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(54) Title: ACTIVATABLE BISPECIFIC ANTIBODIES COMPRISING A LINKER BETWEEN THE TWO BINDING DOMAINS WHICH IS A HUMAN IMMUNOGLOBULIN HINGE REGION, OR A VARIANT THEREOF, AND USES THEREOF

(57) Abstract: Described herein are protein molecules that exhibit activatable target binding in diseased tissues and related nucleic acid molecules, vectors and host cells. Also described herein are medical uses for such protein molecules.

ACTIVATABLE BISPECIFIC ANTIBODIES COMPRISING A LINKER BETWEEN THE TWO BINDING DOMAINS WHICH IS A HUMAN IMMUNOGLOBULIN HINGE REGION, OR A VARIANT THEREOF, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of GB Patent Application No. 2001196.1, filed on January 28, 2020, GB Patent Application No. 1917678.3, filed on December 4, 2019, GB Patent Application No. 1910254.0, filed on July 17, 2019, and GB Patent Application No. 1906685.1, filed on May 13, 2019, the disclosure of each of which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: ULSL_002_04WO_SeqList_ST25.txt, date recorded: May 11, 2020, file size ~390 kb).

FIELD OF THE INVENTION

The invention relates to protein molecules that exhibit activatable target binding in diseased tissues and medical uses therefor.

BACKGROUND OF THE INVENTION

In the use of antibodies and other binding proteins to treat disease, many potential drug targets have been described, but few are exclusively expressed in diseased tissue. The majority of potential targets in this space are, in fact, also expressed in non-diseased tissue. In addition, the majority of drug mechanisms of action employed in challenging areas of therapy such as cancer employ highly potent cell-killing mechanisms of action. As a result, engagement of the target by the drug in non-diseased tissue often causes unwanted side effects. There is a need for engineered forms of binding proteins that are partially, or even fully, inactive in healthy tissue but become highly activated in diseased tissue.

SUMMARY OF THE INVENTION

Provided herein is a protein comprising a first moiety and a second moiety and a peptide linker between the first moiety and the second moiety, wherein the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having from 1 to about 7 amino acid substitutions compared to a human immunoglobulin hinge region; wherein the peptide linker is cleavable by a protease expressed in a diseased tissue; wherein the second moiety is capable of specifically binding to a molecule expressed in the diseased tissue; and wherein the binding of the second moiety to the molecule expressed in the diseased tissue is reduced

or inhibited when the peptide linker is uncleaved. In some embodiments, the peptide linker is between about 5 and about 15 amino acids in length. In some embodiments, the peptide linker comprises or consists of the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, or SEQ ID NO:87.

In some embodiments, the protease is a human matrix metalloprotease (MMP), a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5. In some embodiments, the peptide linker comprises a human MMP cleavage site, a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5 cleavage site. In some embodiments, the human MMP is MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13 or MMP14. In some embodiments, the level or the activity of the human MMP is elevated in the diseased tissue compared to the level or the activity of the human MMP in a non-diseased tissue. In some embodiments, the human cathepsin is Cathepsin A, Cathepsin C, Cathepsin D, Cathepsin G, Cathepsin L or Cathepsin K. In some embodiments, the level or the activity of the human cathepsin is elevated in the diseased tissue compared to the level or the activity of the human cathepsin in a non-diseased tissue.

In some embodiments, the first moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain. In some embodiments, the first moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), a diabody, or a T cell receptor domain. In some embodiments, the first moiety specifically binds to a molecule expressed in a diseased tissue.

In some embodiments, the first moiety specifically binds to a first molecule expressed in a diseased tissue and the second moiety is capable of specifically binding to a second molecule expressed in a diseased tissue, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are different molecules. In some embodiments, the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by the same cell. In some embodiments, the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by different cells. In some embodiments, the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is expressed on the surface of a cell. In some

embodiments, the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is a soluble molecule.

In some embodiments, the first moiety binds specifically to human EGFR, human HER2, human HER3, human CD105, human C-KIT, human PD1, human PD-L1, human PSMA, human EpCAM, human Trop2, human EphA2, human CD20, human BCMA, human GITR, human OX40, human CSF1R, human Lag3 or human cMET.

In some embodiments, the second moiety specifically binds to a molecule expressed by a human immune cell. In some embodiments, the molecule expressed by a human immune cell is human CD3, human CD16A, human CD16B, human CD28, human CD89, human CTLA4, human NKG2D, human SIRPα, human SIRPγ, human PD1, human Lag3, human 4-1BB, human OX40, or human GITR.

In some embodiments, the first moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region. In some embodiments, the first moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region. In some embodiments, the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA, or IgY. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2. In some embodiments, the immunoglobulin constant region is immunologically inert. In some embodiments, the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region.

In some embodiments, the second moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain. In some embodiments, the second moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), or a T cell receptor domain. In some embodiments, the second moiety binds specifically to human CD47. In some embodiments, the second moiety binds specifically to human CD3 or human PD-L1.

In some embodiments, the second moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region. In some embodiments, the second moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region. In

some embodiments, the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2. In some embodiments, the immunoglobulin constant region is immunologically inert. In some embodiments, the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region.

In some embodiments, the protein has an immune effector function or two, three or more immune effector functions. In some embodiments, the immune effector function is ADCC, CDC or ADCP.

In some embodiments, the first moiety prevents or reduces specific binding of the second moiety to the molecule expressed in the diseased tissue. In some embodiments, the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue. In some embodiments, the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue, wherein the first moiety dissociates from the second moiety in the vicinity of the diseased tissue or inside the diseased tissue and wherein the second moiety specifically binds to the molecule expressed in the diseased tissue in the vicinity of the diseased tissue or inside the diseased tissue. In some embodiments, the diseased tissue is a tumour or an inflamed tissue.

In some embodiments, the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:16 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:17.

In some embodiments, the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:26 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:27.

In some embodiments, the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:34 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:35.

In some embodiments, the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:36 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:37.

In some embodiments, the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:38 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:39.

In some embodiments, the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:40 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:41.

In some embodiments, the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:42, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:43; or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:45; or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:46, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:47; or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:48, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:49; or

(e) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:50, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:51; or

(f) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:52, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:53; or

(g) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:54, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:55; or

(h) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:88, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:89; or

(i) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:90, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:91; or

(j) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:92; or

(k) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:93; or

(l) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:94; or

(m) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:95; or

(n) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:96; or

(o) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:97.

In some embodiments, the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:74.

In some embodiments, the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human cMET, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:76.

In some embodiments, the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:98, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:99; or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:100, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:101; or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:102, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:103; or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:104, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:105.

Further provided herein is an immunoconjugate comprising a protein of the invention linked to a therapeutic agent. In some embodiments, the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agent, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

Further provided herein is a pharmaceutical composition comprising a protein of the invention or an immunoconjugate of the invention, and a pharmaceutically acceptable carrier, diluent or excipient.

Further provided herein is a nucleic acid molecule encoding a protein or a portion of a protein of the invention. Further provided herein is a nucleic acid molecule encoding the first polypeptide chain, the second polypeptide chain, or both the first polypeptide chain and the second polypeptide chain of a protein of the invention.

Further provided herein is an expression vector comprising a nucleic acid molecule of the invention.

Further provided herein is a recombinant host cell comprising a nucleic acid molecule of the invention or an expression vector of the invention.

Further provided herein is a method of producing a protein, the method comprising culturing a recombinant host cell comprising an expression vector of the invention under conditions whereby the nucleic acid molecule is expressed, thereby producing the protein; and isolating the protein from the host cell or culture.

Further provided herein is a method for enhancing an anti-cancer immune response in a subject, comprising administering to the subject a therapeutically effective amount of a protein of the invention, an immunoconjugate of the invention, or a pharmaceutical composition of the invention.

Further provided herein is a method of treating cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject a therapeutically effective amount of a protein of the invention, an immunoconjugate of the invention, or a pharmaceutical composition of the invention. In some embodiments, the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues. In some embodiments, the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis. In some embodiments, the cardiovascular disease is coronary heart disease, or atherosclerosis or stroke. In some embodiments, the

fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

Further provided herein is a protein of the invention, an immunoconjugate of the invention, or a pharmaceutical composition of the invention for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease. In some embodiments, the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues. In some embodiments, the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis. In some embodiments, the cardiovascular disease is coronary heart disease, atherosclerosis, or stroke. In some embodiments, the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

Further provided herein is a protein of the invention, an immunoconjugate of the invention, or a pharmaceutical composition of the invention, for use as a medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A – FIG. 1B. Challenges in dosing systemically-active antibody drugs into solid tumours – anti-CD47 as an example. CD47 antibodies (FIG. 1A) have significant challenges such as high expression of CD47 in the bloodstream. Erythrocytes and platelets in particular form a 'sink' and toxicity risk issue. The tumour is also typically a 'hostile' environment with high expression of enzymes such as MMPs which accelerate IgG degradation. Anti-CD47 protein constructs of the invention (FIG. 1B) aim to eliminate CD47 binding in the native protein, which removes the peripheral activity. The tumour-targeting domain then drives high concentration in the tumour environment and the peptide linker system exploits the MMP activity in the tumour to activate the CD47-binding activity in the tumour, rather than the periphery.

FIG. 2A – FIG. 2B. Protein construct IgG^2 design and activation principles. The protein construct IgG^2 design (FIG. 2A) may be based on sequences derived from IgG1, IgG2, IgG3, IgG4, IgA, IgE, or IgM and may or may not have effector function capacity. In this construct,

four polypeptide chains encode for four Fab domains (2x Fab A, 2X Fab B), two linker sequences, and may or may not have an immunoglobulin hinge region and an Fc domain. Each Fab A-Linker domain blocks the binding activity of Fab B. The choice of linker sequence, such as a lower hinge peptide sequence from an immunoglobulin, creates a structure that will be locked in a non-diseased tissue, but might be quickly cleaved and unlocked in the presence of high concentrations of proteases in the tumour environment (FIG. 2B). The linkers may be sequentially cleaved, creating an intermediate unlocked active state which allows Fabs A and B from a single protein construct to bind their cognate targets. Secondary, potentially slower cleavage of the second linker in each Fab A-Fab B protein construct unit may release the Fab A domains from the structure entirely, making a dissociated form. Cleaved linkers based on immunoglobulin hinge sequences may also recruit increased immune effector function at the cell membrane via endogenous anti-hinge antibodies. Variable regions are indicated in white. Constant regions are indicated in grey.

FIG. 3A – FIG. 3B. Protein construct Fab^2 design and activation principles. The protein construct Fab^2 design may be based on sequences derived from IgG1, IgG2, IgG3, IgG4, IgA, IgE, or IgM and may or may not have effector function capacity. In this construct, two (FIG. 3A) or three (FIG. 3B) polypeptide chains may encode for two Fab domains (1x Fab A, 1X Fab B), two or more linker sequences, and may or may not have an immunoglobulin hinge region and an Fc domain in which pairing of heterodimers may or may not be driven by mutations in the Fc. Each Fab A-Linker domain blocks the binding activity of Fab B. The choice of linker sequence, such as a lower hinge peptide sequence, creates a structure that will be locked in a non-diseased tissue but quickly cleaved and unlocked in the presence of high concentrations of proteases in the tumour environment (FIG. 3A). The linkers may be sequentially cleaved, creating an intermediate unlocked active state which allows Fabs A and B from a single protein to bind their cognate targets. Secondary, potentially slower cleavage of the second linker in each Fab A-Fab B protein unit may release the Fab A domains from the structure entirely. Cleaved linkers based on immunoglobulin hinge sequences may also recruit increased immune effector function at the cell membrane via endogenous anti-hinge antibodies. Variable regions are indicated in white. Constant regions are indicated in grey.

FIG. 4. SDS-PAGE analysis of Protein A-purified protein construct IgG^2 and Fab^2 proteins from clones 1-15. Multiple construct example proteins were expressed in CHO cells and purified using Protein A affinity chromatography. Purified proteins were then subjected to SDS-PAGE analysis in both unreduced and reduced (r) states, alongside a Molecular Weight Standard (M). Clones 6, 10 and 14 (all containing LHL linkers) were found to contain the highest proportion of expected-size products and lowest higher and lower molecular weight content.

FIG. 5A – FIG. 5I. Size Exclusion Chromatography of Protein A-purified protein construct IgG^2 and Fab^2 proteins. Selected construct example proteins were analysed and fully purified using SEC. Clones 1 (FIG. 5A), 2 (FIG. 5B), 3 (FIG. 5C), 4 (FIG. 5D), 5 (FIG. 5E), 6 (FIG. 5F), 12 (FIG. 5G), 14 (FIG. 5H) and 10 (FIG. 5I) were analyzed. This data showed that the highest proportion of expected-size products (e.g. highlighted peak, FIG. 5I) and lowest higher/lower molecular weight content were found in the samples from clones 6, 10 and 14 (all containing LHL linkers).

FIG. 6A - FIG. 6B. SDS-PAGE analysis of SEC-purified protein construct IgG^2 and Fab^2 proteins. Protein A affinity-purified key lead protein construct clones were finally purified using SEC. Purified proteins from clones 1, 2, 4, 5, 6 and non-SEC purified 15 (FIG. 6A) were then subjected to SDS-PAGE analysis in unreduced state. Purified proteins from clones 7, 8, 10, 11, 12, 13 and 14 (FIG. 6B) were also subjected to SDS-PAGE analysis in both unreduced and reduced (r) states. All proteins were loaded at approximately 1 µg per lane. Clones 6, 10 and 14 (all containing LHL linkers) were found to contain the highest proportion of expected-size products and lowest higher and lower molecular weight content.

FIG. 7A – FIG. 7B. Direct titration ELISA for purified, intact protein constructs and control antibodies binding to human target proteins. Control antibodies A-D5 anti-CD47, A-D5 Fab-Fc (a monovalent version of the A-D5 antibody), MH7.1 anti-C-MET, and anti-Her2 Trastuzumab, all in human IgG1 format, were titrated (in µg/ml) in a direct binding ELISA against human CD47, C-MET and Her2 proteins (FIG. 7A). The Her2CD47-LH-LH and Her2CD47-LHL-LHL in IgG^2 format (FIG. 7B) and cMETCD47-L2-L2 and cMETCD47-LHL-LHL in Fab^2 format (FIG. 7C) were also analyzed in the same fashion.

FIG. 8A – FIG. 8C. Human erythrocyte hemagglutination assay for purified, intact protein constructs and control antibodies. Control antibodies anti-CD235a (murine) and A-D5 anti-CD47, A-D5 Fab-Fc (a monovalent version of the A-D5 antibody, labelled as 'FabCD47-Only'), MH7.1 anti-C-MET, anti-Her2 Trastuzumab, Her2CD47-LH-LH and Her2CD47-LHL-LHL IgG^2, and cMETCD47-L2-L2 and cMETCD47-LHL-LHL in Fab^2 format, were titrated (in nM) in a human erythrocyte hemagglutination assay using fresh erythrocytes from donor 1 (FIG. 8A), donor 2 (FIG. 8B) and donor 3 (FIG. 8C).

FIG. 9A – FIG. 9C. Direct ELISA for purified, intact and MMP-digested protein constructs binding to human target proteins. Protein constructs were submitted to enzymatic digestion using human MMPs 3, 7 and 12 over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control. Samples from these digest time courses were then applied in direct binding ELISA against human Her2 and CD47 (FIG. 9A, B) or human C-MET and human CD47 (FIG. 9C).

FIG. 10A – FIG. 10C. Functional analyses for purified, intact and MMP-digested Her2CD3 Fab^2 protein construct binding to human target proteins. Antibodies Her2CD3-L1-LH, Her2CD3-L2-L2 and Her2CD3-LHL-LHL in Fab^2 format were analyzed by

ELISA without MMP digest (FIG. 10A), Flow Cytometry (FIG. 10B) and a CD3 reporter assay (FIG. 10C), with or without MMP digest.

FIG. 11. Alternative structures based on protein construct design and activation principles. The protein construct module (1) that is found in both the Fab^2 and IgG^2 designs of FIGs. 2 and 3 may be modified and the functional characteristics of the final molecule altered. In this case, the upper binding unit of the protein construct module or the lower unit, or both, may be an alternative structure to an immunoglobulin Fab domain, allowing alternative molecules based on sequences derived from peptides, receptor ectodomains, binding domains and especially other dimerizing immune recognition receptors such as T cell receptors. These constructs could form many formats and examples are provided here, such as: Four polypeptide chains (2) may encode for an IgG^2-like structure containing two full protein construct modules with 4 binding domain units (1x A, 1X B, or 2x A or B), two or more linker sequences, and may or may not have an immunoglobulin hinge region and an Fc domain in which pairing of heterodimers may or may not be driven by mutations in the Fc. In the expression of 3 polypeptides, the Fab^2 design can be augmented by the addition of a binding domain (3) or peptide that renders the structure potentially trispecific or of altered valency. Trispecificity or altered valency may also be achieved in the Fab^2 design by the addition of a further one (4) or two (5) protein construct -linker-Fab/receptor structures at the c-terminus. It should be noted also that any of the structures outlined in this figure or in FIGs. 2 and 3 may be further functionalized by the addition of n-terminal of c-terminal fusions of any kind of polypeptide chain, or by chemical conjugation. Variable regions are indicated in white. Constant regions are indicated in grey.

FIG. 12. A 'passive' structure based on Fab^2 protein construct principles. In this case, the upper binding unit of the protein construct module may be placed c-terminally to an Fc domain. These constructs may or may not have an immunoglobulin hinge region and an Fc domain in which pairing of heterodimers may or may not be driven by mutations in the Fc. In this construct, the binding of both Fab or receptor domains to their cognate targets should only become fully active after cleavage of at least one linker. It should be noted also that any of the structures outlined in this figure may be further functionalized by the addition of n-terminal or c-terminal fusions of any kind of polypeptide chain, or by chemical conjugation. Variable regions are indicated in white. Constant regions are indicated in grey.

FIG. 13. An 'activatable' antibody drug conjugate (ADC) strategy based on Fab^2 protein construct principles. In this case, the upper and lower binding units of the protein construct module may contain antibodies to the same internalizing receptor target, or two different targets, that are found on the surface of the same cell. These constructs could be chemically conjugated or fused with a 'payload' moiety such as a toxin or other active molecule to form an ADC and may or may not have an immunoglobulin hinge region and an Fc domain in which pairing of heterodimers may or may not be driven by mutations in the Fc. In this

construct, the binding of the upper Fab or receptor domain to its cognate target is constitutively active, causing accumulation of the antibody in tissues where its cognate target is expressed. The construct does not initially drive internalization into the target cell as the binding is monovalent and the receptor is known to only be significantly internalized when 2 or more receptor domains are cross-linked by bivalent antibody binding. The activity of the second (lower) Fab or receptor domain should only be engaged after linker cleavage by a disease-related enzyme, which then drives multivalent receptor binding and internalization of the ADC, allowing delivery of the (e.g. cytotoxic or inflammatory) payload moiety. It should be noted also that any of the structures outlined in this figure may be further functionalized by the addition of n-terminal or c-terminal fusions of any kind of polypeptide chain.

FIG. 14. Direct ELISA for purified, intact protein constructs binding to human and murine target proteins. Samples were applied in direct binding ELISA against human Her2 and human and murine CD47.

FIG. 15A – FIG. 15F. Direct ELISA for purified, intact and MMP-digested protein constructs binding to human target proteins. Protein constructs were submitted to enzymatic digestion using human MMPs 7 (FIG. 15A), 8 (FIG. 15B), 10 (FIG. 15C), 12 (FIG. 15D), 13 (FIG. 15E), and Cathepsin S (FIG. 15F), over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0). Samples from these digest time courses were then applied in direct binding ELISA against human Her2 and CD47.

FIG. 16A – FIG. 16B. Biacore SPR assay for purified, intact and MMP-digested Her47-LHL-LHLF binding to human target proteins. Her47-LHL-LHLF was submitted to enzymatic digestion using human MMP 12 over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (Undigested). Samples from these digest time courses were then captured on anti-Fc antibody coated Biacore chips and human Her2 (FIG. 16A) or human CD47 (FIG. 16B) flowed in solution. Rmax values were plotted to indicate maximal binding observed at the highest concentration of analyte protein.

FIG. 17. Biacore SPR assay for purified, intact and 24h MMP-digested Her47-LHL-LHLF binding to human target proteins. Her47-LHL-LHLF was submitted to enzymatic digestion using human MMP 12 for 24 hours incubation, or without enzyme as a negative control ('before protease treatment'). Samples were then captured on anti-Fc antibody coated Biacore chips and human human CD47 flowed in solution at multiple concentrations. Binding curves indicate no interaction of the undigested (intact) Her47-LHL-LHLF protein to huCD47, even at 400nM huCD47, while strong binding is evident for the same protein after MMP12 activation, at all concentrations tested.

FIG. 18A – FIG. 18B. Structural modelling of full Her47-LHL-LHL IgG^2 structure. FIG. 18A, molecular modelling of the full structure of the IgG^2 molecule, showing the upper

(trastuzumab) Fab domains in contact with their Her2 epitope (grey). FIG. 18B, molecular modelling of the full structure of the IgG^2 molecule, showing the upper (trastuzumab) Fab domains in contact with their Her2 epitope (grey), but the CD47 ectodomain is also superimposed in its likely binding position for the A-D5 lower Fab. This analysis demonstrates that the CD47 epitope cannot be bound when both linkers are intact.

FIG. 19A – FIG. 19I. Structural dynamics of Her47 Fab^2 structure with different linkers. Solvent accessible surface area (SASA) results obtained for 3 of linkers (LHL, LHLF, L2). FIG. 19A, FIG. 19D and FIG. 19G show the absolute SASA values for 9 dynamics runs for LHL and LHLF linkers and 10 runs using L2, all over 6 ns. FIG. 19B, FIG. 19E, FIG. 19H, FIG. 19C, FIG. 19F and FIG. 19I show normalised results representing the difference to the starting SASA value, over the 6 ns dynamics run time and the first 2.5 ns of the 6 ns dynamics runs. FIG. 19A, FIG. 19B and FIG. 19C depict SEQ ID NO:2. FIG. 19D, FIG. 19E and FIG. 19F depict SEQ ID NO:3. FIG. 19G, FIG. 19H and FIG. 19I depict SEQ ID NO:32.

FIG. 20A – FIG. 20B. Structural dynamics of intact and activated Her47 LHL-LHL Fab^2 structure. (FIG. 20A) Overlaid Fab^2 structures in both intact linker and activated (single linker cut by protease) forms. (FIG. 20B) Two poses taken from a molecular dynamics simulation of the Fab^2 regions in which one LHL or LHLF linker has been cleaved. Anti-CD47 Fab is shown in black and the anti-HER2 Fab is shown in grey. The diagram illustrates the furthest degree of travel of the Her2 domain and the resulting exposure of the anti-CD47 Fab CDRs.

FIG. 21. Flow cytometric analyses of protein binding to 'Tg32' mouse erythrocytes. Flow cytometric analyses of binding to erythrocytes was performed using A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL. Binding was measured using anti-human PE-conjugated secondary antibody. A-D5 IgG1 was tested at 0.1 µg/ml, 1 µg/ml and 10 µg/ml. IgG^2 Her47 LHL-LHL was tested at 0.1 µg/ml, 1 µg/ml and 10 µg/ml. IgG^2 Her47 LHL-LHLF was tested at 0.1 µg/ml, 1 µg/ml and 10 µg/ml. Fab^2 Met47 LHL-LHL was tested at 0.1 µg/ml, 1 µg/ml and 10 µg/ml.

FIG. 22. 'Tg32' mouse erythrocyte hemagglutination assay. Agglutination of erythrocytes was performed using A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL. Proteins were titrated (in nM) using pooled fresh erythrocytes from multiple donor mice.

FIG. 23. Tolerability study in 'Tg32' mouse: bodyweight analyses. A tolerability study using A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL was performed dosing all proteins at 2 mg/kg and 10 mg/kg concentrations in Tg32 mice. Body weights were then monitored for 60 days. A-D5 IgG1 10 mg/kg dose was not tolerated, cohort terminated on day 1.

FIG. 24. Tolerability study in 'Tg32' mouse: reticulocyte analyses at Day 5 after dosing. A tolerability study using A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2

Met47 LHL-LHL was performed dosing all proteins at 2 mg/kg and 10 mg/kg concentrations in Tg32 mice. Blood samples were taken and reticulocyte levels measured. A-D5 IgG1 at 2 mg/kg dose demonstrated significantly elevated reticulocyte levels.

FIG. 25A – 25K. Tolerability study in 'Tg32' mouse: haematology analyses at Days 5, 29 and 60 after dosing. A tolerability study using A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL was performed dosing all proteins at 2 mg/kg and 10 mg/kg concentrations in Tg32 mice. Blood samples were taken and reticulocyte (FIG. 25A), erythrocyte (RBC, FIG. 25B), haemoglobin (FIG. 25C), mean corpuscular haemoglobin concentration (MCHC) (FIG. 25D), mean corpuscular volume (MCV) (FIG. 25E), leukocyte (FIG. 25F), monocyte (FIG. 25G), lymphocyte (FIG. 25H), basophil (FIG. 25I), eosinophil (FIG. 25J) and neutrophil (FIG. 25K) levels measured.

FIG. 26. Pharmacokinetics study in 'Tg32' mouse: data per molecule at two doses. A pharmacokinetic study using IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL was performed dosing all proteins at 2 mg/kg and 10 mg/kg concentrations in Tg32 mice. A-D5 IgG1 was dosed at 2 mg/kg. Serum samples were taken and human IgG levels measured (in µg/ml) from 30 mins out to 42 days after dosing.

FIG. 27. Pharmacokinetics study in 'Tg32' mouse: data per dose. A pharmacokinetic study using IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL was performed dosing all proteins at 2 mg/kg and 10 mg/kg concentrations in Tg32 mice. A-D5 IgG1 was dosed at 2 mg/kg. Serum samples were taken and human IgG levels measured (in µg/ml) from 30 mins out to 42 days after dosing. Concentrations were plotted at the 2 mg/kg (FIG. 27A) and 10 mg/kg (FIG. 27B) doses, separately. A-D5 IgG1 2 mg/kg dose was included in both analyses, for reference.

FIG. 28. Pharmacokinetics study in 'Tg32' mouse: AUC data per dose. A pharmacokinetic study using IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL was performed dosing all proteins at 2 mg/kg and 10 mg/kg concentrations in Tg32 mice. A-D5 IgG1 was dosed at 2 mg/kg. Serum samples were taken and human IgG levels measured (in µg/ml) from 30 mins out to 42 days after dosing. Concentration measurements over time were used to calculate Area Under the Curve (AUC) for each dose.

FIG. 29A – FIG. 29B. Flow cytometric analyses of binding to NHP and human erythrocytes. Flow cytometric analyses of binding to erythrocytes was performed using A-D5 3M (effector null) IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Trastuzumab. Binding was measured using anti-human PE-conjugated secondary antibody. A-D5 IgG1 was the only protein that exhibited concentration-dependent binding to both NHP (cynomolgus monkey) erythrocytes (FIG. 29A) and human erythrocytes (FIG. 29B).

FIG. 30A – FIG. 30N. Direct ELISA for purified, intact and MMP-digested protein constructs (digested at pH7.4 and pH6.0) binding to human target proteins. Protein constructs were submitted to enzymatic digestion at either pH7.4 or pH6.0 using human

MMPs, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0). Samples from these digest time courses were then applied in direct binding ELISA against human Her2 and CD47.

FIG. 31A – FIG. 31B. Direct ELISA for purified, intact and Cathepsin-digested protein constructs (digested at pH7.4 and pH6.0) binding to human target proteins. Protein constructs were submitted to enzymatic digestion at either pH7.4 or pH6.0 using human Cathepsin enzymes, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0). Samples from these digest time courses were then applied in direct binding ELISA against human Her2 and CD47.

FIG. 32A – FIG. 32B. Flow cytometric analyses of binding to human cancer cells. Flow cytometric analyses of binding to erythrocytes was performed using anti-CD47, Trastuzumab, IgG1 isotype, and IgG^2 Her47 LHL-LHL or IgG^2 Her47 LHL-LHLF which had both been submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0). Binding was measured using anti-human PE-conjugated secondary antibody. Binding was measured on the Her2-high cell line BT-474 (FIG. 32A, FIG. 32B) and Her2-low MCF-7 (FIG. 32C, FIG. 32D).

FIG. 33. SDS-PAGE analysis of MMP12-digested IgG^2 Her47 LHL-LHL or IgG^2 Her47 LHL-LHLF. SDS-PAGE was performed on samples of IgG^2 Her47 LHL-LHL or IgG^2 Her47 LHL-LHLF which had both been submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0).

FIG. 34A – FIG. 34B. Mass spectrometry analysis of MMP12-digested IgG^2 Her47 LHL-LHL. Mass spec was performed on samples of IgG^2 Her47 LHL-LHL which had been submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0). Presence of peptides indicative of the intact LHL linker (Fig. 34A) and MMP12-cleaved linker (Fig. 34B) was measured. FIG. 34A depicts SEQ ID NO: 110. FIG. 34B depicts SEQ ID NO: 111.

FIG. 35. Size Exclusion Chromatography of Protein A-purified Her47 LHLF-LHL IgG1-2hDAA. Her47 LHLF-LHL IgG1-2hDAA protein was expressed in CHO cells, purified by ProA column and analysed by SEC. Two small, larger MW peaks were observed and a large peak of product of expected size (10.30, approx. 250 kDa).

FIG. 36. SDS-PAGE analysis of purified peak fractions from Size Exclusion Chromatography of Her47 LHLF-LHL IgG1-2hDAA. SDS-PAGE was performed on unreduced samples of Her47 LHLF-LHL IgG1-2hDAA: Lane 1 – Mol wt standard, Lane 2 – total ProA-eluted protein, Lane 3 – blank, Lane 4 – peak 1, Lane 5 – peak two, Lane 6 –

peak 3 (correct product).

FIG. 37. SDS-PAGE analysis of purified peak fractions from Size Exclusion Chromatography of Her47 LHLF-LHL IgG1-2hDAA. SDS-PAGE was performed on reduced samples of Her47 LHLF-LHL IgG1-2hDAA: Lane 1 – Mol wt standard, Lane 2 – total ProA-eluted protein, Lane 3 – blank, Lane 4 – peak 1, Lane 5 – peak two, Lane 6 – peak 3 (correct product).

FIG. 38A – FIG. 38C. Direct ELISA for purified, intact and MMP12-digested Her47 IgG1-2hDAA proteins. Her47 LHL-LHLF IgG1-2hDAA (Fig. 38A) was submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0, 2, 4, 8, 24h incubation). Samples from these digest time courses were then applied in direct binding ELISA against human Her2 and murine EpCAM (Fig. 38A). ELISA was then also performed against human CD47 for digested (dark grey) and undigested (light grey) samples (Fig. 38B). SDS-PAGE was also performed for samples: Lane 1 – Mol wt marker, Lane 2 - 0hr digest, Lane 3 – 2hr digest, Lane 4 – 8hr digest and Lane 4 - 24 hr (Fig. 38C).

FIG. 39A – FIG. 39L. Direct ELISA for purified, intact and MMP12-digested IgG2 Her47 proteins with alternative linker compositions. Purified protein from clones Her47 LHL-LHL-EK, Her47-LHL-LHL-Thr, Her47-LHL-LHL-tPA, Her47-LHL-LHL-uPA, Her47-LHL-LHL-GrB and Her47-LHL-LHL-A5 were all tested in titration ELISA against human Her2 and CD47 targets (Fig. 39A, Fig. 39C, Fig. 39E, Fig. 39G, Fig. 39I, Fig. 39K. Each protein was then also submitted to a time course enzymatic digest and ELISA binding to Her2 and CD47 targets (Fig. 39B, Fig. 39D, Fig. 39F, Fig. 39H, Fig. 39J, Fig. 39L).

FIG. 40. Multi-dose tolerability study in NOD-SCID mouse: bodyweight analyses. A tolerability study using IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF, Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF was performed dosing all proteins every 5 days, with 4 total doses.

FIG. 41A - FIG. 41D. Size Exclusion Chromatography of Protein A-purified Her2CD3 Fab^2 proteins. Fab^2 Her23 LHL-LHL-S (Fig. 41A), Fab^2 Her23 LHLF-LHL-S (Fig. 41B), Fab^2 Her23 LHL-LHL (Fig. 41C) and Fab^2 Her23 LHLF-LHL (Fig. 41D), was expressed in CHO cells, purified by ProA column and analysed by SEC. Fab^2 Her23 LHL-LHL (Fig. 41C) and Fab^2 Her23 LHLF-LHL (Fig. 41D) both exhibited lower molecular weight contaminants (peak 15.38).

FIG. 42A – FIG. 42B. CD3 co-engagement bioassay analyses for purified, intact and MMP-digested Her2CD3 Fab^2 proteins using Her2-Low MCF-7 cells. Antibodies Fab^2 Her23 LHLF-LHL-S (Fig. 42A), Fab^2 Her23 LHL-LHL-S (Fig. 42B), were submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control

(time 0). Samples from these digest time courses were then applied in the Promega Jurkat cell CD3 reporter assay, using MCF-7 cells as the target cells.

