gly Thr
225 230 235 240

Lys Val Glu Ile Lys
245

<210> 184

<211> 245
<212> PRT
<213> Artificial

<220>
<223> #6 VH2-15-VL2

<400> 184

```
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 Ala Phe Ser Ser Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Arg Gly Leu Arg Arg Ala Met Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Met 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 Val Met Thr Gln Ser Pro Leu Ser Leu
    130                 135                 140


Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
145                 150                 155                 160
```

```
Ser Leu Val His Ser Ser Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln
                165                 170                 175


Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
            180                 185                 190


Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
        195                 200                 205


Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
    210                 215                 220


Tyr Cys Ser Gln Ser Thr His Val Pro Leu Thr Phe Gly Gly Gly Thr
225                 230                 235                 240


Lys Val Glu Ile Lys
                245


<210>  185
<211>  283
<212>  PRT
<213>  Artificial

<220>
<223>  hCD8-hCD28-h4-1BB-hCD3

<400>  185

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
1               5                   10                  15


Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            20                  25                  30


Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        35                  40                  45


Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
```

```
    50                  55                  60

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Tyr Cys Asn
65                  70                  75                  80

His Arg Asn Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met
                85                  90                  95

Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro
            100                 105                 110

Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val
        115                 120                 125

Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
    130                 135                 140

Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
145                 150                 155                 160

Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
                165                 170                 175

Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
            180                 185                 190

Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
        195                 200                 205

Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Arg Arg Lys Asn
    210                 215                 220

Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu
225                 230                 235                 240

Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly
```

245 250 255

His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr
260 265 270

Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
275 280

<210> 186
<211> 277
<212> PRT
<213> Artificial

<220>
<223> hCD8-hCD28-h4-1BB-hCD3

<400> 186

Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
1 5 10 15

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
20 25 30

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
35 40 45

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
50 55 60

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Leu Arg Ser Lys
65 70 75 80

Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg
85 90 95

Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp
100 105 110

```
Phe Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys
        115                 120                 125

Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr
    130                 135                 140

Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu
145                 150                 155                 160

Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro
                165                 170                 175

Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly
            180                 185                 190

Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro
        195                 200                 205

Glu Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr
    210                 215                 220

Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly
225                 230                 235                 240

Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln
                245                 250                 255

Gly Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln
            260                 265                 270

Ala Leu Pro Pro Arg
        275
```

<210> 187
<211> 276
<212> PRT

<213> Artificial

<220>
<223> hCD8-hCD28-h4-1BB-hCD3

<400> 187

```
Phe Val Pro Val Phe Leu Pro Ala Lys Pro Thr Thr Thr Pro Ala Pro
1               5                  10                  15


Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
            20                  25                  30


Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
        35                  40                  45


Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
    50                  55                  60


Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Arg Ser Lys Arg
65                  70                  75                  80


Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
                85                  90                  95


Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
            100                 105                 110


Ala Ala Tyr Arg Ser Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys
        115                 120                 125


Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr
    130                 135                 140


Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly
145                 150                 155                 160


Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala
```

```
                165                 170                 175

Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg
            180                 185                 190

Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu
        195                 200                 205

Met Gly Gly Lys Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
    210                 215                 220

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
225                 230                 235                 240

Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
                245                 250                 255

Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
            260                 265                 270

Leu Pro Pro Arg
        275
```

<210> 188
<211> 19
<212> PRT
<213> Homo sapiens

<400> 188

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser
```