FIG. 43A – FIG. 43C. CD3 co-engagement bioassay analyses for purified, intact and MMP-digested Her2CD3 Fab^2 proteins using Her2-high BT-474 cells. Control antibodies (Fig. 43A), and Fab^2 Her23 LHLF-LHL-S (Fig. 43B), or Fab^2 Her23 LHL-LHL-S (Fig. 43C) [which had both been submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0)], were applied at 0.1 µg/ml in the Promega Jurkat cell CD3 reporter assay, using BT-474 cells as the target cells.

FIG. 44A – FIG. 44B. Charge variant analysis for IgG^2 and Fab^2 Her47 proteins - Charge heterogeneity analysis is important in the characterisation of monoclonal antibodies because it provides important information about product quality and stability. Heterogeneity can be caused by enzymatic post-translational modifications (glycosylation, lysine truncation) or chemical modifications during purification and storage (oxidation or deamidation). Charge variant profiling for the provided test articles was performed by a commercial Charge Variant Assay. The charge variant profiles of the IgG^2 Her47 LHL-LHL (Fig. 44A) and Fab^2 Her47 LHL-LHL (Fig. 44B) both displayed a homogeneous profile, with one main isoform (50-57% of total), a major acidic isoform (40-48 % of total) and one minor basic isoform (approx. 3%).

FIG. 45A - FIG. 45B. Size Exclusion Chromatography of Her47 proteins after 5 rounds of freeze-thaw. IgG^2 Her47 LHL-LHL (Fig. 45A) and Fab^2 Her47 LHL-LHL (Fig 45B) were both subjected to 5 rounds of freeze-thaw and then SEC performed for samples from rounds 0-5. No aggregation, fragmentation or loss of product was observed for either protein.

FIG. 46. Alternative protein construct designs. This figure depicts illustrative examples of the protein construct Fab^2 design. This design may be based on sequences that: 1. Remove the upper variable domains. 2. Contain 'dummy' non-binding variable domains. 3. Replace the upper Fab with a diabody (or two scFvs). Variable regions are indicated in white. Constant regions are indicated in grey.

FIG. 47A – FIG. 47B. Cell proliferation analyses for purified, intact Her2CD47 proteins using Her2-high BT-474 cells. Trastuzumab, Isotype control IgG1, IgG^2 Her47 LHL-LHL (Fig. 47A) and Fab^2 Her47 LHL-LHL (Fig 47B), were applied to BT-474 cells over a 72h incubation period and cell proliferation measured. Data is represented as % inhibition of cell growth.

Fig. 48A – Fig. 48G. *In vivo* efficacy analyses of Her47 molecules in NOD-SCID mice (KYSE-410 model). Trastuzumab (Fig. 48A), IgG^2 Her47 LHL-LHLF (Fig. 48B), IgG^2 Her47 LHL-LHL (Fig. 48C), Fab^2 Her47 LHL-LHLF (Fig. 48D) and Fab^2 Her47 LHL-LHL (Fig. 48E) were each dosed (intravenously, on days 0, 5, 10) in NOD-SCID mice bearing KYSE-410

tumours. Measurement of tumour volumes was performed on days 4, 7 and 11 and are plotted in comparison to vehicle. Fab^2 Her47 LHL-LHLF and Fab^2 Her47 LHL-LHL demonstrated differing potencies (Fig. 48F). None of the dosing groups exhibited any weight loss that might indicate toxicity of the molecules dosed (Fig. 48G).

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein are recombinant proteins that are conditionally active in diseased human tissues. In some cases, the protein comprises a binding domain that is masked by another portion of the protein in non-diseased tissues. The protein also comprises a peptide linker that is cleaved by one or more proteases expressed in a diseased tissue. The linker cleavage unmasks the binding domain in the diseased tissue, thus allowing binding and/or function of the protein selectively in the diseased tissue. The proteins of the invention are particularly useful for binding to drug targets that are expressed in both diseased tissue and non-diseased tissue.

Provided herein are a number of activatable protein molecules and medical uses thereof. In some aspects, multiple functional properties of the molecules are considered, including target binding specificity, effective limitation of undesired activity in the native protein but full activity in the activated form, maintained conditional affinity to one or more targets from both human and animal test species (e.g., cynomolgus monkey, also known as the crab-eating macaque, i.e. *Macaca fascicularis*), biophysical stability and/or yield from protein expression platforms used in research, clinical and commercial supply.

In some aspects, there is provided a protein molecule that specifically binds to one or more human drug targets, and optionally also to cynomolgus monkey orthologs of those targets, wherein the protein molecule comprises heavy and light chain regions assembled from one or multiple polypeptides with the following format:

V-C-LINKER-V-C
V-C-LINKER-V-C
or
C-LINKER-V-C
C-LINKER-V-C

In some aspects, the protein molecule comprises two polypeptide chains and has the following format:
VH1-C-LINKER-VH2-C
VL1-C-LINKER-VL2-C

In some aspects, the protein molecule comprises two polypeptide chains and has the following format:

VL1-C-LINKER-VH2-C

VH1-C-LINKER-VL2-C

"V" refers to an immunoglobulin or T cell receptor variable region or the ectodomain of a receptor. "VH1" and "VL1" refer to a heavy chain variable region and a light chain variable region that pair with each other to bind an antigen. "VH2" and "VL2" refer to a heavy chain variable region and a light chain variable region that pair with each other to bind an antigen. "C" refers to an immunoglobulin or T cell receptor constant region. In aspects of the invention, the V-C and V-C units on either side of the linker domain form upper and lower immunoglobulin Fab domains with the lower Fab domain exhibiting binding to its cognate target that is reduced or ablated by the presence of the linker domain which is fused to the N-termini of each V domain in the lower Fab. In another aspect the upper or lower Fab domain may be replaced by an Fc fragment, one or two receptor ectodomains, or any domains having or lacking any specific binding function.

In some aspects, provided herein is a protein comprising a first moiety and a second moiety and a peptide linker between the first moiety and the second moiety,

wherein the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 (e.g., from 1 to about 7) amino acid substitutions compared to a human immunoglobulin hinge region;

wherein the peptide linker is cleavable by a protease expressed in a diseased tissue;

wherein the second moiety is capable of specifically binding to a molecule expressed in the diseased tissue; and

wherein the binding of the second moiety to the molecule expressed in the diseased tissue is reduced or inhibited when the peptide linker is uncleaved.

The linker portion may further comprise a peptide linker derived from an immunoglobulin hinge region, with zero, one, or more mutations away from the germline.

In some aspects, the peptide linker comprises or consists of the sequence set forth in GPAPELL (SEQ ID NO:1), GPAPELLGGGS (SEQ ID NO:2), GPAPLGLGGGS (SEQ ID NO:3), PPCPAPELLGGGS (SEQ ID NO:4), PPCPAPLGLGGGS (SEQ ID NO:5) GPAPELLGGPS (SEQ ID NO:69), GPAPLGLGGPS (SEQ ID NO:70), PPCPAPELLGGPS (SEQ ID NO:71), PPCPAPLGLGGPS (SEQ ID NO:72), GPAPEAAGAGS (SEQ ID NO:81),

GPADDDDKSGS (SEQ ID NO:82) (cleavable by Enterokinase), GPALVPRGSGS (SEQ ID NO:83) (cleavable by Thrombin), GPGPFGRSAGGP (SEQ ID NO:84) (cleavable by tPA), GPAPLEADAGS (SEQ ID NO:85) (cleavable by Granzyme B), GPAPEARRGGS (SEQ ID NO:86) (cleavable by uPA), or GPAPEGEARGS (SEQ ID NO:87) (cleavable by ADAMTs-5). In some aspects, the peptide linker comprises or consists of two, three or four of the aforementioned sequences.

Also provided is an immunoconjugate comprising the protein of the invention linked to a therapeutic agent.

In another aspect the invention provides a nucleic acid molecule encoding the protein or a portion thereof as defined herein. Further provided is a vector comprising the nucleic acid molecule of the invention. Also provided is a host cell comprising the nucleic acid molecule or the vector of the invention.

In a further aspect there is provided a method of producing an conditionally active protein of the invention, comprising culturing the host cell of the invention under conditions that result in expression and/or production of the protein, and isolating the protein from the host cell or culture.

In another aspect of the invention there is provided a pharmaceutical composition comprising a protein of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or an immunoconjugate of the invention as defined herein.

Further provided is a method for enhancing an immune response in a subject, comprising administering an effective amount of a protein of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

In a further aspect there is provided a method for treating or preventing cancer in a subject, comprising administering an effective amount of a protein of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

Further provided is a protein of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use as a medicament.

Further provided is a protein of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use in the treatment of cancer.

Further provided is a protein, or an immunoconjugate, or a nucleic acid molecule, or a vector, or a pharmaceutical composition of the invention as defined herein, for separate, sequential or simultaneous use in a combination with a second therapeutic agent, for example an anti-cancer agent.

In a further aspect there is provided the use of a protein of the invention as defined herein, or an immunoconjugate of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or a pharmaceutical composition of the invention as defined herein, in the manufacture of a medicament for the treatment of cancer.

Further provided is a method for treating or preventing an autoimmune disease or an inflammatory disease in a subject, comprising administering an effective amount of a protein as defined herein, or an immunoconjugate as defined here, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein.

Also provided is a protein as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of an autoimmune disease or an inflammatory disease.

Further provided is the use of a protein as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an autoimmune disease or an inflammatory disease.

Further provided is a method for treating or preventing a cardiovascular disease or a fibrotic disease in a subject, comprising administering an effective amount of a protein as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

Further provided is a protein as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use as a medicament. Also provided is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of a cardiovascular disease or a fibrotic disease.

Further provided is the use of a protein as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an autoimmune disease, an inflammatory disease or a fibrotic disease.

In some aspects, the invention provides a protein comprising a first moiety and a second moiety and a peptide linker between the first moiety and the second moiety, wherein the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having amino acid substitutions (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 amino acid substitutions) compared to a human immunoglobulin hinge region; wherein the peptide linker is cleavable by a protease expressed in a diseased tissue; wherein the second moiety is capable of specifically binding to a molecule expressed in the diseased tissue; and wherein the binding of the second moiety to the molecule expressed in the diseased tissue is reduced or inhibited when the peptide linker is uncleaved. In some aspects, the amino acid substitution is a conservative amino acid substitution. In some aspects, the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having from 1 to about 7 amino acid substitutions compared to a human immunoglobulin hinge region. In some aspects, the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 2-3, 2-4, 2-5, 2-6, 2-7, 3-4, 3-5, 3-6, 3-7, 4-5, 4-6, 4-7, 5-6, 5-7, or 6-7 amino acid substitutions compared to a human immunoglobulin hinge region.

In some aspects, the peptide linker cleavable by a protease expressed in a diseased tissue is cleavable by a human matrix metalloprotease (MMP) or a human cathepsin. In some cases, the peptide linker cleavable by a protease expressed in a diseased tissue is cleavable by human enterokinase (EK), human thrombin (Thr), human tPA (tissue plasminogen activator), human Granzyme B (GrB), human uPA (urokinase-type plasminogen activator), or human ADAMTs-5 (A Disintegrin-like And Metalloproteinase With Thrombospondin Type 1 Motif 5; A5). In some cases, the peptide linker comprises a human MMP cleavage site or a human cathepsin cleavage site. In some cases, the peptide linker comprises a human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5 cleavage site. In some cases, the peptide linker comprises the MMP substrate sequence PLGL (SEQ ID NO:12). In some cases, the peptide linker comprises or consists of the amino acid sequence of GPAPELL (SEQ ID NO:1), GPAPELLGGGS (SEQ ID NO:2), GPAPLGLGGGS (SEQ ID NO:3), PPCPAPELLGGGS (SEQ ID NO:4), or PPCPAPLGLGGGS (SEQ ID NO:5), GPAPELLGGPS (SEQ ID NO:69), GPAPLGLGGPS (SEQ ID NO:70), PPCPAPELLGGPS (SEQ ID NO:71), PPCPAPLGLGGPS (SEQ ID NO:72), GPAPEAAGAGS (SEQ ID NO:81), GPADDDDKSGS (SEQ ID NO:82), GPALVPRGSGS (SEQ ID NO:83), GPGPFGRSAGGP (SEQ ID NO:84), GPAPLEADAGS (SEQ ID NO:85), GPAPEARRGGS (SEQ ID NO:86), or GPAPEGEARGS (SEQ ID NO:87).

In some cases, the peptide linker comprises or consists of two, three, or four of the amino acid sequences in Table 1 fused in a single amino acid chain via peptide bonds. In some cases, the peptide linker is between about 5 amino acids and about 15 amino acids, between about 5 amino acids and about 20 amino acids, or between about 5 amino acids and about 25 amino acids in length.

In some cases, the peptide linker between the first moiety and the second moiety comprises the following amino acid sequence at the N-terminus of the peptide linker sequence: X1-proline-X2. In some aspects, X1 is alanine, glycine, serine, proline or threonine. In some aspects, X1 is alanine, glycine, serine, proline or threonine, aspartic acid, asparagine or valine. In some aspects, X2 is alanine, glycine, serine, proline or threonine. In some aspects, X2 is alanine, glycine, serine, proline or threonine, aspartic acid, asparagine or valine. In some aspects, X1 and X2 are the same amino acid. In some aspects, X1 and X2 are different amino acids.

In some cases, the peptide linker cleavable by a protease expressed in a diseased tissue is cleavable by any one of human MMP1, MMP2, MMP3, MMP4, MMP5, MMP6, MMP7, MMP8, MMP9, MMP10, MMP11, MMP12, MMP13, MMP14, MMP15, MMP16, MMP17,

MMP18, MMP19, MMP20, MMP21, MMP22, MMP23, MMP24, MMP25, MMP26, MMP27, or MMP28. In some cases, the peptide linker cleavable by a protease expressed in a diseased tissue is cleavable by any one of human MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-12 or MMP-13. In some cases, the level or the activity of the human MMP is elevated in the diseased tissue compared to the level or the activity of the human MMP in a non-diseased tissue.

In some cases, the peptide linker cleavable by a protease expressed in a diseased tissue is cleavable by any one of human Cathepsin A, Cathepsin B, Cathepsin C, Cathepsin D, Cathepsin E, Cathepsin F, Cathepsin G, Cathepsin H, Cathepsin K, Cathepsin L1, Cathepsin V, Cathepsin O, Cathepsin S, Cathepsin W, or Cathepsin Z. In some cases, the peptide linker cleavable by a protease expressed in a diseased tissue is cleavable by any one of human Cathepsin D, Cathepsin G, or Cathepsin K. In some cases, the level or the activity of the human cathepsin is elevated in the diseased tissue compared to the level or the activity of the human cathepsin in a non-diseased tissue. In some cases, the level or the activity of the human cathepsin is elevated in tissues with pH < 7.0 compared to the level or the activity of the human cathepsin in a tissue with pH $\geqq$ 7.4.

In some aspects, the first moiety of any of the proteins of the invention comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain. In some cases, the first moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), a diabody, or a T cell receptor domain. An IgNAR is a homodimeric heavy chain-only antibody produced by sharks and other cartilaginous fishes (Feige et al., *PNAS*, 2014, 111(22):8155-8160).

In some cases, the first moiety specifically binds to a molecule expressed in a diseased tissue. In some embodiments, the first moiety specifically binds to a tumour-associated antigen (TAA). In some cases, the first moiety binds specifically to human EGFR, human HER2, human HER3, human CD105, human C-KIT, human PD1, human PD-L1, human PSMA, human EpCAM, human Trop2, human EphA2, human CD20, human BCMA, human GITR, human OX40, human CSF1R, human Lag3 or human cMET. In some embodiments, the first moiety also binds the cynomolgus ortholog of any of these molecules.

In some aspects, the first moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region. In some cases, the first moiety further comprises an

immunoglobulin constant region or a portion of an immunoglobulin constant region. In some cases, the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

In some aspects, the anti-HER2 variable region sequences used in the protein constructs disclosed herein are the variable region sequences of trastuzumab. In some aspects, the anti-CD3 variable region sequences used in the protein constructs disclosed herein are the variable region sequences of OKT3 or SP34. In some aspects, the anti-cMET variable region sequences used in the protein constructs disclosed herein are provided in WO 2019/175186. In some aspects, the anti-CD47 variable region sequences used in the protein constructs disclosed herein are provided in WO 2019/034895.

In some aspects, the second moiety of any of the proteins of the invention comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain. In some cases, the second moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), a diabody, or a T cell receptor domain.

In some cases, the second moiety specifically binds to a molecule expressed in a diseased tissue. In some embodiments, the second moiety specifically binds to a tumour-associated antigen (TAA). In some cases, the second moiety binds specifically to human CD47. In some cases, the second moiety binds specifically to human PD-L1. In some cases, the second moiety specifically binds to a molecule expressed by a human immune cell. In some cases, the molecule expressed by a human immune cell is human CD3, human CD16A, human CD16B, human CD28, human CD89, human CTLA4, human NKG2D, human SIRPα, human SIRPγ, human PD1, human Lag3, human 4-1BB, human OX40, or human GITR. In some embodiments, the second moiety also binds the cynomolgus ortholog of any of these molecules.

In some aspects, the second moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region. In some cases, the second moiety further comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region. In some cases, the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise an immunoglobulin constant region. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgE, or IgM. In additional embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG1null, IgG4(S228P), IgA1, IgA2, IgE, or IgM. In some embodiments, the first moiety and/or the

second moiety of a protein of the invention may comprise an immunologically inert constant region. In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise an immunoglobulin constant region comprising a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S. In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise an immunoglobulin constant region comprising a wild-type human IgG2 constant region or a wild-type human IgG4 constant region. In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise an immunoglobulin constant region comprising any one of the amino acid sequences in Table 10. The Fc region sequences in Table 10 begin at the CH1 domain. In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise an immunoglobulin constant region comprising an amino acid sequence of an Fc region of human IgG4, human IgG4(S228P), human IgG2, human IgG1, human IgG1-3M or human IgG1-4M. For example, the human IgG4(S228P) Fc region comprises the following substitution compared to the wild-type human IgG4 Fc region: S228P. For example, the human IgG1-3M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A and G237A, while the human IgG1-4M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A, G237A and P331S. In some aspects, a position of an amino acid residue in a constant region of an immunoglobulin molecule is numbered according to EU nomenclature (Ward *et al.*, 1995 *Therap. Immunol.* 2:77-94). In some aspects, an immunoglobulin constant region may comprise an RDELT (SEQ ID NO:65) motif or an REEM (SEQ ID NO:66) motif (underlined in Table 10). The REEM (SEQ ID NO:66) allotype is found in a smaller human population than the RDELT (SEQ ID NO:65) allotype. In some aspects, the first moiety and/or the second moiety of a protein of the invention antibody may comprise an immunoglobulin constant region comprising any one of SEQ ID NOS:56-62. In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise the heavy chain amino acid sequence and the light chain amino acid sequence of any one of the clones in Tables 3-9 and any one of the Fc region amino acid sequences in Table 10. In some aspects, the first moiety and/or the second moiety of a protein of the invention may comprise an immunoglobulin heavy chain constant region comprising any one of the Fc region amino acid sequences in Table 10 and an immunoglobulin light chain constant region that is a kappa light chain constant region or a lambda light chain constant region.

In some aspects, a protein of the invention comprises an IgG1 isotype constant region. The IgG1 isotype constant region potently activates all FcγR signalling types, thus driving maximal opsonizing effector function.

In some aspects, the immunoglobulin constant region comprises a hinge region or a truncated hinge region. In some embodiments, a hinge region may comprise one, two, three, four or more amino acid substitutions compared to a wild-type human hinge region amino acid sequence. In some embodiments, the immunoglobulin constant region does not comprise a hinge region.

In some aspects, the first moiety specifically binds to a first molecule expressed in a diseased tissue and the second moiety is capable of specifically binding to a second molecule expressed in a diseased tissue, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are different molecules. In some embodiments, the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by the same cell. In some embodiments, the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by different cells. In some embodiments, the first molecule expressed in a diseased tissue, the second molecule expressed in a diseased tissue, or both the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue is expressed on the surface of a cell. In some embodiments, the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is a soluble molecule.

In some aspects, the first moiety binds specifically to human cMET and the second moiety binds specifically to human CD47. In some aspects, the first moiety binds specifically to human HER2 and the second moiety binds specifically to human CD47. In some aspects, the first moiety binds specifically to human cMET and the second moiety binds specifically to human CD47. In some aspects, the first moiety binds specifically to human HER2 and the second moiety binds specifically to human CD3. In some aspects, the first moiety binds specifically to human cMET and the second moiety binds specifically to human cMET.

In some aspects, a protein of the invention has an immune effector function or two, three or more immune effector functions. For example, an immune effector function may be antibody-dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), or antibody-dependent cellular phagocytosis (ADCP).

In some aspects, the first moiety of a protein of the invention prevents or reduces specific binding of the second moiety to the molecule expressed in the diseased tissue. In some embodiments, the peptide linker of a protein of the invention is cleaved in the vicinity of the diseased tissue or inside the diseased tissue. In some cases, the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue, wherein the first moiety dissociates from the second moiety in the vicinity of the diseased tissue or inside the diseased tissue and wherein the second moiety specifically binds to the molecule expressed in the diseased tissue in the vicinity of the diseased tissue or inside the diseased tissue. In some cases, the cleaved peptide linker comprises a binding site or a target site for anti-hinge antibodies (e.g., a subject's endogenous anti-hinge antibodies), whereas the uncleaved (e.g., intact) peptide linker does not comprise a binding site or a target site for anti-hinge antibodies. Binding of the anti-hinge antibodies to the cleaved peptide linker may increase ADCC, CDC, and/or ADCP in the presence of an activated protein of the invention (see, e.g., Fig. 2B).

In some aspects, a protein of the invention stimulates inflammatory signalling in a diseased tissue. Increased inflammatory signalling may increase immune recruitment to the diseased tissue. In some cases, a protein of the invention increases antigen presentation in a diseased tissue. In some cases, a protein of the invention increases tumour-associated-antigen-specific T cell proliferation.

In some aspects, the diseased tissue may be a tumour, a necrotic tissue, a fibrotic tissue, a tissue undergoing the clotting cascade or an inflamed tissue.

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:16 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:17. The protein comprises only one copy of the first polypeptide chain and only one copy of the second polypeptide chain. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1), each fused at the n-terminus to the first moiety and at the c-terminus to the second moiety, via a peptide bond. This protein is referred to as "Fab2 cMetCD47-LHL-LHL" or "Met47-LHL-LHL". The amino acid sequences are provided in Table 3. The structure of this protein is depicted in Fig. 3A. The second moiety of this protein is linked via a G4S linker (SEQ ID NO:15) and a truncated hinge region to KIH IgG1-Fc.

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:26 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:27. The protein comprises only one copy of the first polypeptide chain and only one copy of the second polypeptide chain. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1) fused via a peptide bond. This protein is referred to as "Fab2 Her2CD3-LHL-LHL" or "Her23-LHL-LHL". The amino acid sequences are provided in Table 4. The structure of this protein is depicted in Fig. 3A. The second moiety of this protein is linked via a G4S linker (SEQ ID NO:15) and a truncated hinge region (3M) to KIH IgG1-Fc.

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:34 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:35. The protein comprises two identical copies of the first polypeptide chain and two identical copies of the second polypeptide chain. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1) fused via a peptide bond. This protein is referred to as "IgG2 Her2CD47-LHL-LHL" or "Her47-LHL-LHL". The amino acid sequences are provided in Table 5. The structure of this protein is depicted in Fig. 2A. The second moiety of this protein may be linked via a hinge region or a truncated hinge region to a human IgG1 Fc sequence (see Table 10).

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:36 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:37. The first polypeptide chain further comprises a human IgG1 amino acid sequence (see Table 10). The second polypeptide chain further comprises a human kappa light chain amino acid sequence. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1) fused via a peptide bond. This protein is referred to as "Fab2 CMET/CD47 'One Arm' style" or "Met47-LHL-LHL". The amino acid sequences are provided in Table 6. The structure of this

protein is depicted in Fig. 3B. The construct is a 'Knob into hole' One-Arm Fab2 construct that has Fab2 on the knob side and a hinge-hole Fc stump on the other. This construct may comprise a human IgG1 Fc sequence that is not effector null (see Table 10).

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:38 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:39. The first polypeptide chain further comprises a human IgG1-3M amino acid sequence (see Table 10). The second polypeptide chain further comprises a human kappa light chain amino acid sequence. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1) fused via a peptide bond. This protein is referred to as “Fab2 Her2/CD3 'One Arm' style” or “Her23-LHL-LHL”. The amino acid sequences are provided in Table 7. The structure of this protein is depicted in Fig. 3B. The construct is a 'Knob into hole' One-Arm Fab2 construct that has Fab2 on the knob side and a hinge-hole Fc stump on the other. This construct is also effector null (IgG1-3M; see Table 10).

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:40 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:41. The first polypeptide chain further comprises a human IgG1-3M amino acid sequence (see Table 10). The second polypeptide chain further comprises a human lambda light chain amino acid sequence. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1) fused via a peptide bond. This protein is referred to as “Fab2 Her2/CD3(34) “One Arm” style” or “Her23(34)-LHL-LHL”. The amino acid sequences are provided in Table 8. The structure of this protein is depicted in Fig. 3B. The construct is a 'Knob into hole' One-Arm Fab2 construct that has Fab2 on the knob side and a hinge-hole Fc stump on the other. This construct is also effector null (IgG1-3M; see Table 10).

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human

CD47, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:42, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:43 (referred to as "Her47-LHLF-LHL"); or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:45 (referred to as "Her47-LHL-LHLF"); or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:46, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:47 (referred to as "Her47 -LHLF-LHLF"); or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:48, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:49 (referred to as "Her47-LHLM-LHLM"); or

(e) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:50, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:51 (referred to as "Her47-LHLM-LHLMF"); or

(f) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:52, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:53 (referred to as "Her47-LHLMF-LHLM"); or

(g) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:54, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:55 (referred to as "Her47-LHLMF-LHLMF"); or

(h) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:92 (referred to as "Her47 LHL-LHL-EK");

(i) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:93 (referred to as "Her47-LHL-LHL-Thr");

(j) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:94 (referred to as "Her47-LHL-LHL-tPA");

(k) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:95 (referred to as "Her47-LHL-LHL-GrB");

(l) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:96 (referred to as "Her47-LHL-LHL-uPA"); or

(m) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:97 (referred to as "Her47-LHL-LHL-A5"). These proteins are generally referred to as "IgG2 Her2/CD47". The amino acid sequences are provided in Table 9 and Table 20. The structure of this protein is depicted in Fig. 2A. The peptide linker sequences for the LHLF, the LHLM and the LHLMF linkers are provided in Table 1. The peptide linker sequences for the EK, Thr, tPA, GrB, uPA, and A5 linkers are provided in Table 21.

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:88, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:89 (referred to as "Her47 LHLF-LHL IgG1-2hDAA"); or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:90, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:91 (referred to as "Her47 LHL-LHLF IgG1-2hDAA"). These proteins are generally referred to as "IgG2 'IgG1-DAA' Her2/CD47". The amino acid sequences are provided in Table 19. These proteins comprise stabilizing mutations in the hinge. The structure of this protein is depicted in Fig. 2A. The peptide linker sequences for the LHLF and the LHL linkers are provided in Table 1.

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:74. The first polypeptide chain further comprises a human IgG1-3M Fc amino acid sequence (e.g. containing 'hole' mutations' to enable heterodimerization with the second polypeptide chain), followed by a linker sequence, the VH and CH1 domains of the first binding moiety, another linker sequence, then the VH and CH1 domains of the second binding moiety (see Table 13). The second polypeptide chain further comprises a human IgG1-3M Fc amino acid sequence (e.g. containing 'knob' mutations' to enable heterodimerization with the second polypeptide chain), followed by a linker sequence, the VL and CL domains of the first binding moiety, another linker sequence, then the VL and CL domains of the second binding moiety (see Table 13). The peptide

linkers of this protein comprise four sequences (see Table 1) fused via a peptide bond, which reside between the Fc and first moiety and between the first and second binding moieties. This protein is referred to as "Fc-Her2/CD3(34)" or "Fc-Her23(34)". The amino acid sequences are provided in Table 13. The structure of this protein is depicted in Fig. 12. The construct is a 'Knob into hole' Fc-Fab2 construct that has light chain polypeptides on either the knob or hole side and heavy chain polypeptides on the other. This construct is also effector null (IgG1-3M; see Table 10).

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human cMET, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:76. The first polypeptide chain further comprises a human IgG1 or human IgG1-3M amino acid sequence (see Table 10). The second polypeptide chain further comprises a human kappa light chain amino acid sequence. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1) fused via a peptide bond. This protein is referred to as "Fab2 CMET/CMET 'One Arm' style" or "MetMet-LHL-LHL". The amino acid sequences are provided in Table 14. The structure of this protein is depicted in Fig. 3B. The construct is a 'Knob into hole' One-Arm Fab2 construct that has Fab2 on the knob side and a hinge-hole Fc stump on the other. This construct may comprise a human IgG1 Fc sequence that is or is not effector null (see Table 10).

In some aspects, provided herein is a protein comprising a first moiety and a second moiety, and a peptide linker between the first moiety and the second moiety, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:98, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:99 (referred to as "Fab2 Her23 LHL-LHLF "); or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:100, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:101 (referred to as "Fab2 Her23 LHL-LHL"); or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:102, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:103 (referred to as "Fab2 Her23 LHLF-LHL-S"); or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:104, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:105 (referred to as "Fab2 Her23 LHL-LHL-S"). This protein is referred to as "Fab2 Her2/CD3". The amino acid sequences are provided in Table 22. The structure of this protein is depicted in Fig. 3A. The protein comprises only one copy of the first polypeptide chain and only one copy of the second polypeptide chain. The peptide linker of this protein comprises two copies of the LHL sequence (see Table 1), or one copy of the LHL sequence and one copy of the LHLF sequence, fused via a peptide bond.

In some aspects, provided herein is an immunoconjugate comprising the protein of the invention as defined herein linked to an additional therapeutic agent.

Examples of suitable therapeutic agents include cytotoxins, radioisotopes, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, antiproliferative agents, pro-apoptotic agents, and cytostatic and cytolytic enzymes (for example RNAses). Further therapeutic agents include a therapeutic nucleic acid, such as a gene encoding an immunomodulatory agent, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent. These drug descriptors are not mutually exclusive, and thus a therapeutic agent may be described using one or more of the above terms.

Examples of suitable therapeutic agents for use in immunoconjugates include the taxanes, maytansines, CC-1065 and the duocarmycins, the calicheamicins and other enediynes, and the auristatins. Other examples include the anti-folates, vinca alkaloids, and the anthracyclines. Plant toxins, other bioactive proteins, enzymes (i.e., ADEPT), radioisotopes, photosensitizers may also be used in immunoconjugates. In addition, conjugates can be made using secondary carriers as the cytotoxic agent, such as liposomes or polymers, Suitable cytotoxins include an agent that inhibits or prevents the function of cells and/or results in destruction of cells. Representative cytotoxins include antibiotics, inhibitors of tubulin polymerization, alkylating agents that bind to and disrupt DNA, and agents that disrupt protein synthesis or the function of essential cellular proteins such as protein kinases, phosphatases, topoisomerases, enzymes, and cyclins.

Representative cytotoxins include, but are not limited to, doxorubicin, daunorubicin, idarubicin, aclarubicin, zorubicin, mitoxantrone, epirubicin, carubicin, nogalamycin, menogaril, pitarubicin, valrubicin, cytarabine, gemcitabine, trifluridine, ancitabine, enocitabine, azacitidine, doxifluhdine, pentostatin, broxuhdine, capecitabine, cladhbine, decitabine, floxuhdine, fludarabine, gougerotin, puromycin, tegafur, tiazofuhn, adhamycin, cisplatin, carboplatin, cyclophosphamide, dacarbazine, vinblastine, vincristine, mitoxantrone,

bleomycin, mechlorethamine, prednisone, procarbazine, methotrexate, flurouracils, etoposide, taxol, taxol analogs, platins such as cis-platin and carbo-platin, mitomycin, thiotepa, taxanes, vincristine, daunorubicin, epirubicin, actinomycin, authramycin, azaserines, bleomycins, tamoxifen, idarubicin, dolastatins/auristatins, hemiasterlins, esperamicins and maytansinoids.

Suitable immunomodulatory agents include anti-hormones that block hormone action on tumours and immunosuppressive agents that suppress cytokine production, down-regulate self-antigen expression, or mask MHC antigens.

Also provided is a nucleic acid molecule encoding the protein or a portion of the protein of the invention as defined herein. Further provided herein is a nucleic acid molecule encoding the first polypeptide chain, the second polypeptide chain, or both the first polypeptide chain and the second polypeptide chain of a protein of the invention that comprises multiple non-identical polypeptide chains. In some aspects, the nucleic acid molecule as defined herein may be isolated.

Further provided is a vector comprising the nucleic acid molecule of the invention as defined herein. The vector may be an expression vector.

Also provided is a host cell comprising the nucleic acid molecule or the vector of the invention as defined herein. The host cell may be a recombinant host cell.

In a further aspect there is provided a method of producing a protein of the invention, comprising culturing the host cell of the invention under conditions that result in expression and/or production of the protein, and isolating the protein from the host cell or culture.

In some aspects, provided herein is a pharmaceutical composition comprising the protein of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein.

Further provided is a method for enhancing an immune response in a subject, comprising administering to the subject an effective amount of the protein the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

In a further aspect there is provided a method for treating or preventing cancer in a subject, or ameliorating a symptom of cancer in a subject, comprising administering to the subject an effective amount of the protein of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

In some aspects, the cancer is a solid tumour. In some cases, the cancer is a hematologic malignancy. For example, the cancer may be Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer (e.g., melanoma), breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues. In some cases, a cancer of haematological tissues is a lymphoma.

In some aspects, provided herein is a protein of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use in the treatment of cancer, or for use in or ameliorating a symptom of cancer.

In some aspects, provided herein is a protein, or an immunoconjugate, or a nucleic acid molecule, or a vector for use, or the method of treatment of the invention as defined herein, for separate, sequential or simultaneous use in a combination combined with a second therapeutic agent, for example an anti-cancer agent.

In a further aspect there is provided the use of a protein of the invention as defined herein, or an immunoconjugate of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or a pharmaceutical composition of the invention as defined herein, in the manufacture of a medicament for the treatment of cancer or for ameliorating a symptom of cancer.

The invention also provides a method for treating or preventing an autoimmune disease or an inflammatory disease in a subject, comprising administering to the subject an effective amount of the protein as defined herein, or the immunoconjugate as defined here, or the

nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

For example, the autoimmune disease or inflammatory disease may be arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease and Hashimoto's thyroiditis, or ankylosing spondylitis.

Also provided is a protein as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of an autoimmune disease or an inflammatory disease.

Further provided is the use of a protein as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an autoimmune disease or an inflammatory disease.

The invention also provides a method for treating or preventing a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject an effective amount of the protein as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

Also provided is a protein as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of a cardiovascular disease or a fibrotic disease.

Further provided is the use of a protein as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of a cardiovascular disease or a fibrotic disease.

The cardiovascular disease in any aspect of the invention may for example be coronary heart disease, atherosclerosis, or stroke.

For example, the fibrotic disease in any aspect of the invention may be myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, asthma, cystic fibrosis or bronchitis.

In some aspects, provided herein is a protein comprising the amino acid sequences disclosed herein and in the format disclosed herein for use in therapy.

In some aspects, the pharmaceutical composition may comprise a pharmaceutically acceptable excipient, carrier or diluent. A pharmaceutically acceptable excipient may be a compound or a combination of compounds entering into a pharmaceutical composition which does not provoke secondary reactions and which allows, for example, facilitation of the administration of the protein as defined herein, an increase in its lifespan and/or in its efficacy in the body or an increase in its solubility in solution. These pharmaceutically acceptable vehicles are well known and will be adapted by the person skilled in the art as a function of the mode of administration of the protein as defined herein.

In some aspects, the protein as defined herein may be provided in a lyophilised form for reconstitution prior to administration. For example, lyophilised protein molecules may be re-constituted in sterile water and mixed with saline prior to administration to an individual.

The protein as defined herein will usually be administered in the form of a pharmaceutical composition, which may comprise at least one component in addition to the protein molecule. Thus pharmaceutical compositions may comprise, in addition to the protein as defined herein, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the protein. The precise nature of the carrier or other material will depend on the route of administration, which may be by bolus, infusion, injection or any other suitable route, as discussed below.

For parenteral, for example sub-cutaneous or intra-venous administration, e.g. by injection, the pharmaceutical composition comprising the protein as defined herein may be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride Injection, Ringe's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives may be employed as required including buffers such as phosphate, citrate and other organic acids; antioxidants, such as ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens, such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3'-pentanol; and m-cresol); low molecular weight polypeptides; proteins, such as serum albumin, gelatin

or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids, such as glycine, glutamine, asparagines, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose or dextrins; chelating agents, such as EDTA; sugars, such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions, such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants, such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

A pharmaceutical composition comprising a protein as defined herein may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

A protein as defined herein may be used in a method of treatment of the human or animal body, including prophylactic or preventative treatment (e.g. treatment before the onset of a condition in an individual to reduce the risk of the condition occurring in the individual; delay its onset; or reduce its severity after onset). The method of treatment may comprise administering the protein as defined herein to an individual in need thereof.

Administration is normally in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the composition, the method of administration, the scheduling of administration and other factors known to medical practitioners. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors and may depend on the severity of the symptoms and/or progression of a disease being treated. Appropriate doses of antibody molecules are well known in the art (Ledermann J.A. *et al.*, 1991, Int. J. Cancer 47: 659-664; Bagshawe K.D. *et al.*, 1991, Antibody, Immunoconjugates and Radiopharmaceuticals 4: 915-922). Specific dosages may be indicated herein or in the Physician's Desk Reference (2003) as appropriate for the type of medicament being administered may be used. A therapeutically effective amount or suitable dose of the protein as defined herein may be determined by comparing its *in vitro* activity and *in vivo* activity in an animal model. Methods for extrapolation of effective dosages in mice and other test animals to humans are known. The precise dose will depend upon a number of factors, including whether the protein is for prevention or for treatment, the size and location of the area to be treated, the precise nature of the protein (e.g. Fab2, IgG) and the nature of any detectable label or other molecule attached to the protein.

A typical protein dose will be in the range 100 µg to 1 g for systemic applications, and 1 µg to 1 mg for topical applications. An initial higher loading dose, followed by one or more lower doses, may be administered. In some aspects, the protein will comprise a whole antibody, e.g., the IgG1 or IgG4 isotype. This is a dose for a single treatment of an adult patient, which may be proportionally adjusted for children and infants, and also adjusted for other protein construct formats in proportion to molecular weight. Treatments may be repeated at daily, twice-weekly, weekly or monthly intervals, at the discretion of the physician. The treatment schedule for an individual may be dependent on the pharmacokinetic and pharmacodynamic properties of the protein composition, the route of administration and the nature of the condition being treated.

Treatment may be periodic, and the period between administrations may be about two weeks or more, e.g. about three weeks or more, about four weeks or more, about once a month or more, about five weeks or more, or about six weeks or more. For example, treatment may be every two to four weeks or every four to eight weeks. Treatment may be given before, and/or after surgery, and/or may be administered or applied directly at the anatomical site of surgical treatment or invasive procedure. Suitable formulations and routes of administration are described above.

In some aspects, proteins as defined herein may be administered as sub-cutaneous injections. Sub-cutaneous injections may be administered using an auto-injector, for example for long or short-term prophylaxis/treatment.

In some aspects, the therapeutic effect of the protein as defined herein may persist for several multiples of the protein half-life in serum, depending on the dose. For example, the therapeutic effect of a single dose of the protein as defined herein may persist in an individual for 1 month or more, 2 months or more, 3 months or more, 4 months or more, 5 months or more, or 6 months or more.

As used herein, the term “CD47” refers to IAP (Integrin Associated Protein) and variants thereof that retain at least part of the biological activity of CD47. As used herein, CD47 includes all mammalian species of native sequence CD47, including human, rat, mouse and chicken. In some embodiments, the term “CD47” is used to include variants, isoforms and species homologs of human CD47. In some cases, as used herein, CD47 includes all mammalian and non-mammalian species of native sequence CD47, including human, monkey, rat, mouse and chicken. In some embodiments, the term “CD47” refers only to wild-type CD47. Proteins of the invention may cross-react with CD47 from species other than human, in particular CD47 from cynomolgus monkey (*Macaca fascicularis*). Examples of

human and cynomolgus CD47 amino acid sequences are provided in Table 11. In certain embodiments, the proteins of the invention may be completely specific for human CD47 and may exhibit no non-human cross-reactivity.

As used herein, the term "cMET" refers to the MET protein and variants thereof that retain at least part of the biological activity of cMET. In some cases, as used herein, cMET includes all mammalian species of native sequence cMET, including human, rat, mouse and chicken. In some embodiments, the term "cMET" may be used to include variants, isoforms and species homologs of human cMET. In some cases, as used herein, cMET includes all mammalian and non-mammalian species of native sequence cMET, including human, monkey, rat, mouse and chicken. In some embodiments, the term "cMET" refers only to wild-type cMET. Antibodies of the invention may cross-react with cMET from species other than human, in particular cMET from cynomolgus monkey (*Macaca fascicularis*). Examples of human and cynomolgus cMET amino acid sequences are provided in Table 12. In certain embodiments, the antibodies may be completely specific for human cMET and may exhibit no non-human cross-reactivity.

As used herein, the term "Her2" refers to the human epidermal growth factor receptor 2 protein and variants thereof that retain at least part of the biological activity of Her2. Her2 is also known as HER2/neu, ErbB2, c-erbB-2 and human EGF receptor 2. In some embodiments, the term "Her2" may be used to include variants, isoforms and species homologs of human Her2. In some cases, as used herein, Her2 includes all mammalian and non-mammalian species of native sequence Her2 (also known as ErbB2), including human, monkey, rat, mouse and chicken. In some embodiments, the term "Her2" refers only to wild-type Her2. Antibodies of the invention may cross-react with Her2 from species other than human, in particular Her2 from cynomolgus monkey (*Macaca fascicularis*). Examples of human and cynomolgus Her2/ErbB2 amino acid sequences are provided in Table 15. In certain embodiments, the antibodies may be completely specific for human Her2 and may exhibit no non-human cross-reactivity.

As used herein, the term "CD3" refers to the "cluster of differentiation 3" multimeric protein complex and variants thereof that retain at least part of the biological activity of CD3. The CD3 complex comprises four distinct polypeptide chains; epsilon (ε), gamma (γ), delta (δ) and zeta (ζ). These polypeptide chains assemble and function as three pairs of dimers (εγ, εδ, ζζ). In some embodiments, the term "CD3" may be used to include variants, isoforms and species homologs of human CD3. In some cases, as used herein, CD3 includes all mammalian and non-mammalian species of native sequence CD3, including human, monkey, rat, mouse and chicken. In some embodiments, the term "CD3" refers only to wild-

type CD3. Antibodies of the invention may cross-react with CD3 from species other than human, in particular CD3 from cynomolgus monkey (*Macaca fascicularis*). Examples of human and cynomolgus CD3 epsilon amino acid sequences are provided in Table 16. In certain embodiments, the antibodies may be completely specific for human CD3 and may exhibit no non-human cross-reactivity.

As used herein, an "antagonist" as used in the context of the protein of the invention refers to a protein which is able to bind to a molecule expressed in a diseased tissue and inhibit the molecule's biological activity and/or downstream pathway(s) mediated by the molecule. For example, an "anti-CD47 antagonist protein" (interchangeably termed "anti-CD47 protein") refers to a protein which is able to bind to CD47 and inhibit CD47 biological activity and/or downstream pathway(s) mediated by CD47 signalling. An anti-CD47 antagonist protein encompasses proteins that can block, antagonize, suppress or reduce (including significantly) CD47 biological activity, including downstream pathways mediated by CD47 signalling, such as receptor binding and/or elicitation of a cellular response to CD47. For the purposes of the present invention, it will be explicitly understood that the term "anti-CD47 antagonist protein" encompass all the terms, titles, and functional states and characteristics whereby CD47 itself, and CD47 biological activity (including but not limited to its ability to enhance the activation of phagocytosis by cells of the myeloid lineage), or the consequences of the activity or biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree.

A protein of the invention "specifically binds" "specifically interacts", "preferentially binds", "binds" or "interacts" with an a molecule (e.g., human CD47, human Her2, human CD3, human cMET, or human PD-L1) if it binds with greater affinity, avidity, more readily and/or with greater duration than the protein binds to other molecules.

An "antibody molecule" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term "antibody molecule" encompasses not only intact polyclonal or monoclonal antibodies, but also any antigen binding fragment (for example, an "antigen-binding portion") or single chain thereof, fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site including, for example without limitation, scFv, single domain antibodies (for example, shark and camelid antibodies), maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv.

An “antibody molecule” encompasses an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), for example IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term “antigen binding portion” of an antibody molecule, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to an antigen. Antigen binding functions of an antibody molecule can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term “antigen binding portion” of an antibody molecule include Fab; Fab'; F(ab')2; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment, and an isolated complementarity determining region (CDR).

The term “Fc region” is used to define a C-terminal region of an immunoglobulin heavy chain. The “Fc region” may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. The Fc region of an immunoglobulin generally comprises two constant domains, CH2 and CH3. As is known in the art, an Fc region can be present in dimer or monomeric form.

A “variable region” of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework regions (FRs) connected by three complementarity determining regions (CDRs) also known as hypervariable regions, and contribute to the formation of the antigen binding site of antibodies. When choosing FR to flank CDRs, for example when humanizing or optimizing an antibody, FRs from antibodies which contain CDR sequences in the same canonical class are preferred.

As used herein the term “conservative substitution” refers to replacement of an amino acid with another amino acid which does not significantly deleteriously change the functional activity. A preferred example of a “conservative substitution” is the replacement of one amino acid with another amino acid which has a value ≥ 0 in the following BLOSUM 62 substitution matrix (see Henikoff & Henikoff, 1992, PNAS 89: 10915-10919):

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4	-1	-2	-2	0	-1	-1	0	-2	-1	-1	-1	-1	-2	-1	1	0	-3	-2	0
R	-1	5	0	-2	-3	1	0	-2	0	-3	-2	2	-1	-3	-2	-1	-1	-3	-2	-3
N	-2	0	6	1	-3	0	0	0	1	-3	-3	0	-2	-3	-2	1	0	-4	-2	-3
D	-2	-2	1	6	-3	0	2	-1	-1	-3	-4	-1	-3	-3	-1	0	-1	-4	-3	-3
C	0	-3	-3	-3	9	-3	-4	-3	-3	-1	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1
Q	-1	1	0	0	-3	5	2	-2	0	-3	-2	1	0	-3	-1	0	-1	-2	-1	-2
E	-1	0	0	2	-4	2	5	-2	0	-3	-3	1	-2	-3	-1	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	-2	6	-2	-4	-4	-2	-3	-3	-2	0	-2	-2	-3	-3
H	-2	0	1	-1	-3	0	0	-2	8	-3	-3	-1	-2	-1	-2	-1	-2	-2	2	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4	2	-3	1	0	-3	-2	-1	-3	-1	3
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4	-2	2	0	-3	-2	-1	-2	-1	1
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5	-1	-3	-1	0	-1	-3	-2	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5	0	-2	-1	-1	-1	-1	1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6	-4	-2	-2	1	3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7	-1	-1	-4	-3	-2
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4	1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5	-2	-2	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11	2	-3
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	-1
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4.

The term “monoclonal antibody” (Mab) refers to an antibody, or antigen-binding portion thereof, that is derived from a single copy or clone, including for example any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Preferably, a monoclonal antibody of the invention exists in a homogeneous or substantially homogeneous population.

A “humanized” antibody molecule refers to a form of non-human (for example, murine) antibody molecules, or antigen-binding portion thereof, that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding sub-sequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies may be human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity.

“Human antibody” or “fully human antibody” refers to an antibody molecule, or antigen-binding portion thereof, derived from transgenic mice carrying human antibody genes or from human cells.

The term “chimeric antibody” is intended to refer to an antibody molecule, or antigen-binding portion thereof, in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody molecule in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

The term “immunoconjugate” refers to a protein of the invention that is conjugated, fused or linked to at least one cytotoxic, cytostatic, or therapeutic agent.

Proteins of the invention can be produced using techniques well known in the art, for example recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art.

The term “isolated molecule” (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or expressed in a cellular system different from the cell from which it naturally originates, will be “isolated” from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The term “epitope” refers to that portion of a molecule capable of being recognized by and bound by a protein of the invention, an antibody molecule, or antigen-binding portion thereof, at one or more of the protein’s or antibody molecule's antigen-binding regions. Epitopes can consist of defined regions of primary secondary or tertiary protein structure and includes combinations of secondary structural units or structural domains of the target recognised by the antigen binding regions of the protein, the antibody, or antigen-binding portion thereof. Epitopes can likewise consist of a defined chemically active surface grouping of molecules such as amino acids or sugar side chains and have specific three-dimensional structural characteristics as well as specific charge characteristics. The term “antigenic epitope” as

used herein, is defined as a portion of a polypeptide to which a protein of the invention or an antibody molecule can specifically bind as determined by any method well known in the art, for example, by conventional immunoassays, antibody competitive binding assays or by x-ray crystallography or related structural determination methods (for example NMR).

The term "binding affinity" or "KD" refers to the dissociation rate of a particular antigen-binding protein interaction or antigen-antibody interaction. The KD is the ratio of the rate of dissociation, also called the "off-rate (k_{off})", to the association rate, or "on-rate (k_{on})". Thus, K_D equals k_{off} / k_{on} and is expressed as a molar concentration (M). It follows that the smaller the K_D, the stronger the affinity of binding. Therefore, a K_D of 1 μM indicates weak binding affinity compared to a K_D of 1 nM. KD values for binding proteins or antibodies can be determined using methods well established in the art. One method for determining the KD of a binding protein or an antibody is by using surface plasmon resonance (SPR), typically using a biosensor system such as a Biacore® system.

The term "potency" is a measurement of biological activity and may be designated as IC_{50}, or effective concentration of a protein of an immunoconjugate of the invention to its binding partner (e.g., a molecule expressed in a diseased tissue) or antigen to inhibit 50% of activity of the binding partner or the antigen measured in an activity assay as described herein.

The phrase "effective amount" or "therapeutically effective amount" as used herein refers to an amount necessary (at dosages and for periods of time and for the means of administration) to achieve the desired therapeutic result. An effective amount is at least the minimal amount, but less than a toxic amount, of an active agent which is necessary to impart therapeutic benefit to a subject.

The term "inhibit" or "neutralize" as used herein with respect to bioactivity of a protein of the invention means the ability of the protein to substantially antagonize, prohibit, prevent, restrain, slow, disrupt, eliminate, stop, reduce or reverse for example progression or severity of that which is being inhibited including, but not limited to, a biological activity or binding interaction of a molecule expressed in a diseased tissue.

A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected *in vivo* with a polynucleotide(s) of the invention.

As used herein, “vector” means a construct, which is capable of delivering, and, preferably, expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

The term “treating”, as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, delaying the progression of, delaying the onset of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as defined above. The term “treating” also includes adjuvant and neoadjuvant treatment of a subject. For the avoidance of doubt, reference herein to “treatment” includes reference to curative, palliative and prophylactic treatment. For the avoidance of doubt, references herein to “treatment” also include references to curative, palliative and prophylactic treatment.

It is understood that wherever embodiments are described herein with the language “comprising,” otherwise analogous embodiments described in terms of “consisting of” and/or “consisting essentially of” are also provided.

Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word “comprise,” or variations such as “comprises” or “comprising” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Any example(s) following the term “e.g.” or “for example” is not meant to be exhaustive or limiting.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art.

Particular non-limiting embodiments of the present invention will now be described with reference to accompanying drawings.

EXAMPLES

EXAMPLE 1. Generation of optimized conditionally active therapeutic antibodies

Introduction

In this example, we successfully generated a panel of optimized conditionally active antibodies. These conditionally active antibodies were well expressed, biophysically stable, highly soluble and of maximized amino acid sequence identity to preferred human germlines.

Materials and methods

Cloning, transient expression, purification and characterization of proteins

Antibody-encoding DNA sequences were cloned via restriction-ligation cloning into separate human IgG1 heavy and light-chain encoding expression cassettes in separate plasmid vectors, to create IgG or IgG^2 format constructs for expression. Similar cassettes were also cloned into 'knob into hole' human IgG1 heterodimerising Fc vectors to create Fab and Fab^2 constructs. Fab^2 cMETCD47 and Her2CD3 protein constructs were constructed using knob-into-hole (KIH) heavy chain expression vectors (CH3 domain T366W and T366S/L368A/Y407V mutations). Fab^2 Her2-CD3 constructs also included effector function-ablating mutations L234A/L235A/G237A. IgG^2 Her2CD47 protein constructs were constructed using "wildtype" IgG1 heavy & kappa light chain expression vectors. IgGs were expressed in CHO cells after transient transfection with endotoxin-free IgG expression plasmid preparations, per manufacturer's protocols.

Produced antibodies were captured from clarified supernatants using a HiTrap MabSelect Sure Protein A 5mL column on an ÄKTA Pure 150 L FPLC system. Eluted protein peaks were immediately buffer exchanged into 1x PBS pH 7.4 by directly loading the eluted protein A peak fractions onto a HiPrep 26/10 Desalting column. Protein concentration was determined by measuring the absorbance at 280 nm and 1 µg of each purified protein was analysed by SDS-PAGE under reducing and/or non-reducing conditions using 4-20% TGX polyacrylamide gradient gels (BioRad, Cat. nr. 456-1093) with 1x Tris/glycine/SDS buffer, separated by 120V field for 1 hour. In order to test for the presence of non-covalently bound aggregates and to complement the SDS PAGE analysis, analytical size-exclusion

chromatography was performed. Aliquots of selected clones were analyzed by analytical Size Exclusion Chromatography (SEC) using a Superdex 200 Increase 10/300 SEC column and 1x PBS pH 7.4 as running buffer, in isocratic mode.

Selected proteins were further purified using preparative SEC. Antibody samples up to 1 ml were loaded onto a Superdex 200 Increase 10/300 SEC column or a HiLoad 26/600 Superdex 200pg column equilibrated in 1x PBS pH 7.4. 1 ml fractions of peak of interest were collected, and main peak fractions were pooled. After size exclusion chromatography, the samples were again analyzed by SDS-PAGE, as above.

Haemagglutination

Red blood cells (RBC) were isolated from fresh uncoagulated human blood (minimum of 3 different donors), diluted to 2% in PBS and incubated for 60-90 minutes in a U bottomed 96 well plate with a titration of IgG or protein construct. In the absence of haemagglutination, cells sedimented to the bottom of the well forming a red pellet. Haemagglutination was observed as non-settled RBC solution. Images of each plate were recorded and the data expressed for each sample as titre for the last well in which haemagglutination was observed.

Metalloprotease Digestion

Protein constructs were incubated for 16 hour at 37°C with either individual human Matrix Metalloprotease (MMP) enzymes or a mix of active MMP3, MMP7 and MMP12 (equal parts of each) at a ratio of 1% total MMP to protein construct (wt/wt) in Tris buffered saline (pH7.4) containing 5mM $CaCl_2$. The reactions were stopped by the addition of 20mM EDTA and then samples tested for binding or functional activity as described.

IgG titration binding ELISAs

To coat ELISA plates, target proteins were diluted to 1 μg/ml in PBS pH7.4 and added at 100 μl per well, at 4°C, o/n. Coated plates were washed 3x with PBS pH7.4, blocked with 4% Skim Milk Protein in PBS (380 μl/ well) for 1 hr at RT, then washed 5x with PBS-Tween 20 (PBST). Antibodies (100 μl/well; diluted in PBST) were then added and then incubated 1 hr at RT. Plates were then washed 3x with PBS and goat anti-human IgG-HRP added (100 μl/well) at RT, for 1 hr. Plates were then washed 3x with PBST and twice with PBS before the addition of 100 μl TMB per well. Reactions were stopped by adding 100 μl 2M H_2SO_4/well and OD was read on a plate reader at 450nm.

Flow Cytometry Binding

Binding of protein constructs (+/- pre-digestion with MMP3/7/12) and control IgG to Jurkat cells and BT-474 cells was assessed by flow cytometry. Viable cells were identified using

Zombie UV™ Fixable Viability Dye (Biolegend). Binding of human IgG and protein constructs was detected with a FITC conjugated goat anti human (H+L) secondary antibody. The mouse monoclonal anti-CD3 control antibody binding was detected using Alexa-Fluor-488 goat anti mouse IgG. Results were analysed by measurement of the Mean Fluorescence Intensity (MFI) of viable cells in the FITC channel detector of a BD Fortessa flow cytometer.

T-Cell Activation Bioassay

Functional activity of Her2CD3 protein constructs was assessed in a co-culture assay using BT474 cells and an NFAT-RE- luciferase Jurkat reporter cell line (Promega – TCR/CD3 Effector cells NFAT). BT-474 cells (40000 cell/well) were seeded into 96-well white clear bottomed tissue culture treated plates in Hybri-Care medium (ATCC) supplemented with 10% FBS and incubated at 37°C overnight in a CO_2 incubator. Medium was removed and control antibodies or protein constructs (+/- pre-digestion with MMP3/7/12) prepared in assay medium (RPMI supplemented with 10% FBS) were added to the cells. TCR/CD3 Effector cells (NFAT) were thawed and diluted according to the manufacturer's protocol, then added to the assay wells. Following a 6 hour incubation at 37°C in a CO_2 incubator the plates were re-equilibrated to room temperature and luciferase activity determined by addition of Bio-Glo reagent for 5-10 minutes and measurement of luminescent signal (RLU). Fold induction was determined by calculating the ratio of the sample RLU/RLU in the absence of antibody following subtraction of background luminescence signal.

Molecular dynamics simulations

Eight systems (linker sequences X1, X2, X3 and X4 and the equivalent sequences with a covalent bond broken in one of the linkers at the GS sequence position XC1, XC2, XC3 and XC4) were modelled and optimised using the AMBER10:EHT forcefield in MOE (Chemical Computing Group Inc). Histidine charges were assigned using protonate3D tool in MOE. Three successive rounds of minimisation were undertaken with a final gradient of 0.001 allowing 10,000 steps without constraints. The individual systems were constrained once again and gradually minimized using NAMD 2.13 with the CHARMM27 forcefield to reduce the total potential energy in a series of three steps of energy minimization. The first step kept all heavy atoms constrained, and only hydrogen atoms were allowed mobility. The second step removed the constraints on the sidechains whilst the third steps freed all atoms, allowing them to move without restriction. Minimisation within CHARMM27 was facilitated since this is the forcefield at work within NAMD molecular dynamics simulations.

For dynamics runs, Generalised Born (GB) solvation was used to describe solvent effects. MD simulations were set up and performed afterwards using NAMD 2.13. Four steps of

equilibration were performed, gradually loosening harmonic constraints in 125 ps increments, for a total equilibration time of 500 ps. The first step heated the system to 310 K while applying a force of 4 kcal/mol to hold the backbone in place. The remaining three steps gradually lifted the backbone constraint force from 4 kcal/mol to 1 kcal/mol with an NVT ensemble (constant number (N), volume (V), and temperature (T)). A switching function was applied at 10 Å to abridge the van der Waals potential function. Electrostatic and vdW cutoff was set at 14 Å as recommended in NAMD. Periodic boundary conditions were not used as they were not compatible with the implicit solvent approach. The constraints applied during equilibration were removed for the free simulation of the antibody complexes. Production runs were conducted for either 6, 15, 20 or 100 ns at 310 K. 100 ns runs were applied to cleaved linker proteins XC1-4 in order to fully explore range of movement whilst the shorter runs (up to 20 ns) were found to be sufficient to map the range of movement for non-cleaved antibody constructs X1-4.

***In vivo* analyses of PK and tolerability**

TOLERABILITY STUDY - Twenty eight (28) 6 - 8 week old male B6.Cg-*Fcgrt*^{tm1Dcr} Tg(FCGRT)32DcrJ ('Tg32' homozygous human FcRn transgenic, JAX stock# 014565) mice were assigned into 7 groups with 4 mice per group. Body weights were measured the day of antibody administration. At 0 hours, test articles were administrated as IV injections at 2 mg/kg or 10mg/kg, and at a dose volume of 10 ml/kg. 200 µL whole blood samples were collected into EDTA, on days 5, 29, and 60 (terminal bleed). Blood was used for CBC/Dif/Retic analysis, including Leucocytes, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Hemoglobin, Erythrocytes, Reticulocytes, MCHC and MCV. Body weight were then monitored weekly for the first month and then monthly until the end of the experiment.

PHARMACOKINETICS STUDY - Thirty two 6 - 8 week old male B6.Cg-*Fcgrt*^{tm1Dcr} Tg(FCGRT)32DcrJ ('Tg32' homozygous human FcRn transgenic, JAX stock #014565) mice were assigned into 8 groups with 4 mice per group. The day before test article administration, 35 µL blood samples from three (3) Tg32 mice were collected into EDTA to test the binding of the test articles to the mouse erythrocytes using flow cytometry. Body weights were measured the day of antibody administration and weekly until the end of the experiment. At 0 hours, the test articles were administrated as IV injections at 2 mg/kg or 10mg/kg, at a dose volume of 10 ml/kg. Blood samples were collected from each mouse according to the bleeding schedule: 30min, 4h, 1, 3, 5, 7, 10, 14, 21, 28 and 42 days. 25 µL blood samples were collected from each mouse according to the bleeding schedule. The blood samples were collected into K_3EDTA, processed to plasma, and stored at -20°C. Plasma samples were then assessed in triplicate by and ELISA for estimation of human IgG concentration.

TOLERABILITY STUDY IN NOD-SCID MICE - NOD-SCID mice were assigned into 4 groups with 3 mice per group. Body weights were measured daily. At Day 0, test articles were administrated as IV injections at 8 mg/kg or 14 mg/kg, with 3 subsequent doses at 4 or 7 mg/kg at 5 day intervals.

Flow cytometry analyses of binding to monkey and human erythrocytes

Erythrocytes were isolated from 3 Cyno (Cynomolgus) monkeys and 3 human donors. Per sample, $5x10^5$ cells (diluted in DMEM + 5% FBS) were stained for one hour with A-D5 IgG1: 0.0032; 0.016; 0.03; 50 µg/mL. Trastuzumab: 0.0032; 0.016; 0.03; 50 µg/mL. IgG^2 Her47 LHL-LHLF 0h: 0.016; 0.08; 0.4; 2; 10; 50 µg/mL. IgG^2 Her47 LHL-LHL 0h: 0.016; 0.08; 0.4; 2; 10; 50 µg/mL. Binding of test samples to erythrocytes was measured using FITC AffiniPure Goat Anti-Human IgG (1:200 dilution; 1-hour incubation time), followed by Flow cytometry measurement of FITC fluorescence intensity (BD LSR FortessaX-20 cell analyser).

Metalloprotease and Cathepsin Digestion at pH6.0 and 7.4

Protein constructs were placed in TBS (containing 5mM $CaCl_2$, pH6.0 or 7.4) then incubated at 37°C with individual human Matrix Metalloprotease (MMP) or Cathepsin enzymes, at a ratio of 1% total enzyme to protein construct (wt/wt), for 0, 2, 4, 8 and 24h. The reactions were stopped by the addition of 20mM EDTA and then samples frozen before testing for binding or functional activity as described.

***In vitro* protein stability analyses**

Forced Oxidation - For forced oxidation analysis, test articles in PBS were treated with 0.5 % H2O2 at room temperature for 2 hours and then stored at -80 °C prior to SEC and RP analysis (intact antibodies and subunits, tryptic peptides) on a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). For intact antibody reduction, DTT was added to a final concentration of 0.33 M and samples were incubated for 1 hour at 22 ℃ and immediately analysed by RP.

SEC Analysis - Chromatographic separation was performed using an Acquity UPLC Protein BEH SEC Column, 200 Å, 1.7 µm, 4.6 mm × 150 mm (Waters, Elstree, UK) and an Acquity UPLC Protein BEH SEC guard column 30 × 4.6 mm, 1.7 µm, 200 Å (Waters, Elstree, UK) connected to a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). The method consisted of an isocratic elution over 10 minutes and the mobile phase was 0.2 M potassium phosphate pH 6.8, 0.2 M potassium chloride. The flow rate was 0.35 mL/minute. Detection was carried out by UV absorption at 280 nm.

Reverse Phase analysis of intact antibodies and subunits - Chromatographic separation was performed using a PLRP-S 1000, 5 µm, 2.1 mm × 50 mm column (Agilent Technologies, Stockport, UK) connected to a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). The method consisted of a linear gradient from 75 % buffer A (0.02 % TFA, 7.5 % acetonitrile in H2O) to 45 % buffer B (0.02 % TFA, 7.5 % H2O in acetonitrile) over 14 minutes. The flow rate was 0.5 mL/minute and the temperature was maintained at 70 °C throughout the analysis. Detection was carried out by UV absorption at 280 nm.

HIC Analysis - Chromatographic separation was performed using a TSKgel Butyl-NPR 4.6 mm × 35 mm HIC column (TOSOH Bioscience Ltd., Reading, UK) connected to a Dionex Ultimate 3000RS HPLC system (ThermoFisher Scientific, Hemel Hempstead, UK). The method consisted of a linear gradient from 60 % Buffer A (100 mM sodium phosphate pH 7.0, 2 M ammonium sulphate) to 90 % Buffer B (100 mM sodium phosphate pH 7.0) over 9 minutes. The flow rate was 1.2 mL/minute. Detection was carried out by UV absorption at 280 nm.

Charge Variant Assay – Charge variant profiling of test articles was determined by Protein Charge Variant Assay on a LabChip GXII Touch HT (PerkinElmer), according to the manufacturer's protocol.

BIACORE® analyses of Fc affinity for human Fc receptors

Interaction affinities for antibody proteins were determined by surface plasmon resonance using a BIACORE® T200 instrument. For most analyses, His6-tagged FcγRI, FcγRIIa (167R and 167H variants), FcγRIIb, FcγRIIIa (176F and 176V variants), and FcγRIIIb receptors (all Sino Biological) were captured on a CM5 sensor chip coated with an anti-HIS antibody by standard amine coupling. Receptor-specific formats of analyses were then applied, as below.

FcγRI is a high-affinity receptor for IgG1 monomers, so 1:1 kinetic analysis was performed under the following conditions: 'single cycle' analysis using flow rate 30 µl/min, receptor protein loaded to ~30 RU at 10 µl/min (diluted 0.25 µg/ml in HBS-P+), 5 point three-fold dilution of purified antibodies titrated 0.411 nM to 33.33 nM applied with an association time of 200 s, dissociation time of 300 s. Regeneration with 2x injections glycine pH 1.5 and analysis using 1:1 fit.

The interactions between monomeric IgG and FcγRII and FcγRIII receptors are relatively low affinity interactions, so 'steady state' affinity analyses were performed under the following conditions: flow rate 30 µl/min, receptor protein loaded to ~60 RU at 10 µl/min (diluted 0.25

µg/ml in HBS-P+), 5 point three-fold dilution series of purified antibodies titrated between 33 nM and 24000 nM applied with an association time of 30 s, dissociation time of 25 s. Regeneration with 2x injections glycine pH 1.5 and analysis using steady state affinity calculation.

Results and Discussion

Protein construct design principles

Standard anti-cancer antigen antibodies suffer from significant pharmacological challenges in the treatment of solid tumours. A key issue that restricts efficacy in this class of potential drugs is that the antigens targeted by the antibodies are not found exclusively in the tumour and are merely highly overexpressed in the tumour. This off-tumour target expression often leads to dose-limiting side effect risks and antigen 'sink' effects where large doses of the antibody must be given to ensure sufficient antibody penetrates the tumour to have a therapeutic effect. One such example is the class of antibodies that target the antigen CD47 (FIG. 1A), where challenges include: High expression of CD47 in the bloodstream (e.g. on erythrocytes and platelets in particular) is a 'sink' that is bound by intravenously-dosed antibody, minimizing the amount of drug penetrating the tumour (even when large doses of IgG are given). The binding of blood cells by anti-CD47 is also a significant toxicity risk. Indeed, anti-CD47 antibodies are known to be capable of causing anaemia and even the cross-linking of human erythrocytes, creating a hemagglutination risk in patients. In addition, the tumour is typically a 'hostile' environment with high expression rates of enzymes such as MMPs which can accelerate IgG degradation. These factors all conspire to minimise the potential safety and efficacy of anti-CD47 antibodies and many other types of anti-tumour target antibodies where target expression is not limited solely to the tumour environment.

Anti-CD47 protein constructs (FIG. 1B) aim to overcome the peripheral sink and toxicity issues experienced with anti-tumour antigen IgGs by eliminating binding of the high risk (but potentially strong mechanism of action) target, in the native protein. This effect is achieved by adding low-risk upper domains (e.g. Fab domains that target another tumour antigen such as Her2) and linkers above (n-terminal to) the binding domains of the high-risk lower domains (such as CD47). The use of appropriate upper domain/linker combinations results in a configuration that fully blocks binding activity in the lower CD47 domain. The tumour-targeting domain (e.g. Her2) then drives high concentration in the tumour environment and the protein construct linker system exploits the elevated MMP activity in the tumour to cleave the linker peptides, exposing the CD47 binding domains and thereby conditionally activating the CD47-binding activity in the tumour, rather than the periphery. This design principle has the potential to be applicable in many different structural formats, examples of which are outlined below.

The protein construct IgG^2 design (FIG. 2A) may be based on sequences derived from IgG1, IgG2, IgG3, IgG4, IgE, IgM, or IgA and may or may not have effector function capacity. In this construct, four polypeptide chains encode for four Fab domains (2x Fab A, 2X Fab B), four linker sequences, and may or may not have an immunoglobulin hinge region and an Fc domain. Each Fab A-Linker domain (upper) blocks the binding activity of Fab B (lower). The target binding specificity of the upper and lower domains may be different, to drive bispecific function, or the same, to drive polyvalent target interaction. The choice of linker sequence, such as a lower hinge peptide sequence, creates a structure that will be locked in a non-diseased tissue, but quickly cleaved and unlocked in the presence of high concentrations of proteases in the tumour environment (FIG. 2B). The linkers in protein construct designs are all proteolytically cleavable and may be sequentially cleaved, with a first 'fast' cleavage taking the 'Locked' intact structure and creating an intermediate 'Unlocked' active state which allows Fabs A and B from a single protein construct to bind their cognate targets. Secondary, potentially slower cleavage of the second linker in each Fab A-Fab B protein construct unit may release the Fab A domains from the structure entirely, creating a 'Dissociated' form where the lower Fab domains are fully liberated for non-targeted (but likely still localized) activity. Cleaved linkers based on immunoglobulin hinge sequences may also recruit increased immune effector function (ADCC, CDC and ADCP) at the cell membrane via endogenous anti-hinge antibodies, which are a known phenomenon in human patients with (and even without) underlying autoreactive disease.

The protein construct Fab^2 design may be based on sequences derived from IgG1, IgG2, IgG3, IgG4, IgE, IgM, or IgA and may or may not have effector function capacity. In this construct, two (FIG. 3A) or three (FIG. 3B) polypeptide chains encode for two Fab domains (1x Fab A, 1X Fab B), two or more linker sequences, and may or may not have an immunoglobulin hinge region and an Fc domain in which pairing of heterodimers may or may not be driven by mutations in the Fc. Each Fab A-Linker domain again blocks the binding activity of Fab B and the choice of linker sequence, such as a lower hinge peptide sequence, creates a structure that will be locked in a non-diseased tissue, but quickly cleaved and unlocked in the presence of high concentrations of linker-cleaving proteases in the tumour environment, eventually becoming dissociated (FIG. 3A).

Protein construct cloning and expression

To produce and purify 15 bispecific, conditionally-active protein constructs formatted as Fab^2 or IgG^2 molecules with different Linker domains (Table 1), DNA cassettes for each construct type (Table 2) were synthesised and cloned into expression vectors encoding human IgG1 heavy and light chain or 'Knob into hole' heterodimeric Fc. Proteins were

named using the nomenclature (format)-(target names [upper domain/lower domain)-(heavy chain linker type)-(light chain linker type). All proteins were produced by transient transfection of CHO cells, then purified by protein A affinity chromatography.

The anti-HER2 variable region sequences used in the protein constructs disclosed herein are the variable region sequences of trastuzumab. The anti-CD3 variable region sequences used in the protein constructs disclosed herein are the variable region sequences of OKT3 or SP34. The anti-cMET variable region sequences used in the protein constructs disclosed herein are provided in WO 2019/175186. The anti-CD47 variable region sequences used in the protein constructs disclosed herein are provided in WO 2019/034895.

Analysis of protein construct expression and purification characteristics

The protein A purified proteins were quantified, showing that using different linker types affected expression yield (Table 2). Protein preparations in 1x PBS pH 7.4 were also examined in analytical size exclusion chromatography for quantification of the percentage desired product. Across all 3 classes of bispecific proteins generated (cMETCD47, Her2CD47 and Her2CD3), constructs containing the LHL linker generated the most optimal combination of the highest yield and production of % main peak of desired product by analytical SEC (Table 2). SDS-PAGE analysis of the protein A-purified proteins (FIG. 4) also demonstrated that clones containing the short linker domains L1 and LH, plus the long linker domain L3 produced highly heterogeneous products, with significant HMW and LMW content in the unreduced samples and LMW content in the reduced samples. This suggested that suboptimal linker types can lead to significant formation of undesirable multimers and breakdown products. For all constructs, HMW impurities were mostly absent in the reduced lanes, suggesting that these HMW impurities are disulfide-bonded dimers or higher, which are not reduced by SDS alone. For the IgG^2 design, clones 12 and 14 both exhibited high yields (Table 2), but clone 14 (containing the LHL linker) demonstrated highest yield and high uniformity of the desired product by SEC (90%) and SDS-PAGE (FIG. 4).

SEC chromatography was then performed on the remaining protein samples from a subset of clones in an attempt to produce fully purified monomeric protein. Chromatography traces for clones 1, 2, 3, 4, 5, 6, 10, 12 and 14 in preparative SEC are shown in FIG. 5. These analyses further demonstrated that the clones 1 (FIG. 5A), 3 (FIG. 5C), 4 (FIG. 5D), 5 (FIG. 5E) and 12 (FIG. 5G) contained a large percentage of higher and often lower molecular weight products around the main peak of desired product (eluting at a CV of approximately 0.5-0.55 in FIG. 5A-5H). In contrast, clones 6 (FIG. 5F), 14 (FIG. 5H) and 10 (FIG. 5I)

exhibited a dominant, well-defined major product peak. For clones 2 and 6, this allowed effective SEC purification of a predominantly monomeric protein, as demonstrated by SDS-PAGE of unreduced samples (FIG. 6A). Attempted SEC purification of clones 1, 4, and 5 failed, producing samples that were still heterogeneous (FIG. 6A). SEC-purified protein from Her2CD3 Fab^2 clones 7, 8 and 10 exhibited improved homogeneity, while of the Her2CD47 IgG^2 clones, only clone 14 achieved full homogeneity and monomeric status as evidenced in SDS-PAGE of unreduced and reduced samples (FIG. 6B). Again, these findings demonstrated that clones 6, 10 and 14, which all contained the LHL linker on both chains, exhibited the most reproducibly beneficial characteristics.

Functional characterization of protein constructs containing CD47 antibody v-domains in the lower Fab

Control IgG antibodies A-D5 anti-CD47, MH7.1 anti-C-MET, anti-Her2 Trastuzumab, and A-D5 Fab-Fc (a monovalent version of the A-D5 antibody containing a single Fab domain), were titrated (in μg/ml) in a direct binding ELISA against human CD47, C-MET and Her2 proteins (FIG. 7A). The Her2CD47-LH-LH and Her2CD47-LHL-LHL clones in IgG^2 format (FIG. 7B) and cMETCD47-L2-L2 and cMETCD47-LHL-LHL in Fab^2 format (FIG. 7C) were also analyzed in the same fashion. The control antibodies demonstrated the expected strong binding activity against their cognate targets, with little or no background to any other target, even at the highest concentration (Fig. 7A).

Importantly, the very strong monovalent binding of A-D5 Fab-Fc (FIG. 7A) demonstrated the intrinsic affinity of the A-D5 anti-CD47 domains and the significant potency that would need to be locked into the protein construct format of the invention, for it to be successful. Protein constructs Her2CD47-LHL-LHL (FIG. 7B) and cMETCD47-LHL-LHL (FIG. 7C) also showed similarly strong, highly specific binding to the cognate target of their upper Fab domains, but no binding signal against CD47, demonstrating that the binding activity of the CD47 v-domains was indeed fully inhibited when this linker combination was used. Importantly, high background signal on human CD47 was observed for Her2CD47-LH-LH and to a lesser extent for cMETCD47-L2-L2, suggesting that the ablation of binding affinity in the lower fab is critically controlled by linker choice. These findings suggested that the protein constructs Her2CD47-LHL-LHL (FIG. 7B) and cMETCD47-LHL-LHL (FIG. 7C) containing the anti-CD47 binding domains of antibody A-D5 that were tested in this assay have reduced ability to bind CD47 by >1000-fold in comparison to A-D5 IgG1, where a binding signal OD of 1.0 is achieved at approximately 1×10^{-2} μg/ml, while neither protein construct exhibits signal above 0.2 at the top concentration tested, of 10 μg/ml.

As hemagglutination is a primary toxicity risk of anti-CD47 antibodies, the prioritized protein constructs were then examined in a human erythrocyte-based hemagglutination assay. Control antibodies anti-CD235a (murine) and A-D5 anti-CD47, A-D5 Fab-Fc, MH7.1 anti-C-MET, anti-Her2 Trastuzumab, Her2CD47-LH-LH and Her2CD47-LHL-LHL IgG^2, and cMETCD47-L2-L2 and cMETCD47-LHL-LHL in Fab^2 format, were titrated (in nM) in a human erythrocyte hemagglutination assay using fresh erythrocytes from healthy donor 1 (FIG. 8A), donor 2 (FIG. 8B) and donor 3 (FIG. 8C). For all 3 donors, control antibodies anti-CD235a, A-D5 anti-CD47 and A-D5 Fab-Fc demonstrated potent concentration-dependent hemagglutination, due to cross-linking their respective surface antigens on adjacent erythrocytes. The low-potency hemagglutination effects observed for A-D5 Fab-Fc (clone 15) may be due to the presence of small amounts of functional dimer in this protein preparation as it was only purified by Protein A column and not fully purified to monomeric state by SEC. Importantly, none of the protein construct samples exhibited any ability to induce hemagglutination effects, even at a highest concentration of 140 nM. This finding suggests that the IgG^2 and Fab^2 format protein constructs containing the anti-CD47 binding domains of antibody A-D5 that were tested in this assay had reduced ability to induce agglutination by >241-fold in comparison to A-D5 IgG1, which exhibited a titre of 0.58 nM.

Prioritized protein constructs were submitted to enzymatic digestion using human MMPs 3, 7 and 12 over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control. Samples from these digest time courses were then applied in direct binding ELISA against human Her2 and CD47 (FIG. 9A, B) or human C-MET and CD47 (FIG. 9C). In each case, no loss of binding was observed over time towards either Her2 or C-MET, suggesting that the addition of proteases does not reduce the functional binding capacity of the upper Fab domains. In contrast, the CD47 binding capacity of all three protein constructs clearly increased over time, in a MMP-dependent fashion. The clone IgG^2 Her2CD47-LH-LH (FIG. 9A) again exhibited high background binding to CD47 and the lowest increase in CD47 binding over time. In contrast, the clones IgG^2 Her2CD47-LHL-LHL (FIG. 9B) and Fab^2 cMETCD47-LHL-LHL (FIG. 9C) again exhibited low background binding to CD47 (OD 450 nM < 0.2) and rapidly increasing binding to CD47 from 2 hours incubation onwards with both MMPs 7 and 12, reaching full saturation (OD 450 nM approximately 4.0) by 24 hours incubation. MMP3 appeared to be the slowest-activating of the 3 MMPs, showing increased CD47 binding signal after 24 hours for all 3 protein construct examples.

Functional characterization of protein constructs containing CD3 antibody v-domains in the lower Fab

Antibodies Fab^2 Her2CD3-L1-LH, Fab^2 Her2CD3-L2-L2 and Fab^2 Her2CD3-LHL-LHL were

analyzed by ELISA (FIG. 10A), Flow Cytometry (FIG. 10B) and a CD3 reporter assay (FIG. 10C). In ELISA analysis, all 3 proteins demonstrated the expected strong binding activity against Her2 (Upper Fab domain), with little or no background binding to any other target, even at the highest concentration (FIG. 10A). All 3 protein construct Fab^2 proteins were then submitted to incubation overnight with, or without mixed MMPs 3, 7 and 12 before further analysis. In flow cytometric binding to the HER2+ human cell line BT474, anti-HER2 Trastuzumab exhibited strong binding, Fab^2 Her2CD3-L1-LH and Fab^2 Her2CD3-L2-L2 showed similarly potent binding before and after MMP digest, while Fab^2 Her2CD3-LHL-LHL exhibited partially reduced binding after MMP digest, suggestive of a proportion of the protein losing the upper fab in the 'dissociated' state (FIG. 10B). As this finding suggested that the MMP digest process was active in the case of Fab^2 Her2CD3-LHL-LHL, the same samples were applied in a reporter assay where Her2+ BT474 cells were mixed with human CD3+ Jurkat cells engineered to provide a measurable signal if CD3 is activated. The data from this assay demonstrated that the bivalent anti-CD3 antibody OKT3 directly activated the CD3 signal in the reporter cells, as expected (FIG. 10C). The protein constructs each exhibited distinct profiles: The Her2CD3-L2-L2 protein, which contains 2xG4S linkers (not cleavable by MMP proteases) showed high background in the assay with no increase in CD3 activation signal after MMP digest, suggesting that the flexible linkers of this construct allow binding of Her2 by the upper Fab and partial activity of the lower fab allowing some background, but non-activating CD3 co-ligation (FIG. 10C). The Fab^2 Her2CD3-L1-LH protein exhibited lower background activity in the assay, with a moderate increase in signal after MMP digest. The Fab^2 Her2CD3-LHL-LHL exhibited no measurable background signaling in the absence of MMP digest, showing minimal activation of CD3 similar to the negative control Trastuzumab and IgG1 Isotype control antibodies in the undigested sample, but potent activation in the MMP digested sample. The data in FIG. 10A-C therefore suggest that the Her2CD3-LHL-LHL Fab^2 format had the best combination of properties as it was simply expressed and purified, has high intrinsic Her2 binding activity, low background CD3-ligating activity, and high CD3 co-ligation activation only when activated by MMP cleavage of the LHL linker.

Second generation construct cloning and expression

The performance of the above multispecific Fab^2 and IgG^2 clones containing the LHL linkers encouraged a second series of constructs to experimentally explore the potential functional sequence space in both tertiary structure and linker sequence content. The following clones were synthesized and assembled to sample these parameters:

1. Clone 'Met47-LHL-LHL', which was a Fab^2 protein in the 'One Arm' style (Table 6, Fig. 3B).

2. Clone 'Her23-LHL-LHL', which was a remodeled 'Clone 10' Fab^2 protein in the 'One Arm' style (Table 7, Fig. 3B).

3. Clone 'Her23(34)-LHL-LHL', which was a Fab^2 protein in the 'One Arm' style (Table 8, Fig. 3B).

4. A series of clones of the IgG^2 type incorporating the Her2 binding domains of Trastuzumab in the upper fab and the CD47 binding domains of clone A-D5 in the lower Fab (Table 9). These clones contained mutated LHL-based linker sequences that might be more sensitive to enzymatic cleavage by a broad family of MMPs (LHLF linkers), linkers of moderately increased length that added a portion of the human IgG1 middle hinge sequence (LHLM linkers), or both (LHLMF linkers).

5. Clone 'Fc-Her23(34)', which was a Fab^2 protein (Table 13, Fig. 12) in which the Fab^2 module is placed at the c-terminal end of the KIH-Fc.

6. Clone 'MetMet-LHL-LHL, which was a Fab^2 protein in the 'One Arm' style (Table 14, Fig. 3B, Fig. 13) containing two copies of the C-Met Fab. In this structural format the binding to the Met receptor in bivalent form can only occur after a single LHL linker has been cleaved by a protease.

These constructs were successfully expressed and purified by protein A and size exclusion chromatography, as described above.

Second generation IgG^2 construct analyses

The performance of the above purified IgG^2 clones was examined in a series of further analyses. Example clones A-D5 IgG1, IgG^2 Her2CD47-LHL-LHL, IgG^2 Her47-LHLF-LHL, IgG^2 Her47-LHL-LHLF and IgG^2 Her47-LHLF-LHLF (Table 9) were firstly examined for binding to human Her2, and human and mouse CD47 (Fig 14). This analysis demonstrated that: 1) The A-D5 anti-CD47 IgG1 protein exhibited high binding signal for both hCD47 and mCD47. 2) All 4 IgG^2 proteins retained high binding signal for hHer2, but no/background binding signal for either hCD47 or mCD47 (Fig 14).

Clones IgG^2 Her2CD47-LHL-LHL and IgG^2 Her47-LHL-LHLF were examined for sensitivity to enzymatic activation (at pH7.4) by multiple proteases that are known to be over-expressed in human tumours (Fig. 15): Incubation with MMP7 (Fig. 15A), MMP8 (Fig. 15B), and MMP10 (Fig. 15C) demonstrated that both proteins could be activated for hCD47 binding by each enzyme, but IgG^2 Her47-LHL-LHLF was activated more rapidly in each case. Incubation with MMP12 demonstrated that both proteins could be activated for hCD47 binding at an equal rate for this enzyme (Fig. 15D). Unexpectedly, incubation with MMP13 demonstrated that IgG^2 Her47-LHL-LHLF could be activated for hCD47 binding by this enzyme, while IgG^2 Her2CD47-LHL-LHL could not (Fig. 15E). Importantly, incubation with the cysteine protease Cathepsin S also demonstrated that both proteins could be activated for hCD47 binding at an equal rate for this enzyme (Fig. 15F). These findings demonstrated that the peptide linker content of the Fab^2 modules contained in IgG^2 proteins

can be 'tuned' to broaden the number of potential activating enzymes and even to make the proteolytic activation process more rapid. To sample this potential, further linker designs in the appropriate length and content to drive sensitivity to specific classes of enzymes were envisioned, where amino acid sequences which show proteolytic sensitivity to the activity of other disease-associated metalloproteinases such as ADAMS, Cysteine, Aspartate and serine proteases, etc., would be used to provide either broader or more selective activation.

To examine the effect of activation on IgG^2 binding affinity, a Biacore assay was established which could sample both Her2 and CD47 binding. In this assay, control antibodies and IgG^2 Her47-LHL-LHLF protein (undigested or activated for 2, 4, 8 or 24 hours with MMP12) were captured on a chip surface via anti-Fc antibody and then binding affinity was measured for soluble Her2 and CD47 ectodomain proteins. Binding analyses were repeated for Trastuzumab IgG1 and A-D5 IgG1 (no enzyme digest) at the beginning and end of experimental runs, with the data being shown in Table 17. These analyses showed that the calculated KD values for each antibody were highly similar in each run. Importantly however, the Rmax values (maximum binding signal at maximal analyte concentration) dropped significantly between runs at the beginning and end of the experiments (e.g. Trastuzumab Rmax 265.80 RU at beginning, 144.13 RU at the end), suggesting that the activity of the anti-Fc antibody capture surface is reduced after the many rounds of regeneration that are inherent to the Biacore method. To examine the effects of MMP12 activation on target reactivity, Rmax and KD values for both Her2 (Fig. 16A, Table 18) and CD47 (Fig. 16B, Table 18) were calculated. This analysis showed that Her2 binding and affinity was maintained over 24 hours of MMP12 activation. Importantly, no CD47 binding (Rmax = 0) was observed in the 0 hour sample (no MMP12 digest), but both Rmax and apparent affinity for CD47 rose rapidly over the activation time course, beginning at 2 hours incubation (Fig. 16B, Table 18). These findings demonstrated that lower Fabs in a Fab^2 module are truly inert and incapable of target interaction in the intact molecule until protease activation occurs. This observation is further illustrated in Fig. 17, where even at 400nM concentration of CD47 analyte, no binding activity is observed, but high binding to CD47 is evident after 24h of MMP12 treatment.

The above findings also demonstrated that the cleavage of the linker peptides in the Fab^2 module (and therefore the activation of the lower Fab), is temporal. This may be a pharmacological benefit to molecules containing the Fab^2 module, as the activation is likely to be strongly biased towards diseased tissues in which both the target antigen of the upper Fab and enzymes capable of activating the lower fab are highly over-expressed.

This would lead to rapid drug accumulation, long residence time and high levels of activation in such diseased tissues.

***In silico* modelling of Fab^2 module structure and molecular dynamics**

To understand the mechanisms by which the Fab^2 module might function, we performed structural modelling and molecular dynamics analyses. The crystal structures of human CD47 ECD bound to Fab domains of IgG1 C47B161 (Protein Data Bank identifier 5TZT), IgG1 C47B222 (Protein Data Bank identifier 5TZ2) and IgG1 B6H12.2 (Protein Data Bank identifier 5TZU) were used as templates to generate a model of the anti-CD47 A-D5 Fab bound to CD47 ECD using the protein modelling suite of MOE software. The structure of trastuzumab Fab in complex with the Her2 extracellular domain was taken from the PDB structure 1N8Z.

The LHL and LHLF linkers between the upper trastuzumab Fab and the lower anti-CD47 Fab were then modelled using the protein modelling suite of MOE software. To assist modelling of the linkers, the C-termini of Fab structures available in Protein Data Bank were examined to help define the conformations with which the LB linkers could exit from each of the heavy and light chain domains of the Trastuzumab Fab. The modelling predicted that the trastuzumab Fab heavy and light chain C-termini can optionally possess the native inter-chain disulphide bond normally present in an IgG1 Fab domain.

A full-length IgG1-based model incorporating the aforementioned, modelled anti-CD47 Fab was constructed using the structure of IgG1 b12 (Protein Data Bank identifier 1HZH) as a template. Structural errors in 1HZH such as missing structural regions were remodelled and corrected. The IgG1 b12 Fab were replaced by the anti-CD47 Fab and the Fc-hinge were attached using the protein modelling suite of MOE software. This model illustrated the likely tertiary structure of an IgG^2 molecule based on Her2 and CD47 with IgG1 (Fig. 18A). In the model, the binding of the Her2 epitope is constitutively active (Fig. 18A), while the binding of the CD47 ECD is fully occluded by both the linker itself and the proximity of the anti-CD47 Fab to the anti-HER2 Fab (Fig. 18B). The model is consistent with a Fab^2 module that could bind HER2 via the upper fab with no observed hindrance, but that is prevented from binding CD47 via the lower fab until the linker is degraded (Fig. 16A, Fig. 16B).

To gain further insights into how the Fab^2 module moves in solution, we performed molecular dynamics simulations using multiple linker compositions, including LHL-LHL, LHL-LHLF and L2L2 (G4SG4S (SEQ ID NO:32) amino acid sequence, Table 1). An RMSD for each residue was calculated for each run. In addition a custom descriptor dSASA was

written in the SVL language (MOE) which calculated the change in solvent accessible surface area (SASA) of each residue, and also an aggregate of only the linker sequence in each case. As such it provided the basis to compare how different uncleaved linkers perform in terms of conformational changes and associated effects on solvent accessibility of the linkers which is expected to impact sequence-specific cleavage potential (Fig. 18).

Fig. 19A – Fig. 19I show 9 graphs, corresponding to the solvent accessible surface area (SASA) results obtained for the 3 linkers tested. The first analyses sampled the absolute SASA values (over 6 ns) for 9 dynamics runs for each of LHL and LHLF linkers and 10 runs using L2 (Fig. 19A, Fig. 19D and Fig. 19G, respectively). This data demonstrated that the L2 linker clearly had the greatest propensity to structural heterogeneity over time (Fig. 8G). Since the starting SASA value at was not the same for each run, secondary analyses normalized results representing the difference to the starting SASA value, calculated by subtracting all SASA values from the starting SASA value. Results over the 6 ns dynamics run time (Fig. 19B, Fig. 19E and Fig. 19H, respectively) and the first 2.5 ns of the 6 ns dynamics runs (Fig. 19C, Fig. 19F and Fig. 19I, respectively) illustrated that the LHL and LHLF linkers were clearly less structurally dynamic than the L2 linker. In particular, the 6 ns molecular dynamics runs show that the L2 exhibits highest flexibility, thus underscoring the concept that different linker sequences will give rise to different flexibilities and, therefore, CDR solvent exposure profiles for the lower Fab in the Fab^2 module.

Comparisons between cleaved and uncleaved linkers show dramatic increases in flexibility for the cleaved linkers compared to uncleaved linkers, consistent with biological observations in Figs 14-17. For example, Fig. 20A shows the limited movement in the Fab^2 module when both linkers are intact, followed by dramatic movement of the upper Fab domain in the context of a single cleaved LHL linker (second linker intact) during a 100 ns dynamics run. This analysis showed that the upper fab domain gains a significant increase in degrees of freedom, leading to multiple positions in which it can move fully out of the way of the lower fab domain, fully exposing its CDRs to allow unfettered interaction with e.g. CD47 (Fig. 20B).

***In vitro and in vivo* analyses of tolerability and pharmacokinetics**

To examine the tolerability and pharmacokinetics of IgG2 and Fab2 in the context of CD47 as the lower Fab domain, multiple example molecules (A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL) were studied in 6 - 8 week old male B6.Cg-*Fcgrt*^{tm1Dcr} Tg(FCGRT)32DcrJ mice. These 'Tg32' mice are human FcRn homozygous transgenic animals, with pharmacokinetics characteristics for human IgGs that mimic those of humans and primates. As the CD47 binding domains contained in A-D5

IgG1 and in the lower Fab domain of IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL are all known to be capable of binding to recombinant mouse CD47 protein, they were first tested for reactivity to mouse membrane-presented CD47 on erythrocytes, by flow cytometry (Fig. 21). This study showed that A-D5 IgG1 exhibited no signal on mouse erythrocytes at 0.1 µg/ml, but clear concentration-dependent binding signal at both 1 and 10 µg/ml (Fig. 21). Importantly, the binding to mouse erythrocytes was sub-saturating at 1 µg/ml (63% binding, Fig. 21) and fully saturating at 10 µg/ml (98% binding, Fig. 21). In contrast, none of the proteins IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF nor Fab^2 Met47 LHL-LHL exhibited any binding at any concentration, indicating that the anti-CD47 variable domains of the lower Fab domains are not capable of interacting with CD47 on mouse erythrocytes (Fig. 21).

Using isolated erythrocytes from the Tg32 mice, hemagglutination assays were also performed. This analysis demonstrated that only A-D5 IgG1 was capable of driving concentration-dependent agglutination of the mouse erythrocytes (at > 3.12 µg/ml), while none of the proteins IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF nor Fab^2 Met47 LHL-LHL exhibited agglutination at any concentration up to 200 µg/ml (Fig. 22). These findings illustrated that the *in vitro* examinations of human CD47 protein and erythrocyte binding outlined above (i.e. full binding to human CD47 by A-D5 IgG1, but no measurable binding for IgG^2 or Fab^2 proteins) are recapitulated in the mouse system, making mice a viable model to study the effects of CD47 binding on both pharmacokinetics and tolerability.

In an *in vivo* tolerability study, A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL were each dosed once (intravenously) at concentrations of 2 mg/kg or 10 mg/kg in Tg32 mice. The 2 mg/kg dose of A-D5 IgG was tolerated, while the 10mg/kg dose was poorly tolerated, causing overt toxicity on day 0 that caused the study in this dosing cohort to be terminated. In contrast, the 2 mg/kg and 10mg/kg doses of IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL were all well tolerated across 60 days of body weight observation (Fig. 23). While the 2 mg/kg dose of A-D5 IgG was tolerated overall, at 5 days after dosing, reticulocytes were observed to be significantly upregulated in this group (Fig. 24). In contrast, neither the 2 mg/kg nor 10mg/kg doses of IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF nor Fab^2 Met47 LHL-LHL were associated with reticulocyte upregulation at day 5 or later (Fig. 24, Fig. 25). Reticulocyte upregulation is a known response to rapid erythrocyte clearance, which suggested that IV dosing of the A-D5 IgG1 antibody led to accelerated clearance of CD47-high erythrocytes.

To sample the effects of the dosed proteins more broadly, full haematological panels were examined at days 5, 29 and 60 after dosing (Fig. 25A – Fig. 25K). These analyses

demonstrated that the reticulocyte upregulation effect for A-D5 IgG1 was transient, returning to baseline by day 29 (Fig. 25A). No significant effects were observed for A-D5 IgG1, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL on days 5, 29 or 60 on erythrocyte (RBC) count, haemoglobin, mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), leukocyte, monocyte, lymphocyte, basophil, eosinophil or neutrophil levels (Fig. 25B - Fig. 25K).

In an *in vivo* pharmacokinetics study, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL were each dosed once (intravenously) at concentrations of 2 or 10 mg/kg and A-D5 IgG1 was dosed at the previously-tolerated concentration of 2 mg/kg, in Tg32 mice. Blood samples were collected from each mouse according to the bleeding schedule: 30min, 4h, 1 day, 3, 5, 7, 10, 14, 21, 28 and 42 days. Analyses of serum antibody concentration demonstrated that A-D5 IgG1 at 2 mg/kg was very rapidly removed from circulation, reaching mean concentrations < 0.5 µg/ml within 5 days (Fig. 26). This rapid drug clearance (known as Tissue-Mediated Drug Disposition, or TMDD) was likely due to the previously-observed strong binding to the mouse erythrocytes, which are then rapidly cleared from the system by phagocytosis. This finding further explains the return of reticulocyte levels to normal by day 29 in A-D5 IgG1 dosing (Fig. 25A), as the molecule has been essentially eliminated by day 10 (Fig. 26).

In contrast, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL all exhibited slow clearance at both 2 and 10 mg/kg doses (Fig. 26). Importantly, the 2 mg/kg doses of each protein took > 25 days to achieve concentrations < 1.0 µg/ml (Fig. 27A) and the 10mg/kg doses of each protein maintained concentrations > 1.0 µg/ml at 42 days (Fig. 27B). Single samples taken from the mice dosed with 10mg/kg of A-D5 IgG1 during the tolerance study on day 0 were also analysed, showing that the maximal serum IgG concentrations achieved (but not tolerated) were similar to those achieved for the IgG^2 and Fab^2 proteins that were fully tolerated (> 50 µg/ml).

IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL at 2mg/kg all showed normal 'Alpha' phase (when IV doses of immunoglobulins quickly distribute from the bloodstream into tissue), followed by a long 'Beta' phase of antibody circulating in the serum (Fig. 26, 27A). These proteins also exhibited normal distribution profiles at 10mg/kg, but with even longer circulation (Fig. 26, 27B). Importantly, the Beta phases of each protein, at both concentrations, exhibited linearity and parallel curves, suggesting that the CD47 domains of these proteins did not lead to the TMDD observed for A-D5 IgG1 (Fig. 26). TMDD would have been expected to show up strongly if the IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF or Fab^2 Met47 LHL-LHL proteins were undergoing activation in the

periphery, as activation would lead to high affinity erythrocyte, endothelium and platelet binding, leading to clearance that would change the Beta phase into a sharp downward trajectory, as seen for the A-D5 IgG1 (Fig. 26). These observations, coupled with lack of reticulocyte amplification in the doses of IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL, suggests that peripheral activation levels are low. This is despite the long pharmacokinetics for these molecules meaning that they have been through FcRn recycling multiple times over the >25 day circulation.

The pharmacokinetic and tolerability findings outlined above for IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL are indicative of normal, FcRn-mediated, antibody-like, half-life extension via the human IgG1 Fc domain. This effect resulted in significant increases in Area Under the Curve (AUC) values for these 3 proteins in comparison to A-D5 IgG1 (Fig. 28). At 2mg/kg, AUC was improved 25-40 fold for IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL over A-D5 IgG1. At 10 mg/kg, which is not a safely-achievable dose for A-D5 IgG1, AUC was improved by approximately 100-250 fold for IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF and Fab^2 Met47 LHL-LHL over A-D5 IgG1 (Fig 28). These improvements in AUC are significant as they suggest the use of CD47 binding domains within the IgG^2 and Fab^2 structure may be used at high concentration from the first dose, maximising distribution towards tumour tissue.

Flow cytometry analyses of binding to monkey and human erythrocytes

Erythrocytes were isolated from 3 cyno NHP (monkeys) and 3 human donors and stained with A-D5 IgG1, Trastuzumab, IgG^2 Her47 LHL-LHLF or IgG^2 Her47 LHL-LHL. Both sets of analyses showed that only A-D5 IgG1 exhibited concentration-dependent binding to either cyno (Fig. 29A), or human (Fig. 29B) erythrocytes. These findings confirmed the above observations that the CD47 binding domains within the IgG^2 (and, therefore, Fab^2) structure are restricted from binding mouse, monkey and human CD47.

Activation by MMPs and Cathepsins at pH6.0 and 7.4

MMPs and Cathepsins have been shown to have the potential to enzymatically cleave the peptide sequences found in either the LHL or LHLF linkers outlined above. Importantly, however, both of these classes of enzyme can exhibit sensitivity to changes in pH conditions that raise or lowering their enzymatic activity. This can be of critical importance as the pH of solid tumours is frequently observed to deviate away from the normal physiological pH in man, pH7.4. In particular, solid tumours (and highly inflamed tissues) may develop acidic pH conditions as low as pH6.0.

Having proven above that multiple MMP enzymes have the ability to activate lower fab binding at pH7.4, we examined the activity of multiple MMP and Cathepsin enzymes (that are all associated with elevated activity in solid tumours) at both pH 6.0 and 7.4. Activation of IgG^2 Her47 LHL-LHL or IgG^2 Her47 LHL-LHLF were examined for MMP3 (Fig. 30A, B), MMP7 (Fig. 30C, D), MMP8 (Fig. 30E, F), MMP10 (Fig. 30G, H), MMP12 (Fig. 30I, J), MMP13 (Fig. 30K, L) and MMP14 (Fig. 30M, N). MMP-treated samples for IgG^2 Her47 LHL-LHL and IgG^2 Her47 LHL-LHLF were then applied in direct binding to both human Her2 and human CD47. These analyses demonstrated that both proteins exhibited measurable activation of CD47 binding by MMPs 8, 10 and 12 at both pH7.4 and pH6.0. In contrast, only IgG^2 Her47 LHL-LHLF was activated by MMP13 at both pH7.4 and pH6.0 (Fig. 30K, L), and MMP7 at pH6.0 (Fig. 30D). IgG^2 Her47 LHL-LHLF also exhibited a relatively higher level of activation, at the majority of time points, than IgG^2 Her47 LHL-LHL by the majority of MMPs tested (Fig. 30A-N). These findings confirmed that the inclusion of the LHLF linker leads to more rapid activation of binding by the lower Fab, by a broader range of MMP enzymes, at both pH6.0 and/or pH7.4.

Cathepsins were also examined as potential activation enzymes. For these enzymes, a clear relationship between pH and activity was observed. Activation of IgG^2 Her47 LHL-LHL (Fig. 31A) or IgG^2 Her47 LHL-LHLF (Fig. 31B) both demonstrated that only Cathepsin S was capable of activating CD47 binding at both pH7.4 and 6.0. In contrast, treatment with Cathepsins A, C, G, K and L showed little or no activation of CD47 binding at pH7.4 even after 24 hours, but strong activation signals were rapidly generated at pH6.0 (Fig. 31A, 31B). These findings suggested that the LHL and LHLF linkers could allow accelerated activation in acidified tissues in comparison to those at pH7.4, via more rapid activation by MMPs and by pH-selective activation by a series of Cathepsins. This may further improve the therapeutic index of IgG^2 and Fab^2 proteins by minimising the activation of lower Fab binding at pH7.4 (pH of non-diseased tissue, where active extracellular MMP and Cathepsin levels are low) and maximising it at pH6.0 (pH of diseased tissue, where MMP and Cathepsin levels are high and Cathepsin activity is potentiated).

Activation of lower Fab binding to Her2/CD47+ cells

Flow cytometry was performed to examine the binding characteristics of IgG^2 Her47 LHL-LHL and IgG^2 Her47 LHL-LHLF to cells expressing different levels of CD47 and Her2 on their cell surface. Staining with Trastuzumab, anti-CD47 and Isotype control IgGs demonstrated that BT474 cells expressed high levels of Her2 and lower levels of CD47 (Fig. 32A, B), whereas MCF7 cells expressed higher levels of CD47 and low levels of Her2 (Fig. 32C, D). Staining both cell types with IgG^2 Her47 LHL-LHLF (Fig. 32A, C) and IgG^2 Her47 LHL-LHL (Fig. 32B, D) after activation with MMP12 for 0, 2, 8 and 24h, was also

performed. Both IgG^2 Her47 LHL-LHLF and IgG^2 Her47 LHL-LHL exhibited binding profiles similar to Trastuzumab on BT474 cells at 0, 2 and 8h time points, but slightly reduced binding after 24h (Fig. 32A, B). In contrast, IgG^2 Her47 LHL-LHLF and IgG^2 Her47 LHL-LHL both exhibited low level binding profiles similar to Trastuzumab on MCF7 cells at 0h of activation, but significantly higher binding at 2, 8 and 24h activation time points, mimicking the anti-CD47 control (Fig. 32C, D). These findings experimentally confirmed that the activation model proposed in Fig. 2B is valid, with Trastuzumab-like binding of Her2 being maintained after activation and CD47 binding profile only becoming highly active after activation. Importantly, these findings also suggested that IgG^2 (and Fab^2) proteins may have the beneficial ability to drive the function of the lower fab binding domains (e.g. CD47) to cells expressing low levels of the upper Fab target (e.g. Her2).

Analysis of MMP12 activation by SDS-PAGE and Mass Spectrometry

IgG^2 Her47 LHL-LHLF and IgG^2 Her47 LHL-LHL proteins were treated with MMP12 as above, over 0, 2, 8 and 24 h. These protein samples were then analysed by SDS-PAGE (Fig. 33). This analysis generated findings that correlate clearly with observations of activation ELISAs (Figs. 15-7, 30) and flow cytometry (Fig. 32): At 0h – two intact chains were observed with the heavy chain running at 75 kDa and light chain running just below the 50 kDa marker (sub-50 kDa). At the 2 h time point, for both IgG^2 Her47 LHL-LHLF and IgG^2 Her47 LHL-LHL, a new ~25 kDa product was observed, plus faint bands that are slightly larger than 25 kDa and at ~50kDa (above the intact light chain). The molecular weights of these new fragments correspond to upper Fab Fd or light chain fragments (1 v domain + 1 c domain = ~25 kDa), Fc (2 x c domains + 1 n-link glycosylation = 28-30 kDa), and intact Fd-hinge-Fc (standard IgG1 heavy chain = 50 kDa), respectively. At 8 and 24h time points, a progressive reduction in intact chains and increase in fragments that were approximately 25 kDa smaller than the intact chains, was observed. In particular, at 8h the 25 kDa (upper fab chain) product became predominant, with a significant (but reduced compared to the 0h sample) amount of both the intact heavy chain (75 kDa) and intact light chain (sub-50 kDa) remaining. This SDS-PAGE analysis (Fig. 33) therefore demonstrated that both linkers between the upper and lower Fabs are actively cleaved by the MMP12 enzyme, whether of the LHL or LHLF sequence.

To examine precisely where in the Fab^2 structure the MMP12 enzyme was activating the IgG^2 molecules, mass spectrometry was carried out using 0, 2, 8 and 24h samples from IgG^2 Her47 LHL-LHL. Peptide samples were prepared by reduction, alkylation and proteolytic digestion using a combination of trypsin and Glu-C. These samples were analysed by LC-MS/MS. Efficiency of cleavage by MMP was determined by comparing the MS responses of peptide derived from the intact MMP-cleavage site (SCGPAPE (SEQ ID

NO: 110)) to those from cleaved protein (SCGPAP (SEQ ID NO: 111)). This analysis successfully identified peptides that mapped to both the uncleaved (SCGPAPE (SEQ ID NO: 110)) and cleaved (SCGPAP (SEQ ID NO: 111)) linkers, proving that in the LHL linker, MMP12 cleaves between the second proline (P) and the glutamic acid (E). Relative signal for the uncleaved (SCGPAPE (SEQ ID NO: 110)) peptide progressively reduced from 0 to 8 to 24h (Fig. 34A), whereas signal for the cleaved (SCGPAP (SEQ ID NO: 111)) peptide progressively increased (Fig. 34B).

Generation and Analysis of IgG^2 in hinge-stabilized 'IgG1-DAA' form

US Patent No. 8871204B2 teaches protease-resistant IgG1 antibody variants which maintained lower hinge and Fc stability in the presence of MMP enzymes. In these mutated IgG1 antibodies, the sequence of E233-L234-L235-G236 (SEQ ID NO: 112) in the hinge is replaced with P233-V234-A235 (with G236 deleted); and the CH2 domain comprises at least one substitution selected from S239D/1332E, K326A/E333A, H268F/S324T/1332E, F243L/R292P/Y300L, S239D/H268F/S324T/1332E, S267E/H268F/S324T/1332E, K326A/1332E/E333A, S239D/K326A/E333A, S267E/I332E and G237X/S239D/1332E where X is A, D, P, Q or S; wherein amino acid residues are numbered according to EU numbering.

To examine the use of the Fab^2 structure in the context of such a protease-stabilised IgG1 Fc, two example constructs were generated (Table 19). These two constructs (Her47 LHLF-LHL IgG1-2hDAA and Her47 LHL-LHLF IgG1-2hDAA) placed the Her47 Fab^2 structure in an IgG^2 built on the '2hDAA' structure (IgG1 containing P233-V234-A235-ΔG236 and S239D/K326A/E333A mutations). Both constructs were readily expressed in transient CHO cell transfections, with Protein A purified protein exhibiting > 80% product of expected molecular weight. Example analytical SEC data for Her47 LHLF-LHL IgG1-2hDAA shows 80% product at 10.30 ml (Fig. 35). SDS-PAGE analysis of unreduced Protein A purified protein and SEC peaks 8.47, 9.03 and 10.30 ml (Fig. 36) demonstrated that peaks 8.47 and 9.03 contained higher molecular weight aggregates, while peak 10.30 contained product of the expected size (approx. 250 kDa). SDS-PAGE analysis of reduced Protein A purified protein and SEC peaks 8.47, 9.03 and 10.30 ml (Fig. 37) demonstrated that all peaks 8.47, 9.03 and 10.30 ml contained heavy and light chain products of the expected size (approx. 80 and 50 kDa, respectively). Intact monomer (250 kDa) product for Her47 LHL-LHLF IgG1-2hDAA was purified by SEC and submitted to enzymatic digestion at pH7.4 using human MMP12, over a time course of 2, 4, 8 and 24 hours incubation, plus a 24h incubation in buffer without enzyme as a negative control (time 0, 2, 4, 8, 24h incubation). In ELISA analysis, all samples exhibited strong binding signal to human Her2, but no measurable binding to control protein murine EpCAM (Fig. 38A). In CD47 binding

ELISA, binding signals were increased after 2, 4, 8 and 24h incubations at 37 °C in the presence or absence of MMP12 enzyme, but no signal above background was observed at 0, 2, 4, 8, or 24 hours without MMP12 (Fig. 38B).

Analysis of 0hr (undigested), and 2, 8 and 24h MMP12-digested samples By SDS-PAGE confirmed that the purified protein contained the expected-size heavy and light chains. Over 2, 8 and 24hr MMP12 digest, a 25kDa band was generated (Fig. 38C), indicating linker peptide cleavage, but demonstrably less breakdown in heavy chain was observed in comparison with IgG^2 Her47 LHL-LHL or IgG^2 Her47 LHL-LHLF (Fig. 33), indicating that the '2hDAA' mutations do indeed stabilise the Fc region to resist MMP12 digest.

Generation and Analysis of IgG^2 with alternative enzyme activation

As the LHL and LHLF linkers were shown above to be susceptible to cleavage by multiple MMP and Cathepsin enzymes, six Fab^2 construct types were examined in IgG^2 format (Table 20). These constructs used a series of linker designs (Table 21) that were designed to be susceptible to cleavage by enzymes of several classes that are associated with upregulated activity in solid tumours and highly inflamed tissues, such as: enterokinase (EK), thrombin (Thr), tPA, Granzyme B (GrB), uPA and ADAMTs-5 (A5). All 6 constructs were readily expressed by CHO cells and purified by ProA chromatography.

Purified protein from clones Her47 LHL-LHL-EK, Her47-LHL-LHL-Thr, Her47-LHL-LHL-tPA, Her47-LHL-LHL-uPA, Her47-LHL-LHL-GrB and Her47-LHL-LHL-A5 were all tested in titration ELISA against human Her2 and CD47 targets (Fig. 39A, 39C, 39E, 39G, 39I, 39K). In all cases, these proteins exhibited low/background binding on CD47 at all concentrations tested (white bars), but concentration-dependent binding to Her2 (grey bars). Each protein was then also submitted to a time course enzymatic digest with MMP12, and ELISA binding to Her2 and CD47 targets (Fig. 39B, 39D, 39F, 39H, 39J, 39L). These findings showed that all proteins retained Her2 binding and exhibited increased activation of CD47 binding, across the time course of enzymatic activation. The functional activities of clones Her47 LHL-LHL-EK, Her47-LHL-LHL-Thr, Her47-LHL-LHL-tPA, Her47-LHL-LHL-uPA, Her47-LHL-LHL-GrB and Her47-LHL-LHL-A5 demonstrated that the Fab2 structure is capable of utilising linker peptide sequences with a wide variety of protease-recognition sites to tailor activation to a given application. For example, in this case, the retention of MMP activation potential in the LHL linker, combined with any of 6 different disease-associated enzyme cleavage motifs in the accompanying linker, would allow tailoring to environments in which MMP and/or Cathepsin enzymes are active, with added activation potential when Enterokinase, thrombin, tPA, Granzyme B, uPA, ADAMTs-5 or other protease enzymes are associated with disease status.

***In vivo* multi-dose tolerability of Her47 molecules in NOD-SCID mice**

In an *in vivo* multi-dose tolerability study, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF, Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF were each dosed four times (intravenously) in NOD-SCID mice. IgG^2 proteins were dosed at 14 mg/kg on day 0 and 7mg/kg on days 5, 10 and 15. Fab^2 proteins were dosed at 8 mg/kg on day 0 and 4mg/kg on days 5, 10 and 15. All proteins were fully tolerated, with no clinical signs of toxicity for any individual animals and no loss of bodyweight (Fig. 40). These findings corroborated and expanded upon the tolerability findings for Her47 Fab^2-based molecules in single doses in Tg32 mice, outlined above. In the Tg32 mouse study even a single dose of the A-D5 CD47 IgG was not tolerated at 10 mg/kg. In this NOD-SCID mouse study, all four doses of IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF, Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF were fully tolerated. This findings confirmed that the CD47 binding domains of the Her47 molecules were not being activated in the circulation, even after repeated dosing, as significant activation would have induced the CD47-driven toxicity signals observed for A-D5 IgG1.

Generation and analysis of additional 2-chain Her2CD3 Fab^2 'One Arm' constructs

Further Her2CD3 constructs were generated to examine novel sequences for their ability to improve product uniformity and activity (Table 22). All Her2CD3 constructs were expressed by CHO cells, purified from supernatant by ProA and then analysed by SEC. These analyses showed that Fab^2 Her23 LHL-LHL-S and Fab^2 Her23 LHLF-LHL-S both exhibited greater uniformity of the main product (Fig. 41 A, Fig. 41B) than did Fab^2 Her23 LHL-LHL and Fab^2 Her23 LHL-LHLF, which both exhibited a greater proportion of higher and lower molecular weight products (Fig. 41C, Fig. 41D). These findings suggested that improved uniformity had been created by swapping the orientation upper fabs in constructs Fab^2 Her23 LHL-LHL-S and Fab^2 Her23 LHLF-LHL-S so that the chains are [VL-CL-Linker-VH-CH-Fc] plus [VH-CH-Linker-VL-CL-Fc]. This is in contrast to Fab^2 Her23 LHL-LHL and Fab^2 Her23 LHL-LHLF, where the two chains are both [VL-CL-Linker-VL-CL-Fc] plus [VH-CH-Linker-VH-CH-Fc].

Control proteins Fab^2 mEpCam3 LHLF-LHL-S and Fab^2 mEpCam3 LHL-LHL-S (upper Fab contains the v domains of the anti-murine EpCAM antibody G8.8) were then also designed and expressed (Table 22). The correct MW products for clones Fab^2 Her23 LHL-LHL-S, Fab^2 Her23 LHLF-LHL-S, Fab^2 mEpCam3 LHLF-LHL-S and Fab^2 mEpCam3 LHL-LHL-S were isolated by preparative SEC and analysed in a Promega Jurkat cell-based CD3 ligation reporter cell bioassay, using either MCF-7 or BT-474 as human Her2+ target cells (according to manufacturer's instructions). Primary analyses using MCF-7 as (very low

Her2-expressing) target cells demonstrated that positive control Her2-CD3 BITE protein and OKT3 IgG1 both generated strong positive, concentration-dependent, CD3 activation signal. Clones Fab^2 mEpCam3 LHLF-LHL-S and Fab^2 mEpCam3 LHL-LHL-S, treated with MMP12 for 2h, generated no signal at any concentration (Fig. 42 A, B). In contrast, clones Fab^2 Her23 LHLF-LHL-S (Fig. 42A) and Fab^2 Her23 LHL-LHL-S (Fig. 42B) both showed no measurable signal at 0h, but gradually increasing signal at 2, 8 and 24h, in similar concentration ranges to the Her2-CD3 BITE, but with maximal signal in both cases being higher than that achieved for the positive controls.

In a secondary assay using Her2 high-expressing BT-474 cells as target cells, all of the above test samples and controls were assayed at 0.1 µg/ml (Figure 43A-C). Positive control proteins Her2-CD3 BITE and OKT3 IgG1 both induced strong CD3 activation signaling, while negative controls Fab^2 mEpCam3 LHLF-LHL-S and Trastuzumab did not. Clones Fab^2 Her23 LHLF-LHL-S (Fig. 43B) and Fab^2 Her23 LHL-LHL-S (Fig. 43C) both showed no measurable signal at 0h, but gradually increasing signal at 2 hours and maximal at 8. Importantly, at 24h signal significantly decreased in comparison to 8h. This finding suggests that progressive enzyme activity, which may cleave both linkers (Fig. 33) may lead to eventual separation of the upper and lower Fabs. This may be a beneficial characteristic for a CD3-targeting molecule, as it would be ideal for a such a molecule to be preferentially activated in the highly proteolytic tumour environment, but also to be gradually deactivated there, minimising the risk of the molecule leaking out into healthy tissue, in an active form.

In vitro measurements of molecular stability of Her2-CD47 IgG^2 and Fab^2 proteins

Historically, engineered antibody formats have often suffered from structural heterogeneity, leading to manufacturing issues. To examine the stability of the IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL proteins, a series of in vitro measurements were made:

Forced Oxidation - Oxidation of exposed amino acid residues, such as tryptophan and methionine, is a common degradation pathway for mAbs, with impact on their biological activity. In this study, forced oxidation with 0.5 % H2O2 in PBS for 2 hours at room temperature was applied to the IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL proteins. As oxidation can alter overall hydrophobicity of an antibody, either by increasing the polarity of the oxidised form or through conformational changes, potential changes induced by forced oxidation were analysed by Reverse Phase (RP) and Size Exclusion (SEC) chromatographies. SEC analysis revealed no changes in the proportion of monomeric species, in either test sample (IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL both exhibited 99.5 and 97.4 % monomeric species, respectively, before and after oxidation). In

RP analysis of intact antibodies, a decrease of 0.5 min in the retention time of IgG^2 Her47 LHL-LHL and 0.4 min in the retention time of Fab^2 Her47 LHL-LHL was observed for the intact (non-reduced) antibodies after forced oxidation with 0.5 % H2O2. In RP analysis of subunits, a decrease of 0.5 min in the retention time of the heavy chain and no shift in the retention time of the light chain was observed for IgG^2 Her47 LHL-LHL after forced oxidation. The reduced Fab^2 Her47 LHL-LHL showed a different profile on RP analysis, with 3 peaks observed, representing light chain, heavy chain and truncated hinge-Fc stump. Upon oxidation 0.4-0.5 min shifts were observed for the heavy chain and truncated hinge-Fc stump, but not the light chain. The shifts in the retention time, after H2O2 treatment, observed for both reduced IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL samples, suggest minor oxidation of the exposed amino acids (limited to the Fc regions of the proteins).

Charge variant analysis - Charge heterogeneity analysis is important in the characterisation of monoclonal antibodies because it provides important information about product quality and stability. Heterogeneity can be caused by enzymatic post-translational modifications (glycosylation, lysine truncation) or chemical modifications during purification and storage (oxidation or deamidation). Charge variant profiling for the provided test articles was performed by a commercial Charge Variant Assay. The charge variant profiles of the IgG^2 Her47 LHL-LHL (Fig. 44A) and Fab^2 Her47 LHL-LHL (Fig 44B) both displayed a homogeneous profile, with one main isoform (50-57 % of total), a major acidic isoform (40-48 % of total) and one minor basic isoform (approx. 3%).

Retention on HIC - Overall hydrophobicity is an indicator of a protein's tendency to self-associate, which can be a significant risk factor for aggregation and viscosity during bioprocessing. Proteins have hydrophobic 'patches' on their surface, generated by the presence of the side chains of hydrophobic or non-polar amino-acids. Depending on their number, size and distribution, the resulting surface hydrophobicity will be a specific characteristic for each protein. HIC separates proteins based on differences in their surface hydrophobicity, utilising reversible binding between the protein and the hydrophobic surface of the HIC resin. IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL exhibited HIC column retention times of 5.4 and 5.0 mins, respectively. These values are towards the lower range of hydrophobicity in comparison to those obtained for clinical monoclonal antibodies, such as Adalimumab (4.5 mins), Cetuximab (5.9 minutes), Brentuximab (6.3 mins) and Golimumab (8.1 mins). Indeed, these values suggest an aggregation propensity and stability similar to that of anti-Her2 Trastuzumab (5.4 mins retention), from which the Her2 binding domains in both IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL are derived.

Freeze-thaw stability analyses – Instability of proteins during freeze-thaw steps is an indicator of difficulty in manufacturing and bioprocessing, as increased aggregation or fragmentation of the protein is a risk for reduction in product quality. To assess this risk for proteins containing Fab^2 structures, IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL proteins were subjected to 5 rounds of Freeze-thaw , followed by SEC analyses after each round. These analyses showed that neither IgG^2 Her47 LHL-LH L (Fig. 45A), nor Fab^2 Her47 LHL-LH L (Fig. 45B) proteins exhibited any change in monodispersity (no aggregation or breakdown products observed) over the 5 rounds of freezing.

Collectively, these findings suggested that both IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL proteins had low aggregation risk, low hydrophobicity, low charge heterogeneity and low propensity towards oxidation.

BIACORE® analyses of affinity of IgG variants for human Fc receptors

Antibodies targeting receptors on diseased cells must bind to Fcγ receptors if they are to mediate ADCC and ADCP activities. To examine whether these binding functions were retained in Fab2-based constructs, IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL proteins were examined for binding affinity to all human and mouse Fc receptors via surface plasmon resonance analyses. These analyses demonstrated that both the isotype control human IgG1 and IgG4 exhibited the expected strong and weak binding affinities (respectively) for all human Fcγ receptors, including both the high and low affinity variants of FcγRIIA and FcγRIIIA (Table 23). Similarly, isotype control mouse IgG2a and IgG1 exhibited the expected strong and weak binding affinities (respectively) for mouse FcγRI, FcγRIII and FcγRIV receptors. For IgG^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHL, the binding to each of the human and mouse Fc receptors tested is highly similar to that observed for the isotype control human IgG1. These data suggest that both IgG^2 and Fab^2 proteins that are built on an IgG1 Fc should be capable of binding to Fc receptors, when bound at the surface of diseased cells, in both humans and mice.

Further protein construct designs

Further protein constructs are envisioned (Fig. 46). The constructs may contain: 1. Only constant domains in the 'upper fab' position, meaning that the activity of the 'lower Fab' is prevented from binding its target, but may become active in an appropriate proteolytic environment. 2. Dummy 'non-binding' variable domains in the 'upper fab'. These dummy variable domains would be proven not to bind any known target in the body, so only the 'lower fab' exhibits potential drug target-binding ability, and only after activation by proteolysis of one of the linker domains. 3. The 'upper Fab' is replaced by a 'diabody' structure containing 4 variable domains. This diabody structure may or may not contain

disulphide linkage, as found in 'DART' proteins. Diabody structures may facilitate the binding of 2 copies of the same target, or two separate targets, with the activity of the 'lower Fab' being prevented from binding its target, until rendered active in an appropriate proteolytic environment. In any of the constructs envisaged here, or demonstrated above, the Fab^2 structures may be free, or fused to another functionalising structure, such as an Fc fragment, a small domain or peptide that extends half-life such as an albumin binding moiety. They may also be chemically conjugated to small molecules, peptides or other proteins that mediate further biological functions.

Cell proliferation analyses for Her2CD47 proteins using Her2-high BT-474 cells

As the Her2 binding domains of the upper Fab of IgG^2 Her47 and Fab^2 Her47 proteins are capable of mediating inhibition of the kinase activity of this receptor, a cell proliferation analysis was performed. This assay used BT-474 cells as they are a cell line with a known sensitive response to Her2 inhibition. Trastuzumab, Isotype control IgG1, IgG^2 Her47 LHL-LHL (Fig. 47A) and Fab^2 Her47 LHL-LHL (Fig 47B), were applied to the BT-474 cells over a 72h incubation period and cell proliferation measured. Data was represented as percent inhibition of cell growth (Fig. 47). These analyses showed that while Trastuzumab demonstrated strong, concentration-dependent inhibition of BT-474 cell proliferation, IgG^2 Her47 LHL-LHL (Fig. 47A) demonstrated slightly lower potency and Fab^2 Her47 LHL-LHL (Fig. 47B) was lower again in potency (reflecting its monovalent binding capacity).

***In vivo* efficacy analyses of Her47 molecules in tumour xenograft-bearing NOD-SCID mice (KYSE-410 model)**

In *in vivo* multi-dose efficacy studies, Trastuzumab, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF, Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF (Fab^2 structures containing a human IgG1 Fc, as in Fig. 3B) were each dosed four times (intravenously, on days 0, 5, 10, 15) in NOD-SCID mice bearing tumours generated by sub-cutaneous inoculation with the Her2-expressing oesophageal cancer cell line KYSE-410. Dosing began once tumours were established at >125 mm^2. IgG^2 proteins were dosed at 14 mg/kg on day 0 and 7mg/kg on days 5, 10 and 15. Fab^2 proteins were dosed at 8 mg/kg on day 0 and 4mg/kg on days 5, 10 and 15. Trastuzumab was dosed at 8 mg/kg on day 0 and 4mg/kg on days 5, 10 and 15. Tumour volumes were measured by caliper measurements.

After 3 doses, on day 11, Trastuzumab (Fig. 48A), IgG^2 Her47 LHL-LHLF (Fig. 48B), IgG^2 Her47 LHL-LHL (Fig. 48C) and Fab^2 Her47 LHL-LHLF (Fig. 48D) all demonstrated significantly reduced tumour growth in comparison to vehicle (2-way ANOVA: $p = 0.005$, 0.005, 0.019 and 0.003, respectively). In contrast, Fab^2 Her47 LHL-LHL (Fig. 48E) did not significantly reduce tumour growth by day 11 (2-way ANOVA: $p = 0.66$). Importantly, the

sequences of Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF are identical (apart from the two point mutations in the LHLF linker that accelerate and broaden protease sensitivity versus the LHL linker, as shown above), but lead to significant differences in potency (Fig. 48F). In addition, the data in Fig. 47 demonstrates that the 1-arm Fab^2 structure leads to weaker Her2-driven inhibition of cell proliferation than observed for Trastuzumab, which contains identical Her2-binding VH and VL domain sequences to those found in both Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF. As a result, it follows that: 1. The approximately equivalent potency at day 11 observed for both Trastuzumab (Fig. 48A) and Fab^2 Her47 LHL-LHLF (Fig. 48D) cannot be driven by high Her2 kinase activity in Fab^2 Her47 LHL-LHLF. 2. The high potency of Fab^2 Her47 LHL-LHLF is therefore most likely driven by protease activation in the KYSE-410 tumour microenvironment, leading to CD47 blockade and innate immune engagement.

In aggregate, the findings outlined above therefore demonstrate that the Fab^2 structure allows efficient ablation of 'lower Fab' activities, with both CD47 and CD3 binding domains acting as examples. Binding capacity of the 'upper fab' domains is fully maintained, but significant activity in the lower fab domains is only observed after activation by proteases such as MMPs and Cathepsins, that are associated with high activity in diseased tissues such as tumours and fibrotic tissues. The modulation of linker sequences in the Fab^2 structure allows the tuning of lower fab activation to be maximised in the disease microenvironment and to avoid both peripheral sink problems and toxicities, as exemplified by the performance of the Her47 molecules, in vitro and in vivo.

***In vivo* pharmacokinetics of Her47 molecules in NOD-SCID mice**

In an *in vivo* multi-dose PK study, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF, Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF would each be dosed once (intravenously) in NOD-SCID mice. IgG^2 proteins would be dosed at 14 mg/kg and Fab^2 proteins would be dosed at 8 mg/kg. Blood samples would be taken at 15 mins, 30 mins, 1h, 3h, 6h and 24h and serum antibody levels measured using an anti-human IgG1 ELISA.

***In vivo* efficacy analyses of Her47 molecules in tumour xenograft-bearing NOD-SCID mice (SKOV-3, JIMT-1 and NUGC-4 models)**

In *in vivo* multi-dose efficacy studies, IgG^2 Her47 LHL-LHL, IgG^2 Her47 LHL-LHLF, Fab^2 Her47 LHL-LHL and Fab^2 Her47 LHL-LHLF would be each dosed four times (intravenously) in NOD-SCID mice bearing tumours generated by sub-cutaneous inoculation with the cell lines SKOV-3, JIMT-1 and NUGC-4. IgG^2 proteins would be dosed at 14 mg/kg on day 0 and 7mg/kg on days 5, 10 and 15. Fab^2 proteins would be dosed at 8 mg/kg on day 0 and 4mg/kg on days 5, 10 and 15. Trastuzumab would be dosed at 8

mg/kg on day 0 and 4mg/kg on days 5, 10 and 15. Tumour volumes would be measured by caliper measurements.

***In vivo* analyses of tolerability and pharmacokinetics in cynomolgus monkey**

To examine the tolerability and pharmacokinetics of IgG^2 and/or Fab^2 in the context of CD47 or CD3 as the lower Fab domain, multiple example molecules would be studied in cynomolgus monkeys. For example, IgG^2 and/or Fab^2 might each be dosed once, twice or three times (intravenously) at concentrations of 2 mg/kg or above. Blood samples would be collected from each animal according to a bleeding schedule. Analyses of serum antibody concentration would be measured to calculate PK and to assess the risk of TMDD). To sample the effects of the dosed proteins more broadly, full haematological panels would also be examined at a series of days after dosing. These analyses would measure reticulocyte, erythrocyte (RBC), haemoglobin, mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), leukocyte, monocyte, lymphocyte, basophil, eosinophil and/or neutrophil levels.

Biosensor measurements of target co-engagement

To examine the effect of activation on Fab^2 binding affinity to both Her2 and CD47 (or CD3), a biosensor assay would be established which could sample both Her2 and CD47 (or CD3) binding on the same chip surface, such as a Dynamic Biosensors instrument. In this assay, control antibodies and IgG^2 or Fab^2 proteins (undigested or activated for e.g. 2, 4, 8 or 24 hours with an MMP or Cathepsin enzyme) would be applied to a sensor chip surface that had been differentially labelled with purified Her2 and CD47 (or CD3) ectodomain proteins separately, or together at different densities. Affinity for Her2 and CD47 (or CD3) would be measured to ascertain the influence of multivalent interaction on functional affinity for both targets separately, and on the same surface.

Although the present invention has been described with reference to preferred or exemplary embodiments, those skilled in the art will recognize that various modifications and variations to the same can be accomplished without departing from the spirit and scope of the present invention and that such modifications are clearly contemplated herein. No limitation with respect to the specific embodiments disclosed herein and set forth in the appended claims is intended nor should any be inferred.

No limitation with respect to the specific embodiments disclosed herein and set forth in the appended claims is intended nor should any be inferred. All documents, or portions of documents, cited herein, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for

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NUMBERED EMBODIMENTS

Notwithstanding the appended claims, the disclosure sets forth the following numbered embodiments:

1. A protein comprising a first moiety and a second moiety and a peptide linker between the first moiety and the second moiety,

wherein the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having from 1 to about 7 amino acid substitutions compared to a human immunoglobulin hinge region;

wherein the peptide linker is cleavable by a protease expressed in a diseased tissue;

wherein the second moiety is capable of specifically binding to a molecule expressed in the diseased tissue; and

wherein the binding of the second moiety to the molecule expressed in the diseased tissue is reduced or inhibited when the peptide linker is uncleaved.

2. The protein of embodiment 1, wherein the peptide linker is between about 5 and about 15 amino acids in length.

3. The protein of embodiment 1 or 2, wherein the peptide linker comprises or consists of the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, or SEQ ID NO:87.

4. The protein of any one of embodiments 1-3, wherein the protease is a human matrix metalloprotease (MMP), a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5.

5. The protein of any one of embodiments 1-4, wherein the peptide linker comprises a human MMP cleavage site, a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5 cleavage site.

6. The protein of any one of embodiments 1-5, wherein the human MMP is MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13 or MMP14.

7. The protein of any one of embodiments 1-6, wherein the level or the activity of the human MMP is elevated in the diseased tissue compared to the level or the activity of the human MMP in a non-diseased tissue.

8. The protein of any one of embodiments 1-5, wherein the human cathepsin is Cathepsin A, Cathepsin C, Cathepsin D, Cathepsin G, Cathepsin L or Cathepsin K.

9. The protein of any one of embodiments 1-5 and 8, wherein the level or the activity of the human cathepsin is elevated in the diseased tissue compared to the level or the activity of the human cathepsin in a non-diseased tissue.

10. The protein of any one of embodiments 1-9, wherein the first moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain.

11. The protein of embodiment 10, wherein the first moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), a diabody, or a T cell receptor domain.

12. The protein of any one of embodiments 1-11, wherein the first moiety specifically binds to a molecule expressed in a diseased tissue.

13. The protein of any one of embodiments 1-12, wherein the first moiety specifically binds to a first molecule expressed in a diseased tissue and the second moiety is capable of specifically binding to a second molecule expressed in a diseased tissue, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are different molecules.

14. The protein of embodiment 13, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by the same cell.

15. The protein of embodiment 13, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by different cells.

16. The protein of embodiment 13, wherein the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is expressed on the surface of a cell.

17. The protein of embodiment 13, wherein the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is a soluble molecule.

18. The protein of any one of embodiments 1-17, wherein the first moiety binds specifically to human EGFR, human HER2, human HER3, human CD105, human C-KIT, human PD1, human PD-L1, human PSMA, human EpCAM, human Trop2, human EphA2, human CD20, human BCMA, human GITR, human OX40, human CSF1R, human Lag3 or human cMET.

19. The protein of any one of embodiments 1-17, wherein the second moiety specifically binds to a molecule expressed by a human immune cell.

20. The protein of embodiment 19, wherein the molecule expressed by a human immune cell is human CD3, human CD16A, human CD16B, human CD28, human CD89, human CTLA4, human NKG2D, human SIRPα, human SIRPγ, human PD1, human Lag3, human 4-1BB, human OX40, or human GITR.

21. The protein of any one of embodiments 1-20, wherein the first moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region.

22. The protein of any one of embodiments 1-21, wherein the first moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region.

23. The protein of embodiment 22, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA, or IgY.

24. The protein of embodiment 22, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2.

25. The protein of embodiment 22, wherein the immunoglobulin constant region is immunologically inert.

26. The protein of embodiment 22, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region.

27. The protein of any one of embodiments 1-26, wherein the second moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain.

28. The protein of embodiment 27, wherein the second moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), or a T cell receptor domain.

29. The protein of any one of embodiments 1-28, wherein the second moiety binds specifically to human CD47.

30. The protein of any one of embodiments 1-28, wherein the second moiety binds specifically to human CD3 or human PD-L1.

31. The protein of any one of embodiments 1-30, wherein the second moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region.

32. The protein of any one of embodiments 1-31, wherein the second moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region.

33. The protein of embodiment 32, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

34. The protein of embodiment 32, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.

35. The protein of embodiment 32, wherein the immunoglobulin constant region is immunologically inert.

36. The protein of embodiment 32, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region.

37. The protein of embodiment 1, wherein the protein has an immune effector function or two, three or more immune effector functions.

38. The protein of embodiment 37, wherein the immune effector function is ADCC, CDC or ADCP.

39. The protein of any one of embodiments 1-38, wherein the first moiety prevents or reduces specific binding of the second moiety to the molecule expressed in the diseased tissue.

40. The protein of any one of embodiments 1-39, wherein the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue.

41. The protein of any one of embodiments 1-40, wherein the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue, wherein the first moiety dissociates from the second moiety in the vicinity of the diseased tissue or inside the diseased tissue and wherein the second moiety specifically binds to the molecule expressed in the diseased tissue in the vicinity of the diseased tissue or inside the diseased tissue.

42. The protein of any one of embodiments 1-41, wherein the diseased tissue is a tumour or an inflamed tissue.

43. The protein of embodiment 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid

sequence of SEQ ID NO:16 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:17.

44. The protein of embodiment 1, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:26 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:27.

45. The protein of embodiment 1, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:34 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:35.

46. The protein of embodiment 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:36 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:37.

47. The protein of embodiment 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:38 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:39.

48. The protein of embodiment 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:40 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:41.

49. The protein of embodiment 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:42, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:43; or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:45; or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:46, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:47; or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:48, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:49; or

(e) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:50, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:51; or

(f) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:52, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:53; or

(g) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:54, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:55; or

(h) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:88, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:89; or

(i) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:90, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:91; or

(j) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:92; or

(k) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:93; or

(l) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:94; or

(m) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:95; or

(n) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:96; or

(o) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:97.

50. The protein of embodiment 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:74.

51. The protein of embodiment 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human cMET, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:76.

52. The protein of embodiment 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:98, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:99; or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:100, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:101; or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:102, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:103; or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:104, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:105.

53. An immunoconjugate comprising the protein of any one of embodiments 1-52 linked to a therapeutic agent.

54. The immunoconjugate of embodiment 53, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agent, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

55. A pharmaceutical composition comprising the protein of any one of embodiments 1-52 or the immunoconjugate of embodiment 53 or 54, and a pharmaceutically acceptable carrier, diluent or excipient.

56. A nucleic acid molecule encoding the protein or a portion of the protein of any one of embodiments 1-52.

57. A nucleic acid molecule encoding the first polypeptide chain, the second polypeptide chain, or both the first polypeptide chain and the second polypeptide chain of the protein of any one of embodiments 43-52.

58. An expression vector comprising the nucleic acid molecule of embodiment 56 or 57.

59. A recombinant host cell comprising the nucleic acid molecule of embodiment 56 or 57 or the expression vector of embodiment 58.

60. A method of producing a protein, the method comprising:

culturing a recombinant host cell comprising the expression vector of embodiment 57 under conditions whereby the nucleic acid molecule is expressed, thereby producing the protein; and

isolating the protein from the host cell or culture.

61. A method for enhancing an anti-cancer immune response in a subject, comprising administering to the subject a therapeutically effective amount of the protein of any one of embodiments 1-52, the immunoconjugate of embodiment 53 or 54, or the pharmaceutical composition of embodiment 55.

62. A method of treating cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject a therapeutically effective amount of the protein of any one of embodiments 1-52, the immunoconjugate of embodiment 53 or 54, or the pharmaceutical composition of embodiment 55.

63. The method of embodiment 62, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

64. The method of embodiment 62, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.

65. The method of embodiment 62, wherein the cardiovascular disease is coronary heart disease, or atherosclerosis or stroke.

66. The method of embodiment 62, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

67. The protein of any one of embodiments 1-52, the immunoconjugate of embodiment 53 or 54, or the pharmaceutical composition of embodiment 55 for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.

68. The protein or the pharmaceutical composition for use according to embodiment 67, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer,

salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

69. The protein or the pharmaceutical composition for use according to embodiment 67, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.

70. The protein or the pharmaceutical composition for use according to embodiment 67, wherein the cardiovascular disease is coronary heart disease, atherosclerosis, or stroke.

71. The protein or the pharmaceutical composition for use according to embodiment 67, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

72. The protein of any one of embodiments 1-52, the immunoconjugate of embodiment 53 or 54, or the pharmaceutical composition of embodiment 55, for use as a medicament.

Table 1. Peptide linker sequences.

Constant domain	Linker name	Unique linker sequence	Unique Linker length (bp)
CH1	L1	GGGGS (SEQ ID NO:15)	5
	L2	GGGGSGGGGS (SEQ ID NO:32)	10
	L3	GGGGSGGGGSGGGGS (SEQ ID NO:33)	15
	LH	GPAPELL (SEQ ID NO:1)	7
	LHL	GPAPELLGGGS (SEQ ID NO:2)	11
	LHL-F	GPAP**LG**LGGGS (SEQ ID NO:3)	11
	LHL-M	PPCPAPELLGGGS (SEQ ID NO:4)	13
	LHL-MF	PPCPAP**LG**LGGGS (SEQ ID NO:5)	13
CL (Kappa or Lambda)	L1	GGGGS (SEQ ID NO:15)	5
	L2	GGGGSGGGGS (SEQ ID NO:32)	10
	L3	GGGGSGGGGSGGGGS (SEQ ID NO:33)	15
	LH	GPAPELL (SEQ ID NO:1)	7
	LHL	GPAPELLGGGS (SEQ ID NO:2)	11
	LHL-F	GPAP**LG**LGGGS (SEQ ID NO:3)	11
	LHL-M	PPCPAPELLGGGS (SEQ ID NO:4)	13
	LHL-MF	PPCPAP**LG**LGGGS (SEQ ID NO:5)	13

Underlined linker peptide sequences are human IgG1 germline.
Non-underlined peptide sequences in bold (LG) are mutations that instate the rapidly-digested MMP peptide substrate sequence 'PLGL' (SEQ ID NO:12).

Table 2. Protein clone numbers, names (ID) and observed expression characteristics.

Clone #	Antibody ID	Protein yield* (mg)	Percentage Main Peak (SEC)	Expected** Molecular Weight (kDa)	
				non-reduced	reduced
1	Fab2 cMETCD47-L1-L1	2.7	52	146.49	72.96; 73.55
2	Fab2 cMETCD47-L2-L2	1.1	66	147.12	73.28; 73.86
3	Fab2 cMETCD47-L3-L3	5.7	45	147.75	73.59; 74.18
4	Fab2 cMETCD47-L1-LH	2.3	49	146.85	72.96; 73.91
5	Fab2 cMETCD47-LH-L1	3.4	49	146.85	73.33; 73.55
6	Fab2 cMETCD47-LHL-LHL	3.4	66	147.73	73.58; 74.17
7	Fab2 Her2CD3-L2-L2	3.1	61	146.55	74.09; 72.47
8	Fab2 Her2CD3-L1-LH	3.6	73	146.28	73.78; 72.52
9	Fab2 Her2CD3-LH-L1	0.2	ND	146.28	74.14; 72.16
10	Fab2 Her2CD3-LHL-LHL	1.3	58	147.16	74.40; 72.78
11	IgG2 Her2CD47-L1-LH	2.4	29	241.56	72.66; 48.15
12	IgG2 Her2CD47-LH-L1	8.1	49	241.56	73.02; 47.78
13	IgG2 Her2CD47-LH-LH	1.96	62	242.28	73.02; 48.15
14	IgG2 Her2CD47-LHL-LHL	18	90	243.32	73.28; 48.40
15	FabCD47-Only	1.5	82	98.49	49.13; 49.37

* Total protein after Protein A column affinity purification

** Based on amino acid sequence only

ND = not done

Table 3. Sequences of bispecific proteins binding to cMet and CD47.

Construct Type:	Fab2 CMET/CD47		
Clone Name:	Met47-L1-L1		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-L1	QVQLVQSGAEVKKPGASVKVSCKASGY TFTSYTMHWVRQAPGQGLEWMGIINP SGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARQEITTEFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC GGGGSQVQLVQSGAEVKKPGESLKISCK GSGYTFTNYYIFWVRQMPGKGLEWMG IINPVDGDTNYNPSFQGQVTISADKSIST AYLQWSSLKASDTAMYYCARGGYTMD RWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKGGGGSGGGGSCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPG (SEQ ID NO:6)	Met47 hole-L1	EIVLTQSPGTLSLSPGERATLSCRASQSV SSYANSYLHWYQQKPGQAPRLLIYRGST RESGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSKSEPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGGGGSDIV MTQSPLSLPVTPGEPASISCRSSQSLLHS NGYNYLHWYLQKPGQSPQLLIYKVSNR LSGVPDRFSGSGSGTDFTLKISRVEAEDV GVYYCFQNTHTPRTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGGGGSGGG GSCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:7)
Clone name:	Met47-L2-L2		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-L2	QVQLVQSGAEVKKPGASVKVSCKASGY TFTSYTMHWVRQAPGQGLEWMGIINP SGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARQEITTEFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC GGGGSGGGGSQVQLVQSGAEVKKPGE SLKISCKGSGYTFTNYYIFWVRQMPGKG LEWMGIINPVDGDTNYNPSFQGQVTIS ADKSISTAYLQWSSLKASDTAMYYCARG GYTMDRWGQGTLVTVSSASTKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKGGGGSGGGGSCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLWCLVKG FYPSDIAVEWESNGQPENNYKTTPPVL	Met47 hole-L2	EIVLTQSPGTLSLSPGERATLSCRASQSV SSYANSYLHWYQQKPGQAPRLLIYRGST RESGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSKSEPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGGGGSGGG GSDIVMTQSPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLHWYLQKPGQSPQLLIYK VSNRLSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCFQNTHTPRTFGGGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKV YACEVTHQGLSSPVTKSFNRGECGGGG SGGGGSCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVD

	DSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPG (SEQ ID NO:8)		KSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG (SEQ ID NO:9)
Clone name:	Met47-L3-L3		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-L3	QVQLVQSGAEVKKPGASVKVSCKASGY TFTSYTMHWVRQAPGQGLEWMGIINP SGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARQEITTEFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC GGGGSGGGGSGGGGSQVQLVQSGAE VKKPGESLKISCKGSGYTFTNYYIFWVRQ MPGKGLEWMGIINPVDGDTNYNPSFQ GQVTISADKSISTAYLQWSSLKASDTAM YYCARGGYTMDRWGQGTLVTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKGGGGSGGGGS CPPCPAPELLGGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSL WCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:10)	Met47 hole-L3	EIVLTQSPGTLSLSPGERATLSCRASQSV SSYANSYLHWYQQKPGQAPRLLIYRGST RESGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSKSEPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGGGGSGGG GSGGGGSDIVMTQSPLSLPVTPGEPASI SCRSSQSLLHSNGYNYLHWYLQKPGQS PQLLIYKVSNRLSGVPDRFSGSGSGTDFT LKISRVEAEDVGVYYCFQNTHTPRTFGG GTKVRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGN SQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC GGGGSGGGGSCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLSCAVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLV SKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG (SEQ ID NO:11)
Clone name:	Met47-L1-LH		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-L1	QVQLVQSGAEVKKPGASVKVSCKASGY TFTSYTMHWVRQAPGQGLEWMGIINP SGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARQEITTEFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC GGGGSQVQLVQSGAEVKKPGESLKISCK GSGYTFTNYYIFWVRQMPGKGLEWMG IINPVDGDTNYNPSFQGQVTISADKSIST AYLQWSSLKASDTAMYYCARGGYTMD RWGQGTLVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKGGGGSGGGGSCPPCPAPELLGG PSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSF	Met47 hole-LH	EIVLTQSPGTLSLSPGERATLSCRASQSV SSYANSYLHWYQQKPGQAPRLLIYRGST RESGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSKSEPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGPAPELLDI VMTQSPLSLPVTPGEPASISCRSSQSLLH SNGYNYLHWYLQKPGQSPQLLIYKVSN RLSGVPDRFSGSGSGTDFTLKISRVEAED VGVYYCFQNTHTPRTFGGGTKVEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYAC EVTHQGLSSPVTKSFNRGECGGGGSGG GGSCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLVSKLTVDKSR

	FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:6)		WQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:13)
Clone name:	Met47-LH-L1		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-LH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYTMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARQEITTEFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCGPAPELLQVQLVQSGAEVKKPGESLKISCKGSGYTFTNYYIFWVRQMPGKGLEWMGIINPVDGDTNYNPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGGYTMDRWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKGGGGSGGGGSCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:14)	Met47 hole-L1	EIVLTQSPGTLSLSPGERATLSCRASQSVSSYANSYLHWYQQKPGQAPRLLIYRGSTRESGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQSKSEPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLHWYLQKPGQSPQLLIYKVSNRLSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQNTHTPRTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSGGGGSCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:7)
Clone name:	Met47-LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-LHL	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYTMHWVRQAPGQGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARQEITTEFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKGGGGSGGGGSCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCQVMHEALHNHYTQKSLSLSPGGGGSQVQLVQSGAEVKKPGESLKISCKGSGYTFTNYYIFWVRQMPGKGLEWMGIINPVDGDTNYNPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGGYTMDRWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKGGGGSGGGGSCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL	Met47 hole-LHL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSYANSYLHWYQQKPGQAPRLLIYRGSTRESGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQSKSEPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGPAPELLGGGSDIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLHWYLQKPGQSPQLLIYKVSNRLSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQNTHTPRTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGSGGGGSCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVD

	SVMHEALHNHYTQKSLSLSPG (SEQ ID NO:16)		KSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG (SEQ ID NO:17)
Clone name:	A-D5 Fab-Fc (negative control, has only the CD47 Fab, no targeting domain at the N-terminus)		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	QVQLVQSGAEVKKPGESLKISCKGSGYT FTNYYIFWVRQMPGKGLEWMGIINPV DGDTNYNPSFQGQVTISADKSISTAYLQ WSSLKASDTAMYYCARGGYTMDRWG QGTLVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDKKVEPKSCDK GGGGSGGGGSCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLWCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG (SEQ ID NO:18)		DIVMTQSPLSLPVTPGEPASISCRSSQSL LHSNGYNYLHWYLQKPGQSPQLLIYKVS NRLSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCFQNTHTPRTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGECGGGGSG GGGSCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLVSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG (SEQ ID NO:19)

Table 4. Sequences of bispecific proteins binding to Her2 and CD3.

Construct Type:	Fab2 Her2/CD3		
Clone Name:	Her23-L2-L2		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her23 knob-L2	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGGGGSGGGGSQVQLQQSGAELAR PGASVKMSCKASGYTFTRYTMHWVKQ RPGQGLEWIGYINPSRGYTNYNQKFKD KATLTTDKSSSTAYMQLSSLTSEDSAVYY CARYYDDHYCLDYWGQGTTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKGGGGSGGGGS CPPCPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQ	Her23 hole-L2	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGGGGSGGGGS QIVLTQSPAIMSASPGEKVTMTCSASSS VSYMNWYQQKSGTSPKRWIYDTSKLAS GVPAHFRGSGSGTSYSLTISGMEAEDAA TYYCQQWSSNPFTFGSGTKLEINRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGECGGGGSGGG GSCPPCPAPEAAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:21)

	GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:20)		
Clone name:	Her23-L1-LH		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her23 knob-L1	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGGGGSQVQLQQSGAELARPGASV KMSCKASGYTFTRYTMHWVKQRPGQG LEWIGYINPSRGYTNYNQKFKDKATLTT DKSSSTAYMQLSSLTSEDSAVYYCARYY DDHYCLDYWGQGTTLTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKGGGGSGGGGSCPPCP APEAAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLWC LVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:22)	Her23 hole-LH	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLQIVLT QSPAIMSASPGEKVTMTCSASSSVSYM NWYQQKSGTSPKRWIYDTSKLASGVPA HFRGSGSGTSYSLTISGMEAEDAATYYC QQWSSNPFTFGSGTKLEINRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGECGGGGSGGGGSCPP CPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:23)
Clone name:	Her23-LH-L1		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her23 knob-LH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLQVQLQQSGAELARPGAS VKMSCKASGYTFTRYTMHWVKQRPGQ GLEWIGYINPSRGYTNYNQKFKDKATLT TDKSSSTAYMQLSSLTSEDSAVYYCARYY DDHYCLDYWGQGTTLTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKGGGGSGGGGSCPPCP APEAAGAPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVSLWC LVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGN	Her23 hole-L1	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGGGGSQIVLT QSPAIMSASPGEKVTMTCSASSSVSYM NWYQQKSGTSPKRWIYDTSKLASGVPA HFRGSGSGTSYSLTISGMEAEDAATYYC QQWSSNPFTFGSGTKLEINRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGECGGGGSGGGGSCPP CPAPEAAGAPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSRDELTKNQVSLS CAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQG

	VFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:24)		NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:25)
Clone name:	Her23-LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her23 knob-LHL	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQVQLQQSGAELAR PGASVKMSCKASGYTFTRYTMHWVKQ RPGQGLEWIGYINPSRGYTNYNQKFKD KATLTTDKSSSTAYMQLSSLTSEDSAVYY CARYYDDHYCLDYWGQGTTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKGGGGSGGGGS CPPCPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:26)	Her23 hole-LHL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS QIVLTQSPAIMSASPGEKVTMTCSASSS VSYMNWYQQKSGTSPKRWIYDTSKLAS GVPAHFRGSGSGTSYSLTISGMEAEDAA TYYCQQWSSNPFTFGSGTKLEINRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGECGGGGSGGG GSCPPCPAPEAAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLSCAVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLVSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:27)

Table 5. Sequences of bispecific proteins binding to Her2 and CD47.

Construct Type:	IgG Her2/CD47		
Clone Name:	Her47 -L1-LH		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 L1-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGGGGSQVQLVQSGAEVKKPGESLKI SCKGSGYTFTNYYIFWVRQMPGKGLEW MGIINPVDGDTNYNPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARGGYT MDRWGQGTLVTVSS (SEQ ID NO:28)	Her47 LH-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLDIVM TQSPLSLPVTPGEPASISCRSSQSLLHSN GYNYLHWYLQKPGQSPQLLIYKVSNRLS GVPDRFSGSGSGTDFTLKISRVEAEDVG VYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:29)
Clone name:	Her47 -LH-L1		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LH-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ	Her47 L1-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT

	MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLQVQLVQSGAEVKKPGESL KISCKGSGYTFTNYYIFWVRQMPGKGLE WMGIINPVDGDTNYNPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARGGY TMDRWGQGTLVTVSS (SEQ ID NO:30)		YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGGGSDIVMTQ SPLSLPVTPGEPASISCRSSQSLLHSNGY NYLHWYLQKPGQSPQLLIYKVSNRLSGV PDRFSGSGSGTDFTLKISRVEAEDVGVY YCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:31)
Clone name:	Her47 -LH-LH		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LH-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLQVQLVQSGAEVKKPGESL KISCKGSGYTFTNYYIFWVRQMPGKGLE WMGIINPVDGDTNYNPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARGGY TMDRWGQGTLVTVSS (SEQ ID NO:30)	Her47 LH-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLDIVM TQSPLSLPVTPGEPASISCRSSQSLLHSN GYNYLHWYLQKPGQSPQLLIYKVSNRLS GVPDRFSGSGSGTDFTLKISRVEAEDVG VYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:29)
Clone name:	Her47 -LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQVQLVQSGAEVKK PGESLKISCKGSGYTFTNYYIFWVRQMP GKGLEWMGIINPVDGDTNYNPSFQGQ VTISADKSISTAYLQWSSLKASDTAMYY CARGGYTMDRWGQGTLVTVSS (SEQ ID NO:34)	Her47 LHL-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS DIVMTQSPLSLPVTPGEPASISCRSSQSL LHSNGYNYLHWYLQKPGQSPQLLIYKVS NRLSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:35)

Table 6. Sequences of bispecific protein binding to cMET and CD47.

Construct Type:	Fab2 CMET/CD47 “One Arm” style		
Clone Name:	Met47-LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Met47 knob-LHL	QVQLVQSGAEVKKPGASVKVSCKASGY TFTSYTMHWVRQAPGQGLEWMGIINP SGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARQEITTEFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTS	Met47 hole-LHL	EIVLTQSPGTLSLSPGERATLSCRASQSV SSYANSYLHWYQQKPGQAPRLLIYRGST RESGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSKSEPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY

	GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC GPAPELLGGGSQVQLVQSGAEVKKPGE SLKISCKGSGYTFTNYYIFWVRQMPGKG LEWMGIINPVDGDTNYNPSFQGQVTIS ADKSISTAYLQWSSLKASDTAMYYCARG GYTMDRWGQGTLVTVSS (SEQ ID NO:36)		PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGPAPELLGG GSDIVMTQSPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLHWYLQKPGQSPQLLIYK VSNRLSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:37)

Table 7. Sequences of bispecific protein binding to Her2 and CD3.

Construct Type:	Fab2 Her2/CD3 "One Arm" style		
Clone Name:	Her23-LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her23 knob-LHL	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQVQLQQSGAELAR PGASVKMSCKASGYTFTRYTMHWVKQ RPGQGLEWIGYINPSRGYTNYNQKFKD KATLTTDKSSSTAYMQLSSLTSEDSAVYY CARYYDDHYCLDYWGQGTTLTVSS (SEQ ID NO:38)	Her23-LHL (underlined terminal K residue replaces an N that may cause N-link heterogeneity)	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS QIVLTQSPAIMSASPGEKVTMTCSASSS VSYMNWYQQKSGTSPKRWIYDTSKLAS GVPAHFRGSGSGTSYSLTISGMEAEDAA TYYCQQWSSNPFTFGSGTKLEI**K** (SEQ ID NO:39)

Table 8. Sequences of bispecific protein binding to Her2 and CD3.

Construct Type:	Fab2 Her2/CD3(34) "One Arm" style		
Clone Name:	Her23(34)-LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her23-LHL	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSEVKLLESGGGLVQP KGSLKLSCAASGFTFNTYAMNWVRQAP GKGLEWVARIRSKYNNYATYYADSVKD RFTISRDDSQSILYLQMNNLKTEDTAMY YCVRHGNFGNSYVSWFAYWGQGTLVT VSS (SEQ ID NO:40)	Her23-LHL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS QAVVTQESALTTSPGETVTLTCRSSTGA VTTSNYANWVQEKPDHLFTGLIGGTNK RAPGVPARFSGSLIGDKAALTITGAQTE DEAIYFCALWYSNLWVFGGGTKLTVL (SEQ ID NO:41)

Table 9. Sequences of bispecific proteins binding to Her2 and CD47.

Construct Type:	IgG2 Her2/CD47		
Clone Name:	Her47-LHLF-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHLF-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAP**LG**LGGGSQVQLVQSGAEVK KPGESLKISCKGSGYTFTNYYIFWVRQM PGKGLEWMGIINPVDGDTNYNPSFQG QVTISADKSISTAYLQWSSLKASDTAMY YCARGGYTMDRWGQGTLVTVSS (SEQ ID NO:42)	Her47 LHL-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS DIVMTQSPLSLPVTPGEPASISCRSSQSL LHSNGYNYLHWYLQKPGQSPQLLIYKVS NRLSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:43
Clone name:	Her47-LHL-LHLF		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQVQLVQSGAEVKK PGESLKISCKGSGYTFTNYYIFWVRQMP GKGLEWMGIINPVDGDTNYNPSFQGQ VTISADKSISTAYLQWSSLKASDTAMYY CARGGYTMDRWGQGTLVTVSS (SEQ ID NO:44)	Her47 LHLF-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAP**LG**LGG GSDIVMTQSPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLHWYLQKPGQSPQLLIYK VSNRLSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:45)
Clone name:	Her47-LHLF-LHLF		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHLF-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAP**LG**LGGGSQVQLVQSGAEVK KPGESLKISCKGSGYTFTNYYIFWVRQM PGKGLEWMGIINPVDGDTNYNPSFQG QVTISADKSISTAYLQWSSLKASDTAMY YCARGGYTMDRWGQGTLVTVSS (SEQ ID NO:46)	Her47 LHLF-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAP**LG**LGG GSDIVMTQSPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLHWYLQKPGQSPQLLIYK VSNRLSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:47)
Clone name:	Her47-LHLM-LHLM		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence

Her47 LHLM-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSC**PPC**PAPELLGGGSQVQLVQSGAEV KKPGESLKISCKGSGYTFTNYYIFWVRQ MPGKGLEWMGIINPVDGDTNYNPSFQ GQVTISADKSISTAYLQWSSLKASDTAM YYCARGGYTMDRWGQGTLVTVSS (SEQ ID NO:48)	Her47 LHLM-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC**PPC**PAPELLG GGSDIVMTQSPLSLPVTPGEPASISCRSS QSLLHSNGYNYLHWYLQKPGQSPQLLIY KVSNRLSGVPDRFSGSGSGTDFTLKISRV EAEDVGVYYCFQNTHTPRTFGGGTKVEI K (SEQ ID NO:49)
Clone name:	Her47-LHLM-LHLMF		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSC**PPC**PAPELLGGGSQVQLVQSGAEV KKPGESLKISCKGSGYTFTNYYIFWVRQ MPGKGLEWMGIINPVDGDTNYNPSFQ GQVTISADKSISTAYLQWSSLKASDTAM YYCARGGYTMDRWGQGTLVTVSS (SEQ ID NO:50)	Her47 LHLF-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC**PPC**PAP**LG**L GGGSDIVMTQSPLSLPVTPGEPASISCRS SQSLLHSNGYNYLHWYLQKPGQSPQLLI YKVSNRLSGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCFQNTHTPRTFGGGTKV EIK (SEQ ID NO:51)
Clone name:	Her47-LHLMF-LHLM		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHLMF-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSC**PPC**PAP**LG**LGGGSQVQLVQSGAE VKKPGESLKISCKGSGYTFTNYYIFWVRQ MPGKGLEWMGIINPVDGDTNYNPSFQ GQVTISADKSISTAYLQWSSLKASDTAM YYCARGGYTMDRWGQGTLVTVSS (SEQ ID NO:52)	Her47 LHLM-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC**PPC**PAPELLG GGSDIVMTQSPLSLPVTPGEPASISCRSS QSLLHSNGYNYLHWYLQKPGQSPQLLIY KVSNRLSGVPDRFSGSGSGTDFTLKISRV EAEDVGVYYCFQNTHTPRTFGGGTKVEI K (SEQ ID NO:53)
Clone name:	Her47 -LHLMF-LHLMF		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHLF-VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP	Her47 LHLF-VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT

	SSSLGTQTYICNVNHKPSNTKVDKKVEP KSC**PPC**PAP**LG**LGGGSQVQLVQSGAE VKKPGESLKISCKGSGYTFTNYYIFWVRQ MPGKGLEWMGIINPVDGDTNYNPSFQ GQVTISADKSISTAYLQWSSLKASDTAM YYCARGGYTMDRWGQGTLVTVSS (SEQ ID NO:54)		HQGLSSPVTKSFNRGEC**PPC**PAP**LG**L GGGSDIVMTQSPLSLPVTPGEPASISCRS SQSLLHSNGYNYLHWYLQKPGQSPQLLI YKVSNRLSGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCFQNTHTPRTFGGGTKV EIK (SEQ ID NO:55)

Table 10. Examples of immunoglobulin Fc region amino acid sequences.

Human IgG4 wild type
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:56)

Human IgG4(S228P)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:57)

Human IgG1 wild type
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:58)

Human IgG1-3M
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGA
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:59)

Human IgG2 wild type
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF
RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:60)

Human IgG1 wild type “REEM” allotype
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE

MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:61)

Human IgG1-3M "REEM" allotype
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGA
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:62)

Table 11. Examples of CD47 protein amino acid sequences.

Human CD47 sequence
MWPLVAALLLGSACCGSAQLLFNKTKSVEFTFCNDTVVIPCFVTNMEAQNTTEVYVKWKFKGRD
IYTFDGALNKSTVPTDFSSAKIEVSQLLKGDASLKMDKSDAVSHTGNYTCEVTELTREGETIIE
LKYRVVSWFSPNENILIVIFPIFAILLFWGQFGIKTLKYRSGGMDEKTIALLVAGLVITVIVIV
GAILFVPGEYSLKNATGLGLIVTSTGILILLHYYVFSTAIGLTSFVIAILVIQVIAYILAVVGL
SLCIAACIPMHGPLLISGLSILALAQLLGLVYMKFVASNQKTIQPPRKAVEEPLNAFKESKGMM
NDE (SEQ ID NO:63)

Cynomolgus monkey CD47 sequence
MWPLVAALLLGSACCGSAQLLFNKTKSVEFTFCNDTVVIPCFVTNMEAQNTTEVYVKWKFKGRD
IYTFDGALNKSTAPANFSSAKIEVSQLLKGDASLKMDKSDAVSHTGNYTCEVTELTREGETIIE
LKYRVVSWFSPNENILIVIFPIFAILLFWGQFGIKTLKYRSGGMDEKTIALLVAGLMITVIVIV
GAILFVPGEYSLKNATGLGLIVTSTGILILLHYYVFSTAIGLTSFVIAILVIQVIAYILAVVGL
SLCIAACIPMHGPLLISGLSILALAQLLGLVYMKFVASNQKTIQPPRKAVEEPLNAFKESKGMM
NDE (SEQ ID NO:64)

Table 12. Examples of cMET protein amino acid sequences.

Human cMET sequence
MKAPAVLAPGILVLLFTLVQRSNGECKEALAKSEMNVNMKYQLPNFTAETPIQNVILHEH
HIFLGATNYIYVLNEEDLQKVAEYKTGPVLEHPDCFPCQDCSSKANLSGGVWKDNINMAL
VVDTYYDDQLISCGSVNRGTCQRHVFPHNHTADIQSEVHCIFSPQIEEPSQCPDCVVSAL
GAKVLSSVKDRFINFFVGNTINSSYFPDHPLHSISVRRLKETKDGFMFLTDQSYIDVLPE
FRDSYPIKYVHAFESNNFIYFLTVQRETLDAQTFHTRIIRFCSINSGLHSYMEMPLECIL
TEKRKKRSTKKEVFNILQAAYVSKPGAQLARQIGASLNDDILFGVFAQSKPDSAEPMDRS
AMCAFPIKYVNDFFNKIVNKNNVRCLQHFYGPNHEHCFNRTLLRNSSGCEARRDEYRTEF
TTALQRVDLFMGQFSEVLLTSISTFIKGDLTIANLGTSEGRFMQVVVSRSGPSTPHVNFL
LDSHPVSPEVIVEHTLNQNGYTLVITGKKITKIPLNGLGCRHFQSCSQCLSAPPFVQCGW
CHDKCVRSEECLSGTWTQQICLPAIYKVFPNSAPLEGGTRLTICGWDFGFRRNNKFDLKK
TRVLLGNESCTLTLSESTMNTLKCTVGPAMNKHFNMSIIISNGHGTTQYSTFSYVDPVIT
SISPKYGPMAGGTLLTLTGNYLNSGNSRHISIGGKTCTLKSVSNSILECYTPAQTISTEF
AVKLKIDLANRETSIFSYREDPIVYEIHPTKSFISGGSTITGVGKNLNSVSVPRMVINVH
EAGRNFTVACQHRSNSEIICCTTPSLQQLNLQLPLKTKAFFMLDGILSKYFDLIYVHNPV
FKPFEKPVMISMGNENVLEIKGNDIDPEAVKGEVLKVGNKSCENIHLHSEAVLCTVPNDL
LKLNSELNIEWKQAISSTVLGKVIVQPDQNFTGLIAGVVSISTALLLLLGFFLWLKKRKQ
IKDLGSELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGS
CRQVQYPLTDMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAVQHVVIGPSSLIVHF
NEVIGRGHFGCVYHGTLLDNDGKKIHCAVKSLNRITDIGEVSQFLTEGIIMKDFSHPNVL
SLLGICLRSEGSPLVVLPYMKHGDLRNFIRNETHNPTVKDLIGFGLQVAKGMKYLASKKF
VHRDLAARNCMLDEKFTVKVADFGLARDMYDKEYYSVHNKTGAKLPVKWMALESLQTQKFTTKS
DVWSFGVLLWELMTRGAPPYPDVNTFDITVYLLQGRRLLQPEYCPDPLYEVMLKCWHPKAEMRP
SFSELVSRISAIFSTFIGEHYVHVNATYVNVKCVAPYPSLLSSEDNADDEVD

TRPASFWETS (SEQ ID NO:67)

Cynomolgus Monkey cMET sequence

mkapavlvpg ilvllftlvq rsngeckeal aksemnvnmk yqlpnftaet
aiqnvilheh hiflgatnyi yvlneedlqk vaeyktgpvl ehpdcfpcqd
csskanlsgg vwkdninmal vvdtyyddql iscgsvnrgt cqrhvfphnh
tadiqsevhc ifspqieepn qcpdcvvsal gakvlssvkd rfinffvgnt
inssyfphhp lhsisvrrlk etkdgfmflt dqsyidvlpe frdsypikyi
hafesnnfiy fltvqretln aqtfhtriir fcslnsglhs ymemplecil
tekrkkrstk kevfnilqaa yvskpgaqla rqigaslndd ilfgvfaqsk
pdsaepmdrs amcafpikyv ndffnkivnk nnvrclqhfy gpnhehcfnr
tllrnssgce arrdeyraef ttalqrvdlf mgqfsevllt sistfvkgdl
tianlgtseg rfmqvvvsrs gpstphvnfl ldshpvspev ivehplnqng
ytlvvtgkki tkiplnglgc rhfqscsqcl sappfvqcgw chdkcvrsee
cpsgtwtqqi clpaiykvfp tsapleggtr lticgwdfgf rrnnkfdlkk
trvllgnesc tltlsestmn tlkctvgpam nkhfnmsiii snghgttqys
tfsyvdpiit sispkygpma ggtlltltgn ylnsgnsrhi siggktctlk
svsnsilecy tpaqtistef avklkidlan retsifsyre dpivyeihpt
ksfisggsti tgvgknlhsv svprmvinvh eagrnftvac qhrsnseiic
cttpslqqln lqlplktkaf fmldgilsky fdliyvhnpv fkpfekpvmi
smgnenvlei kgndidpeav kgevlkvgnk scenihlhse avlctvpndl
lklnselnie wkqaisstvl gkvivqpdqn ftgliagvvs isiallllg
lflwlkkrkq ikdlgselvr ydarvhtphl drlvsarsvs pttemvsnes
vdyratfped qfpnssqngs crqvqypltd mspiltsgds disspllqnt
vhidlsalnp elvqavqhvv igpsslivhf nevigrghfg cvyhgtlldn
dgkkihcavk slnritdige vsqfltegii mkdfshpnvl sllgiclrse
gsplvvlpym khgdlrnfir nethnptvkd ligfglqvak gmkylaskkf
vhrdlaarnc mldekftvkv adfglardmy dkeyysvhnk tgaklpvkwm
aleslqtqkf ttksdvwsfg vllwelmtrg appypdvntf ditvyllqgr
rllqpeycpd plyevmlkcw hpkaemrpsf selvsrisai fstfigehyv
hvnatyvnvk cvapypslls sednaddevdt (SEQ ID NO:68)

Table 13. Sequences of bispecific protein binding to Her2 and CD3.

Construct Type:	Fc-Her2/CD3(34)		
Clone Name:	Fc-Her23(34)		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
FC-Her23(34) (Hole)	CPPCPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG GPAPLGLGGGSEVQLVESGGGLVQPGG SLRLSCAASGFNIKDTYIHWVRQAPGKG LEWVARIYPTNGYTRYADSVKGRFTISA DTSKNTAYLQMNSLRAEDTAVYYCSRW GGDGFYAMDYWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCGPAPLGLGGGSEVKL LESGGGLVQPKGSLKLSCAASGFTFNTY AMNWVRQAPGKGLEWVARIRSKYNN YATYYADSVKDRFTISRDDSQSILYLQM NNLKTEDTAMYYCVRHGNFGNSYVSW FAYWGQGTLVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTV PSSSLGTQTYICNVNHKPSNTKVDKKVE PKSC (SEQ ID NO:73)	FC-Her23(34) (Knob)	CPPCPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LWCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG GPAPLGLGGGSDIQMTQSPSSLSASVG DRVTITCQASQDISNYLNWYQQKPGKA PKLLIYDASNLETGVPSRFSGSGSGTDFT FTISSLQPEDIATYFCQHFDHLPLAFGGG TKVEIKRTVAAPSVFIFPPSDEQLKSGTA SVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC GPAPELLGGGSQAVVTQESALTTSPGET VTLTCRSSTGAVTTSNYANWVQEKPDH LFTGLIGGTNKRAPGVPARFSGSLIGDKA ALTITGAQTEDEAIYFCALWYSNLWVFG GGTKLTVLGQPKAAPSVTLFPPSSEELQ ANKATLVCLISDFYPGAVTVAWKADSSP VKAGVETTTPSKQSNNKYAASSYLSLTP EQWKSHRSYSCQVTHEGSTVEKTVAPT ECS (SEQ ID NO:74)

Table 14. Sequences of Fab2-based protein binding to cMET and cMET.

Construct Type:	Fab2 CMET/CMET "One Arm" style		
Clone Name:	MetMet-LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
MetMet-LHL-LHL VH	QVQLVQSGAEVKKPGASVKVSCKASGY TFTSYTMHWVRQAPGQGLEWMGIINP SGGSTSYAQKFQGRVTMTRDTSTSTVY MELSSLRSEDTAVYYCARQEITTEFDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKKVEPKSC GPAPELLGGGSQVQLVQSGAEVKKPGA SVKVSCKASGYTFTSYTMHWVRQAPG QGLEWMGIINPSGGSTSYAQKFQGRVT MTRDTSTSTVYMELSSLRSEDTAVYYCA RQEITTEFDYWGQGTLVTVSS (SEQ ID NO:75)	Met47 hole-LHL VL	EIVLTQSPGTLSLSPGERATLSCRASQSV SSYANSYLHWYQQKPGQAPRLLIYRGST RESGIPDRFSGSGSGTDFTLTISRLEPEDF AVYYCQQSKSEPLTFGGGTKVEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGPAPELLGG GSEIVLTQSPGTLSLSPGERATLSCRASQ SVSSYANSYLHWYQQKPGQAPRLLIYR GSTRESGIPDRFSGSGSGTDFTLTISRLEP EDFAVYYCQQSKSEPLTFGGGTKVEIK (SEQ ID NO:76)

Table 15. Examples of Her2 protein amino acid sequences.

HUMAN Her2 (erbB-2) sequence

MELAALCRWGLLLALLPPGAASTQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGN
LELTYLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNG
DPLNNTTPVTGASPGGLRELQLRSLTEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALT
LIDTNRSRACHPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTDCCHEQC
AAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTACP
YNYLSTDVGSCTLVCPLHNQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSA
NIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLPD
LSVFQNLQVIRGRILHNGAYSLTLQGLGISWLGLRSLRELGSGLALIHHNTHLCFVHTVPW
DQLFRNPHQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVNCSQFLRGQE
CVEECRVLQGLPREYVNARHCLPCHPECQPQNGSVTCFGPEADQCVACAHYKDPPFCV
ARCPSGVKPDLSYMPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTSIISA
VVGILLVVVLGVVFGILIKRRQQKIRKYTMRRLLQETELVEPLTPSGAMPNQAQMRILKETE
LRKVKVLGSGAFGTVYKGIWIPDGENVKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSP
YVSRLLGICLTSTVQLVTQLMPYGCLLDHVRENRGRLGSQDLLNWCMQIAKGMSYLEDV
RLVHRDLAARNVLVKSPNHVKITDFGLARLLDIDETEYHADGGKVPIKWMALESILRRRFT
HQSDVWSYGVTVWELMTFGAKPYDGIPAREIPDLLEKGERLPQPPICTIDVYMIMVKCWM
IDSECRPRFRELVSEFSRMARDPQRFVVIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDA
EEYLVPQQGFFCPDPAPGAGGMVHHRHRSSSTRSGGGDLTLGLEPSEEEAPRSPLAPS
EGAGSDVFDGDLGMGAAKGLQSLPTHDPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQP
EYVNQPDVRPQPPSPREGPLPAARPAGATLERPKTLSPGKNGVVKDVFAFGGAVENPEY
LTPQGGAAPQPHPPPAFSPAFDNLYYWDQDPPERGAPPSTFKGTPTAENPEYLGLDVPV
(SEQ ID NO:77)

Cynomolgus monkey Her2 (erbB2) sequence

MAESPASAFRDSLRKSVRTAAGNPGVPELGGTHPGLREEREKVKLGVATPRLVGMQLEG
ASWERACSQSQEEEEVEEEGCLRKYKNEVVELRFPSIGTGETRGAPWAAVRPFPRGSFR
RRAPGPHPSPHPAPHALPAGSSRSHGAGAAVSTMELAAWYRWGLLLALLPPGATGTQV
CTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELTYLPTNASLSFLQDIQEVQGYVL
IAHNQVRQVPLQRLRIVRGTQLFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSL
TEILKGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRACHPCSPVCKGSRCWG
ESSEDCQSLTRTVCAGGCARCKGPLPTDCCHEQCAAGCTGPKHSDCLACLHFNHSGICE
LHCPALVTYNTDTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLHNQEVTAE
DGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSANIQEFAGCKKIFGSLAFLPESFDGDP
ASNTAPLQPEQLRVFETLEEITGYLYISAWPDSLPDLSVLQNLQVIRGRILHNGAYSLTLQG
LGISWLGLRSLRELGSGLALIHHNTRLCFVHTVPWDQLFRNPHQALLHTANRPEDECVGE
GLACHQLCARGHCWGPGPTQCVNCSQFLRGQECVEECRVLQGLPREYVNARHCLPCH
PECQPQNGSVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIWKFPDEEGT
CQSCPINCTHSCVDLDDKGCPAEQRASPLTSIISAVVGILLVVVLGVVFGILIKRRQQKIRKY
TMRRLLQETELVEPLTPSGAMPNQAQMRILKETELRKVKVLGSGAFGTVYKGIWIPDGEN
VKIPVAIKVLRENTSPKANKEILDEAYVMAGVGSPYVSRLLGICLTSTVQLVTQLMPYGCLL
DHVRENRGRLGSQDLLNWCMQIAKGMSYLEDVRLVHRDLAARNVLVKSPNHVKITDFGL
ARLLDIDETEYHADGGKVPIKWMALESILRRRFTHQSDVWSYGVTVWELMTFGAKPYDGI
PAREIPDLLEKGERLPQPPICTIDVYMIMVKCWMIDSECRPRFRELVSEFSRMARDPQRFV
VIQNEDLGPASPLDSTFYRSLLEDDDMGDLVDAEEYLVPQQGFFCPDPAPGTGGMVHHR
HRSSSTRSGGGDLTLGLEPSEEEAPRSPRAPSEGTGSDVFDGDLGMGAAKGLQSLPAH
DPSPLQRYSEDPTVPLPSETDGYVAPLTCSPQPEYVNQPDVRPQPPSPQEGPLSPARPT
GATLERPKTLSPGKNGVVKDVFAFGGAVENPEYLAPRGGAAPQPHLPPAFSPAFDNLYY
WDQDPSERGAPPSTFKGTPTAENPEYLGLDVPV (SEQ ID NO:78)

Table 16. Examples of CD3 epsilon domain amino acid sequences.

Human CD3 epsilon sequence

MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILQHNDKN
IGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMDVMS
VATIVIVDICITGGLLLLVYYWSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRK
GQRDLYSGLNQRRI (SEQ ID NO:79)

Cynomolgus monkey CD3 epsilon sequence

MQSGTRWRVLGLCLLSIGVWGQDGNEEMGSITQTPYQVSISGTTVILTCSQHLGSEAQWQHNGK
NKEDSGDRLFLPEFSEMEQSGYYVCYPRGSNPEDASHHLYLKARVCENCMEMDVMAVATIVIVD
ICITLGLLLLVYYWSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQQDLYSG
LNQRRI (SEQ ID NO:80)

Table 17. Biacore binding values for control anti-Her2 and anti-CD47 antibodies

Clone ID	Analyte	ka (1/Ms)	kd (1/s)	Rmax (RU)	Concentration range (nM)	KD (M)	Chi^2	KD (nM)
Trastuzumab IgG1 (beginning)	hHer2	2.34E+05	5.06E-04	265.80	100-12.5	2.16E-09	3.40	2.16
Trastuzumab IgG1 (end)	hHer2	2.52E+05	6.18E-04	144.13	100-12.5	2.45E-09	1.73	2.45
A-D5 IgG1 (beginning)	hCD47	8.33E+05	1.07E-03	122.87	100-25	1.29E-09	8.58	1.29
A-D5 IgG1 (end)	hCD47	7.75E+05	1.03E-03	85.51	100-25	1.32E-09	5.34	1.32

Table 18. Biacore binding for Her2 and CD47 during MMP12 activation of IgG^2 Her47-LHL-LHLF protein.

Digestion Time Point	Analyte	ka (1/Ms)	kd (1/s)	Rmax (RU)	Concentration range (nM)	KD (M)	Chi^2	KD (nM)
Undigested		3.62E+05	3.67E-04	172.38	100-12.5	1.02E-09	2.64	1.02
2 hours		3.71E+05	3.39E-04	156.08	100-12.5	9.14E-10	2.38	0.91
4 hours	hHer2	4.52E+05	3.56E-04	128.53	50-12.5	7.87E-10	0.62	0.79
8 hours		3.83E+05	3.67E-04	125.18	100-12.5	9.59E-10	2.05	0.96
24 hours		3.89E+05	4.19E-04	103.96	100-12.5	1.08E-09	1.83	1.08
Undigested		N/A	N/A	N/A	N/A	N/A	N/A	N/A
2 hours		2.95E+05	7.12E-03	8.3	400-25	2.42E-08	0.02	24.16
4 hours	hCD47	4.57E+05	5.92E-03	12.09	400-25	1.30E-08	0.1	12.96
8 hours		4.81E+05	4.10E-03	17.27	200-25	8.52E-09	0.32	8.52
24 hours		8.00E+05	3.97E-03	23.93	200-25	4.97E-09	0.64	4.97

N/A = Not Applicable. No binding signal observed.

Table 19. Sequences of bispecific proteins binding to Her2 and CD47.

Construct Type:	IgG2 'IgG1-DAA' Her2/CD47		
Clone Name:	Her47 LHLF-LHL IgG1-2hDAA		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHLF-LHL IgG1-2hDAA VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPLGLGGGSQVQLVQSGAEVKK PGESLKISCKGSGYTFTNYYIFWVRQMP GKGLEWMGIINPVDGDTNYNPSFQGQ VTISADKSISTAYLQWSSLKASDTAMYY CARGGYTMDRWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPPVA GPDVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNAALPAPIAKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPG (SEQ ID NO:88)	Her47 LHLF-LHL IgG1-2hDAA VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS DIVMTQSPLSLPVTPGEPASISCRSSQSL LHSNGYNYLHWYLQKPGQSPQLLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCFQNTHTPRTFGGGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYA CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 89)
Clone name:	Her47 LHL-LHLF IgG1-2hDAA		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL-LHLF IgG1-2hDAA VH	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQVQLVQSGAEVKK PGESLKISCKGSGYTFTNYYIFWVRQMP GKGLEWMGIINPVDGDTNYNPSFQGQ VTISADKSISTAYLQWSSLKASDTAMYY CARGGYTMDRWGQGTLVTVSSASTKG PSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPPVA GPDVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNAALPAPIAKTISKAKGQPREP QVYTLPPSRDELTKNQVSLTCLVKGFYPS	Her47 LHL-LHLF IgG1-2hDAA VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPLGLGGG SDIVMTQSPLSLPVTPGEPASISCRSSQS LLHSNGYNYLHWYLQKPGQSPQLLIYKV SNRFSGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCFQNTHTPRTFGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVY ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:91)

	DIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPG (SEQ ID NO:90)		

Table 20. Sequences of bispecific proteins binding to Her2 and CD47.

Construct Type:	IgG2 Her2/CD47		
Clone Name:	Her47 LHL-LHL-EK		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL VH	(SEQ ID NO:44)	Her47 LHL-EK VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPADDDDKSG SDIVMTQSPLSLPVTPGEPASISCRSSQS LLHSNGYNYLHWYLQKPGQSPQLLIYKV SNRFSGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:92)
Clone name:	Her47-LHL-LHL-Thr		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL VH	(SEQ ID NO:44)	Her47 LHL-Thr VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPALVPRGSGS DIVMTQSPLSLPVTPGEPASISCRSSQSL LHSNGYNYLHWYLQKPGQSPQLLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:93)
Clone name:	Her47-LHL-LHL-tPA		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL VH	(SEQ ID NO:44)	Her47 LHL-tPA VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPGPFGRSAG GPDIVMTQSPLSLPVTPGEPASISCRSSQ SLLHSNGYNYLHWYLQKPGQSPQLLIYK VSNRFSGVPDRFSGSGSGTDFTLKISRVE AEDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:94)

Clone name:	Her47-LHL-LHL-GrB		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL VH	(SEQ ID NO:44)	Her47 LHL-GrB VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPLEADAG SDIVMTQSPLSLPVTPGEPASISCRSSQS LLHSNGYNYLHWYLQKPGQSPQLLIYKV SNRFSGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:95)
Clone name:	Her47-LHL-LHL-uPA		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL VH	(SEQ ID NO:44)	Her47 LHL-uPA VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPEARRGG SDIVMTQSPLSLPVTPGEPASISCRSSQS LLHSNGYNYLHWYLQKPGQSPQLLIYKV SNRFSGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:96)
Clone name:	Her47-LHL-LHL-A5		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
Her47 LHL VH	(SEQ ID NO:44)	Her47 LHL-A5 VL	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPEGEARG SDIVMTQSPLSLPVTPGEPASISCRSSQS LLHSNGYNYLHWYLQKPGQSPQLLIYKV SNRFSGVPDRFSGSGSGTDFTLKISRVEA EDVGVYYCFQNTHTPRTFGGGTKVEIK (SEQ ID NO:97)

Table 21. Sequences of linker peptides containing protease cleavage motifs.

Protease	Linker sequence
Enterokinase(EK)	GPADDDDKSGS (SEQ ID NO: 82)
Thrombin (Thr)	GPALVPRGSGS (SEQ ID NO: 83)

tPA	GPGPFGRSAGGP (SEQ ID NO: 84)
Granzyme B (GrB)	GPAPLEADAGS (SEQ ID NO: 85)
uPA	GPAPEARRGGS (SEQ ID NO: 86)
ADAMTs-5 (A5)	GPAPEGEARGS (SEQ ID NO: 87)

Table 22. Sequences of bispecific proteins binding to Her2 and CD3 or to EpCAM and CD3.

Construct Type:	Fab2 Her2/CD3		
Clone Name:	Fab2 Her23 LHL-LHLF		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQVQLQQSGAELAR PGASVKMSCKASGYTFTRYTMHWVKQ RPGQGLEWIGYINPSRGYTNYNQKFKD KATLTTDKSSSTAYMQLSSLTSEDSAVYY CARYYDDHYCLDYWGQGTTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCGPAPEAAGAPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLSCAVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLV SKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG (SEQ ID NO:98)		DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPLGLGGG SQIVLTQSPAIMSASPGEKVTMTCSASS SVSYMNWYQQKSGTSPKRWIYDTSKLA SGVPAHFRGSGSGTSYSLTISGMEAEDA ATYYCQQWSSNPFTFGSGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACE VTHQGLSSPVTKSFNRGECGPAPEAAG APSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLWCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPG (SEQ ID NO:99)
Clone name:	Fab2 Her23 LHL-LHL		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP		DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS

	KSCGPAPELLGGGSQVQLQQSGAELAR PGASVKMSCKASGYTFTRYTMHWVKQ RPGQGLEWIGYINPSRGYTNYNQKFKD KATLTTDKSSSTAYMQLSSLTSEDSAVYY CARYYDDHYCLDYWGQGTTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCGPAPEAAGAPSVF LFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTL PPSRDELTKNQVSLSCAVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLV SKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPG (SEQ ID NO:100)		QIVLTQSPAIMSASPGEKVTMTCSASSS VSYMNWYQQKSGTSPKRWIYDTSKLAS GVPAHFRGSGSGTSYSLTISGMEAEDAA TYYCQQWSSNPFTFGSGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGECGPAPEAAGA PSVFLFPPKPKDTLMISRTPEVTCVVVDV SHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPG (SEQ ID NO:101)
Clone name:	Fab2 Her23 LHLF-LHL-S		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPLGLGGG SQVQLQQSGAELARPGASVKMSCKAS GYTFTRYTMHWVKQRPGQGLEWIGYI NPSRGYTNYNQKFKDKATLTTDKSSSTA YMQLSSLTSEDSAVYYCARYYDDHYCLD YWGQGTTLTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:102)		EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQIVLTQSPAIMSAS PGEKVTMTCSASSSVSYMNWYQQKSG TSPKRWIYDTSKLASGVPAHFRGSGSGT SYSLTISGMEAEDAATYYCQQWSSNPF TFGSGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFN RGECGPAPEAAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:103)
Clone name:	Fab2 Her23 LHL-LHL-S		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	DIQMTQSPSSLSASVGDRVTITCRASQD VNTAVAWYQQKPGKAPKLLIYSASFLYS GVPSRFSGSRSGTDFTLTISSLQPEDFAT YYCQQHYTTPPTFGQGTKVEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPR EAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGECGPAPELLGGGS QVQLQQSGAELARPGASVKMSCKASG YTFTRYTMHWVKQRPGQGLEWIGYIN		EVQLVESGGGLVQPGGSLRLSCAASGF NIKDTYIHWVRQAPGKGLEWVARIYPT NGYTRYADSVKGRFTISADTSKNTAYLQ MNSLRAEDTAVYYCSRWGGDGFYAM DYWGQGTLVTVSSASTKGPSVFPLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQIVLTQSPAIMSAS PGEKVTMTCSASSSVSYMNWYQQKSG

	PSRGYTNYNQKFKDKATLTTDKSSSTAY MQLSSLTSEDSAVYYCARYYDDHYCLDY WGQGTTLTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPK SCGPAPEAAGAPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELTKNQVSL SCAVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:104)		TSPKRWIYDTSKLASGVPAHFRGSGSGT SYSLTISGMEAEDAATYYCQQWSSNPF TFGSGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFN RGECGPAPEAAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:105)
Clone name:	Fab2 mEpCam3 LHLF-LHL-S		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	DIQMTQSPASLSASLGETVSIECLASEGIS NDLAWYQQKSGKSPQLLIYATSRLQDG VPSRFSGSGSGTRYSLKISGMQPEDEAD YFCQQSYKYPWTFGGGTKLELKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGECGPAPLGLGG GSQVQLQQSGAELARPGASVKMSCKA SGYTFTRYTMHWVKQRPGQGLEWIGYI NPSRGYTNYNQKFKDKATLTTDKSSSTA YMQLSSLTSEDSAVYYCARYYDDHYCLD YWGQGTTLTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:106)		EVQLAESGGGLVQPGRSMKLSCAASGF TFSNFPMAWVRQAPTKGLEWVATISTS GGSTYYRDSVKGRFTISRDNAKSTLYLQ MNSLRSEDTATYYCTRTLYILRVFYFDY WGQGVMVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQIVLTQSPAIMSAS PGEKVTMTCSASSSVSYMNWYQQKSG TSPKRWIYDTSKLASGVPAHFRGSGSGT SYSLTISGMEAEDAATYYCQQWSSNPF TFGSGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFN RGECGPAPEAAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:107)
Clone name:	Fab2 mEpCam3 LHL-LHL-S		
Chain name	Heavy chain amino acid sequence	Chain name	Light chain amino acid sequence
	DIQMTQSPASLSASLGETVSIECLASEGIS NDLAWYQQKSGKSPQLLIYATSRLQDG VPSRFSGSGSGTRYSLKISGMQPEDEAD YFCQQSYKYPWTFGGGTKLELKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGECGPAPELLGGG SQVQLQQSGAELARPGASVKMSCKAS GYTFTRYTMHWVKQRPGQGLEWIGYI NPSRGYTNYNQKFKDKATLTTDKSSSTA YMQLSSLTSEDSAVYYCARYYDDHYCLD		EVQLAESGGGLVQPGRSMKLSCAASGF TFSNFPMAWVRQAPTKGLEWVATISTS GGSTYYRDSVKGRFTISRDNAKSTLYLQ MNSLRSEDTATYYCTRTLYILRVFYFDY WGQGVMVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPELLGGGSQIVLTQSPAIMSAS PGEKVTMTCSASSSVSYMNWYQQKSG TSPKRWIYDTSKLASGVPAHFRGSGSGT SYSLTISGMEAEDAATYYCQQWSSNPF

	YWGQGTTLTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHKPSNTKVDKKVEP KSCGPAPEAAGAPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVS LSCAVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:108)		TFGSGTKLEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFN RGECGPAPEAAGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKN QVSLWCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLS LSPG (SEQ ID NO:109)

Table 23. Binding affinities to human and murine Fc receptors by Biacore.

FcγR	Isotype hIgG1	Isotype hIgG4	Isotype mIgG1	Isotype mIgG2a	IgG[2] Her47 LHL-LHL	Fab[2] Her47 LHL-LHL
hFcγRI	3.9×10^{-9}	1.2×10^{-8}	ND	ND	5.8×10^{-9}	5.5×10^{-9}
hFcγRIIA 167 Arg	8.1×10^{-6}	NB	ND	ND	1.5×10^{-5}	6.8×10^{-6}
hFcγRIIA 167 His	4.4×10^{-6}	NB	ND	ND	3.5×10^{-6}	4.2×10^{-6}
hFcγRIIB	1.3×10^{-5}	2.2×10^{-5}	ND	ND	2.3×10^{-5}	1.2×10^{-5}
hFcγRIIIA 176 Val	6.4×10^{-6}	NB	ND	ND	1.7×10^{-6}	1.8×10^{-6}
hFcγRIIIA 176 Phe	2.6×10^{-6}	NB	ND	ND	8.9×10^{-7}	7.3×10^{-7}
hFcγRIIIB	6.8×10^{-6}	NB	ND	ND	3.4×10^{-6}	3.9×10^{-6}
mFcγRI	1.1×10^{-7}	2.7×10^{-7}	NB	2.6×10^{-8}	1.9×10^{-7}	1.6×10^{-7}
mFcγRIIB	1.3×10^{-5}	NB	ND	ND	1.2×10^{-5}	1.0×10^{-5}
mFcγRIII	1.8×10^{-5}	NB	3.2×10^{-5}	1.7×10^{-5}	2.3×10^{-5}	1.5×10^{-5}
mFcγRIV	1.8×10^{-6}	NB	NB	1.2×10^{-6}	2.0×10^{-6}	1.1×10^{-6}

ND = Not Done
NB = No Binding

CLAIMS

1. A protein comprising a first moiety and a second moiety and a peptide linker between the first moiety and the second moiety,

wherein the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having from 1 to about 7 amino acid substitutions compared to a human immunoglobulin hinge region;

wherein the peptide linker is cleavable by a protease expressed in a diseased tissue;

wherein the second moiety is capable of specifically binding to a molecule expressed in the diseased tissue; and

wherein the binding of the second moiety to the molecule expressed in the diseased tissue is reduced or inhibited when the peptide linker is uncleaved.

2. The protein of claim 1, wherein the peptide linker is between about 5 and about 15 amino acids in length.

3. The protein of claim 1 or 2, wherein the peptide linker comprises or consists of the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, or SEQ ID NO:87.

4. The protein of any one of claims 1-3, wherein the protease is a human matrix metalloprotease (MMP), a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5.

5. The protein of any one of claims 1-4, wherein the peptide linker comprises a human MMP cleavage site, a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5 cleavage site.

6. The protein of any one of claims 1-5, wherein the human MMP is MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13 or MMP14.

7. The protein of any one of claims 1-6, wherein the level or the activity of the human MMP is elevated in the diseased tissue compared to the level or the activity of the human MMP in a non-diseased tissue.

8. The protein of any one of claims 1-5, wherein the human cathepsin is Cathepsin A, Cathepsin C, Cathepsin D, Cathepsin G, Cathepsin L or Cathepsin K.

9. The protein of any one of claims 1-5 and 8, wherein the level or the activity of the human cathepsin is elevated in the diseased tissue compared to the level or the activity of the human cathepsin in a non-diseased tissue.

10. The protein of any one of claims 1-9, wherein the first moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain.

11. The protein of claim 10, wherein the first moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), a diabody, or a T cell receptor domain.

12. The protein of any one of claims 1-11, wherein the first moiety specifically binds to a molecule expressed in a diseased tissue.

13. The protein of any one of claims 1-12, wherein the first moiety specifically binds to a first molecule expressed in a diseased tissue and the second moiety is capable of specifically binding to a second molecule expressed in a diseased tissue, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are different molecules.

14. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by the same cell.

15. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by different cells.

16. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is expressed on the surface of a cell.

17. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is a soluble molecule.

18. The protein of any one of claims 1-17, wherein the first moiety binds specifically to human EGFR, human HER2, human HER3, human CD105, human C-KIT, human PD1, human PD-L1, human PSMA, human EpCAM, human Trop2, human EphA2, human CD20, human BCMA, human GITR, human OX40, human CSF1R, human Lag3 or human cMET.

19. The protein of any one of claims 1-17, wherein the second moiety specifically binds to a molecule expressed by a human immune cell.

20. The protein of claim 19, wherein the molecule expressed by a human immune cell is human CD3, human CD16A, human CD16B, human CD28, human CD89, human CTLA4, human NKG2D, human SIRPα, human SIRPγ, human PD1, human Lag3, human 4-1BB, human OX40, or human GITR.

21. The protein of any one of claims 1-20, wherein the first moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region.

22. The protein of any one of claims 1-21, wherein the first moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region.

23. The protein of claim 22, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA, or IgY.

24. The protein of claim 22, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2.

25. The protein of claim 22, wherein the immunoglobulin constant region is immunologically inert.

26. The protein of claim 22, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region.

27. The protein of any one of claims 1-26, wherein the second moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain.

28. The protein of claim 27, wherein the second moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), or a T cell receptor domain.

29. The protein of any one of claims 1-28, wherein the second moiety binds specifically to human CD47.

30. The protein of any one of claims 1-28, wherein the second moiety binds specifically to human CD3 or human PD-L1.

31. The protein of any one of claims 1-30, wherein the second moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region.

32. The protein of any one of claims 1-31, wherein the second moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region.

33. The protein of claim 32, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

34. The protein of claim 32, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.

35. The protein of claim 32, wherein the immunoglobulin constant region is immunologically inert.

36. The protein of claim 32, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region.

37. The protein of claim 1, wherein the protein has an immune effector function or two, three or more immune effector functions.

38. The protein of claim 37, wherein the immune effector function is ADCC, CDC or ADCP.

39. The protein of any one of claims 1-38, wherein the first moiety prevents or reduces specific binding of the second moiety to the molecule expressed in the diseased tissue.

40. The protein of any one of claims 1-39, wherein the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue.

41. The protein of any one of claims 1-40, wherein the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue, wherein the first moiety dissociates from the second moiety in the vicinity of the diseased tissue or inside the diseased tissue and wherein the second moiety specifically binds to the molecule expressed in the diseased tissue in the vicinity of the diseased tissue or inside the diseased tissue.

42. The protein of any one of claims 1-41, wherein the diseased tissue is a tumour or an inflamed tissue.

43. The protein of claim 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:16 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:17.

44. The protein of claim 1, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:26 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:27.

45. The protein of claim 1, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:34 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:35.

46. The protein of claim 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:36 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:37.

47. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:38 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:39.

48. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:40 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:41.

49. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:
(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:42, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:43; or
(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:45; or
(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:46, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:47; or
(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:48, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:49; or
(e) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:50, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:51; or

(f) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:52, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:53; or

(g) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:54, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:55; or

(h) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:88, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:89; or

(i) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:90, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:91; or

(j) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:92; or

(k) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:93; or

(l) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:94; or

(m) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:95; or

(n) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:96; or

(o) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:97.

50. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:74.

51. The protein of claim 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human cMET, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:76.

52. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:
(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:98, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:99; or
(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:100, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:101; or
(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:102, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:103; or
(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:104, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:105.

53. An immunoconjugate comprising the protein of any one of claims 1-52 linked to a therapeutic agent.

54. The immunoconjugate of claim 53, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agent, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

55. A pharmaceutical composition comprising the protein of any one of claims 1-52 or the immunoconjugate of claim 53 or 54, and a pharmaceutically acceptable carrier, diluent or excipient.

56. A nucleic acid molecule encoding the protein or a portion of the protein of any one of claims 1-52.

57. A nucleic acid molecule encoding the first polypeptide chain, the second polypeptide chain, or both the first polypeptide chain and the second polypeptide chain of the protein of any one of claims 43-52.

58. An expression vector comprising the nucleic acid molecule of claim 56 or 57.

59. A recombinant host cell comprising the nucleic acid molecule of claim 56 or 57 or the expression vector of claim 58.

60. A method of producing a protein, the method comprising:

culturing a recombinant host cell comprising the expression vector of claim 57 under conditions whereby the nucleic acid molecule is expressed, thereby producing the protein; and

isolating the protein from the host cell or culture.

61. A method for enhancing an anti-cancer immune response in a subject, comprising administering to the subject a therapeutically effective amount of the protein of any one of claims 1-52, the immunoconjugate of claim 53 or 54, or the pharmaceutical composition of claim 55.

62. A method of treating cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject a therapeutically effective amount of the protein of any one of claims 1-52, the immunoconjugate of claim 53 or 54, or the pharmaceutical composition of claim 55.

63. The method of claim 62, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

64. The method of claim 62, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.

65. The method of claim 62, wherein the cardiovascular disease is coronary heart disease, or atherosclerosis or stroke.

66. The method of claim 62, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

67. The protein of any one of claims 1-52, the immunoconjugate of claim 53 or 54, or the pharmaceutical composition of claim 55 for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.

68. The protein or the pharmaceutical composition for use according to claim 67, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

69. The protein or the pharmaceutical composition for use according to claim 67, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto’s thyroiditis or ankylosing spondylitis.

70. The protein or the pharmaceutical composition for use according to claim 67, wherein the cardiovascular disease is coronary heart disease, atherosclerosis, or stroke.

71. The protein or the pharmaceutical composition for use according to claim 67, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

72. The protein of any one of claims 1-52, the immunoconjugate of claim 53 or 54, or the pharmaceutical composition of claim 55, for use as a medicament.

Figure 1A

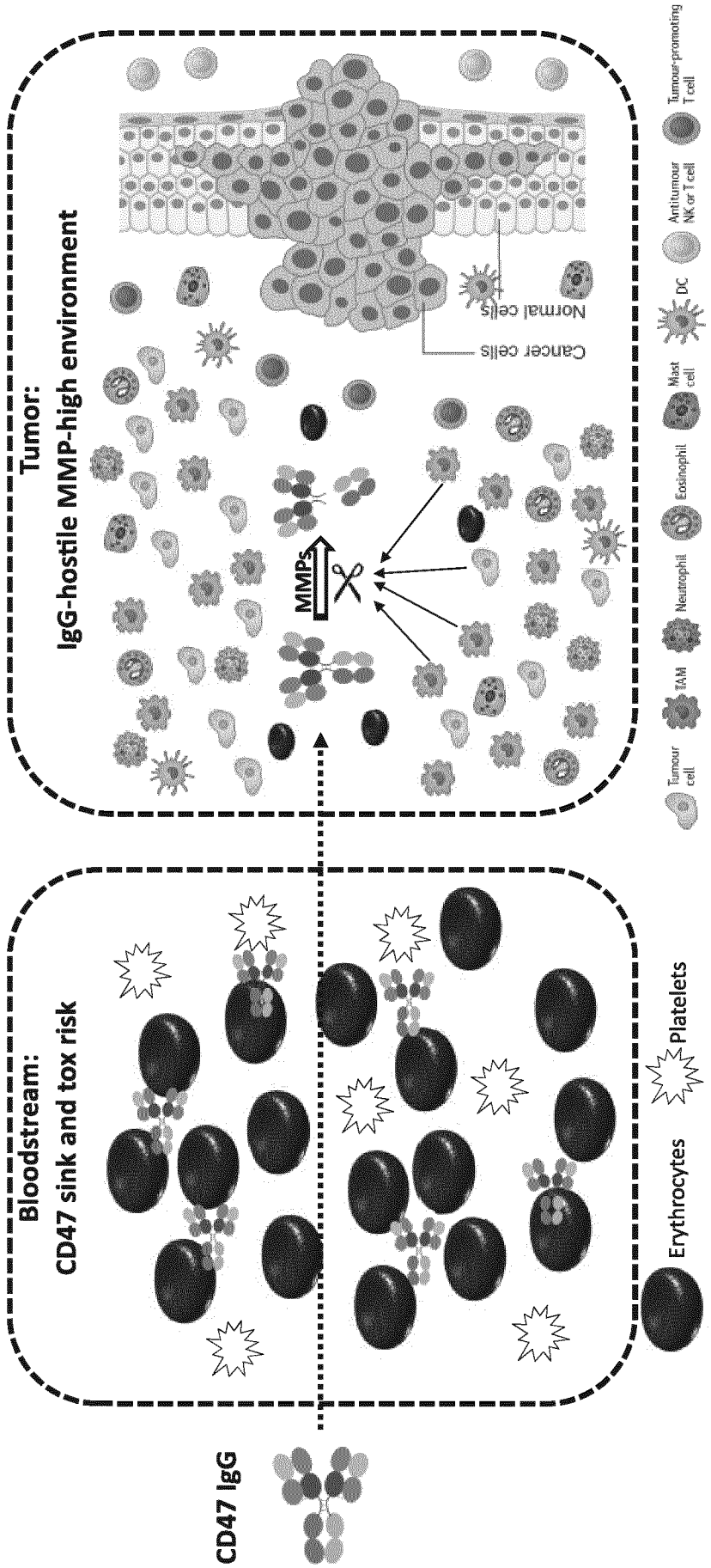

Tumor:
IgG-hostile MMP-high environment
Cancer cells
Normal cells
MMPs
Tumour cell
TAM
Neutrophil
Eosinophil
Mast cell
DC
Antitumour NK or T cell
Tumour-promoting T cell
Bloodstream:
CD47 sink and tox risk
Erythrocytes
Platelets
CD47 IgG

Figure 1B

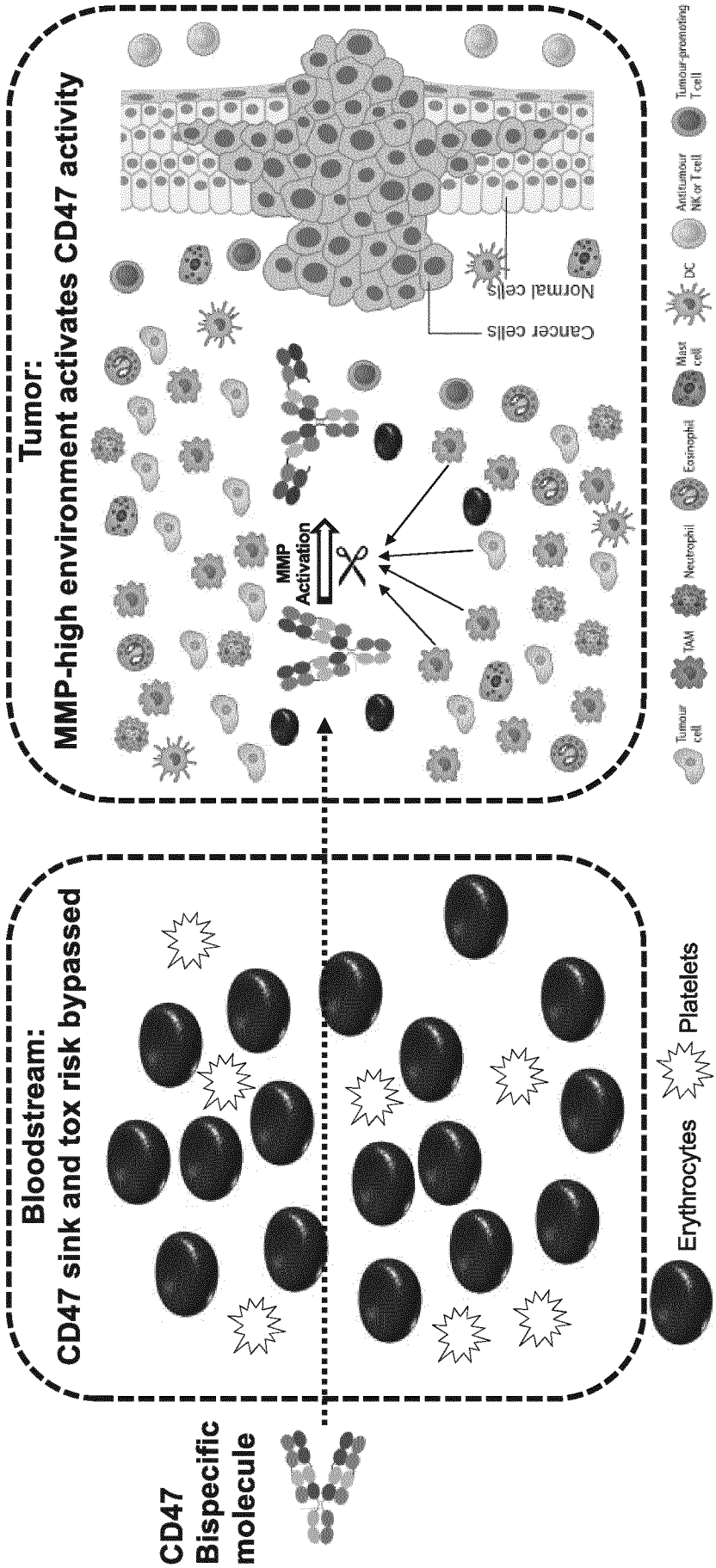

Tumor:
MMP-high environment activates CD47 activity
Cancer cells
Normal cells
MMP Activation
Tumour cell
TAM
Neutrophil
Eosinophil
Mast cell
DC
Antitumour NK or T cell
Tumour-promoting T cell
Bloodstream:
CD47 sink and tox risk bypassed
Platelets
Erythrocytes
CD47 Bispecific molecule

Figure 2A

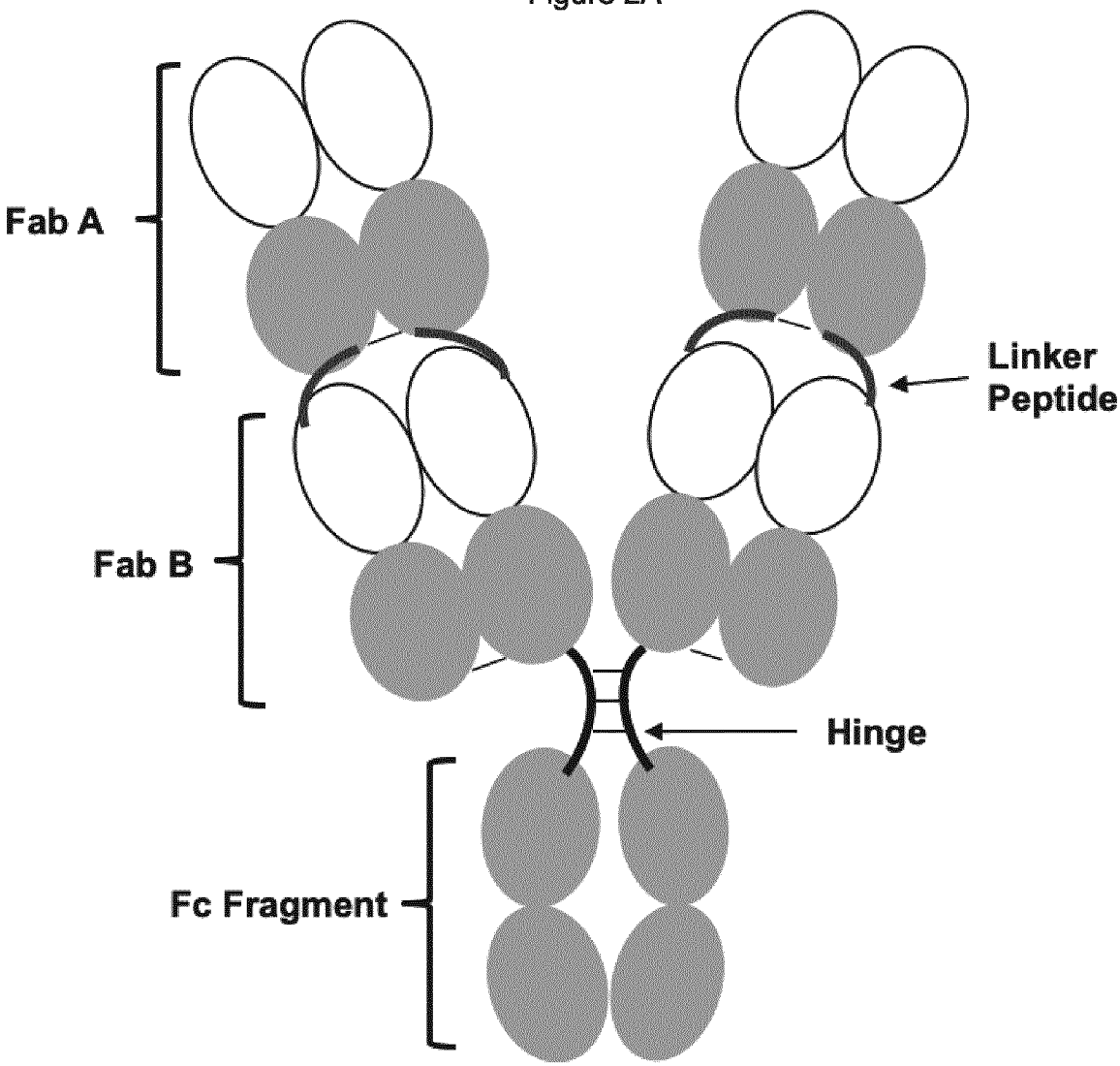


Figure 2B

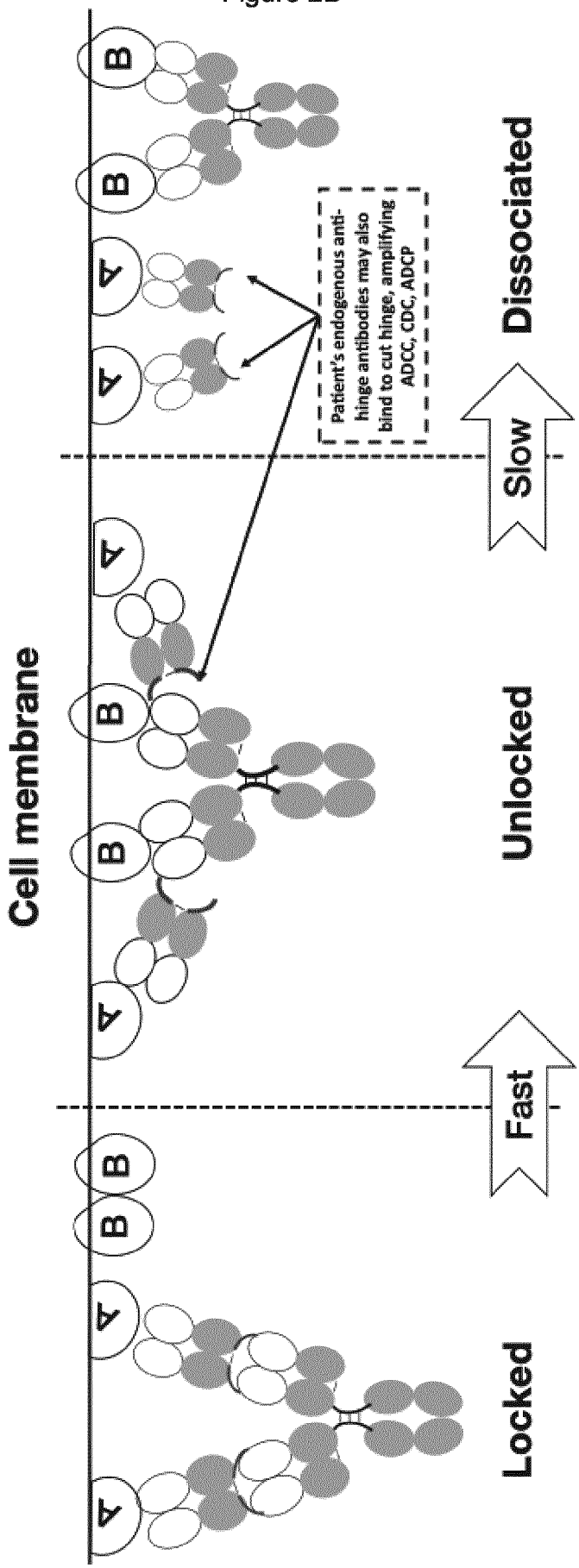

Cell membrane
Locked
Fast
Unlocked
Slow
Dissociated
Patient's endogenous anti-hinge antibodies may also bind to cut hinge, amplifying ADCC, CDC, ADCP

Figure 3A

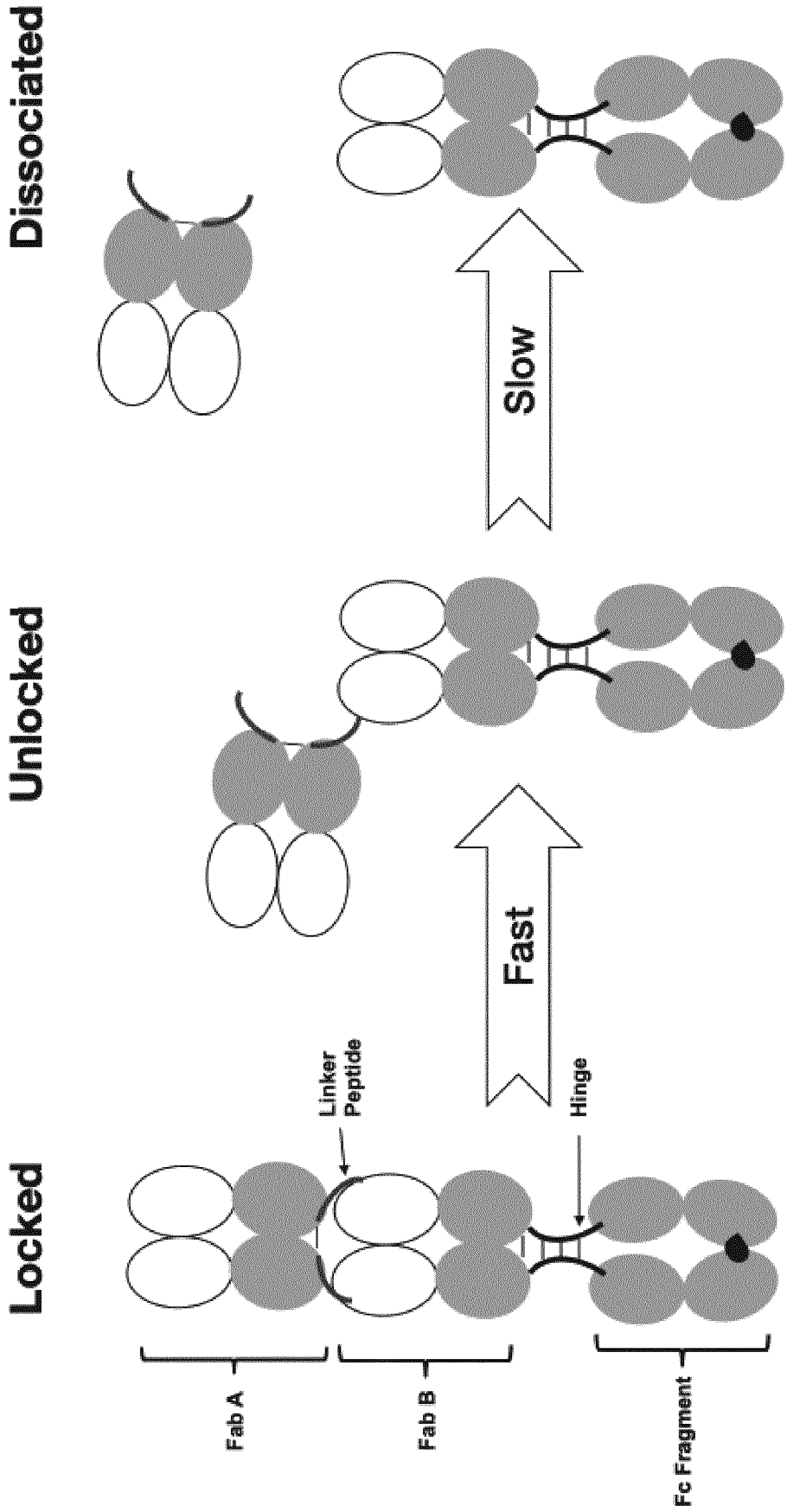

Dissociated
Slow
Unlocked
Fast
Locked
Linker Peptide
Hinge
Fab A
Fab B
Fc Fragment

Figure 3B

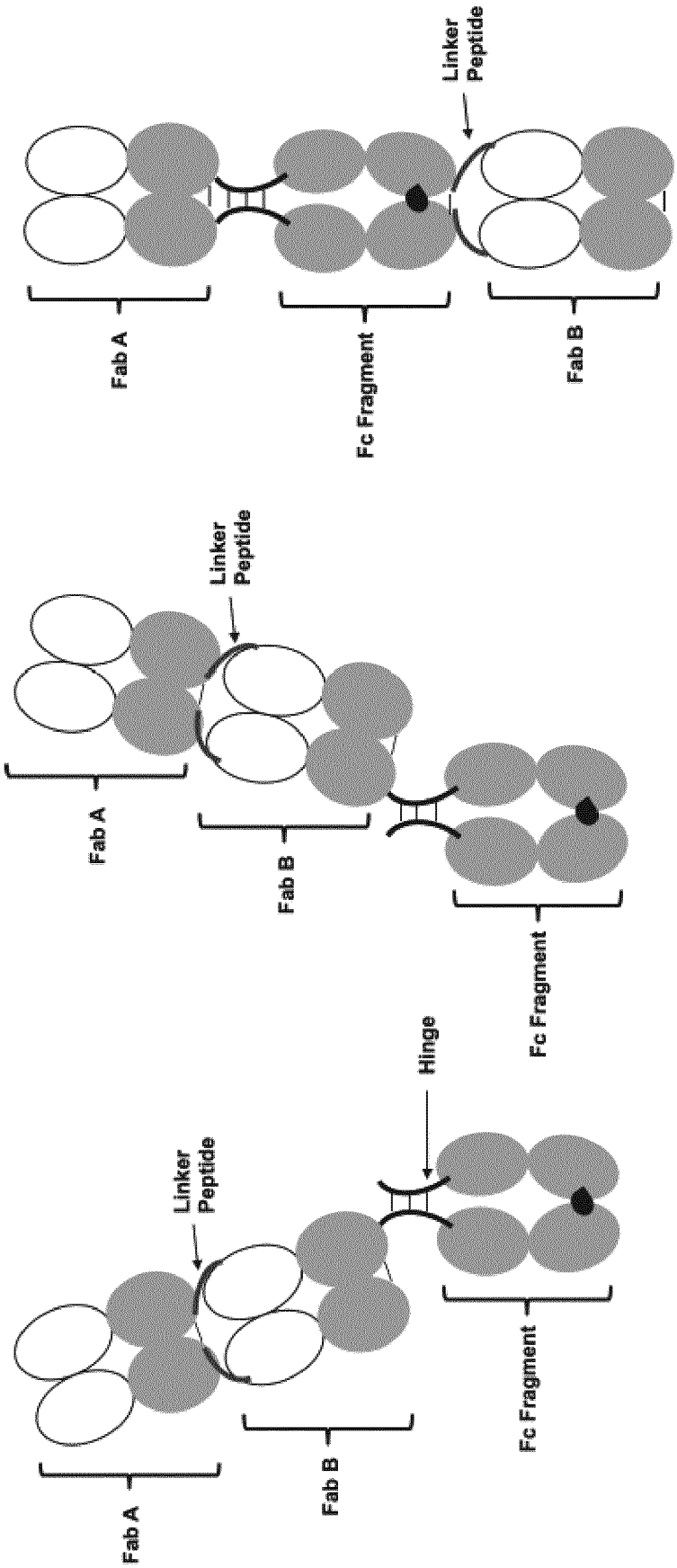

Linker Peptide
Fab A
Fc Fragment
Fab B
Linker Peptide
Fab A
Fab B
Fc Fragment
Hinge
Linker Peptide
Fab A
Fab B
Fc Fragment

Figure 4

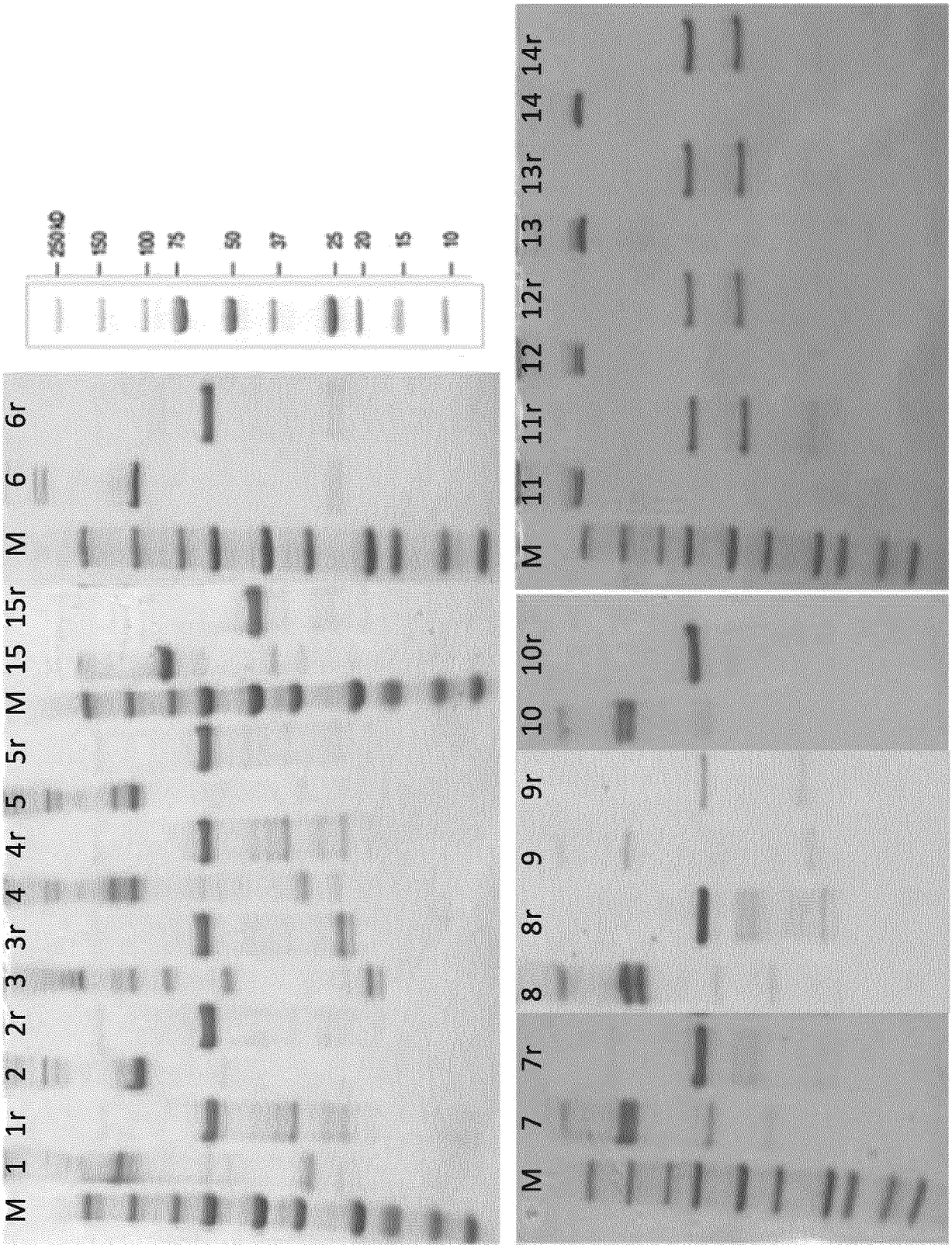

250 kb
150
100
75
50
35
25
20
15
10
M 1 1r 2 2r 3 3r 4 4r 5 5r M 15 15r 6 6r
M 7 7r 8 8r 9 9r 10 10r
M 11 11r 12 12r 13 13r 14 14r

Figure 5A

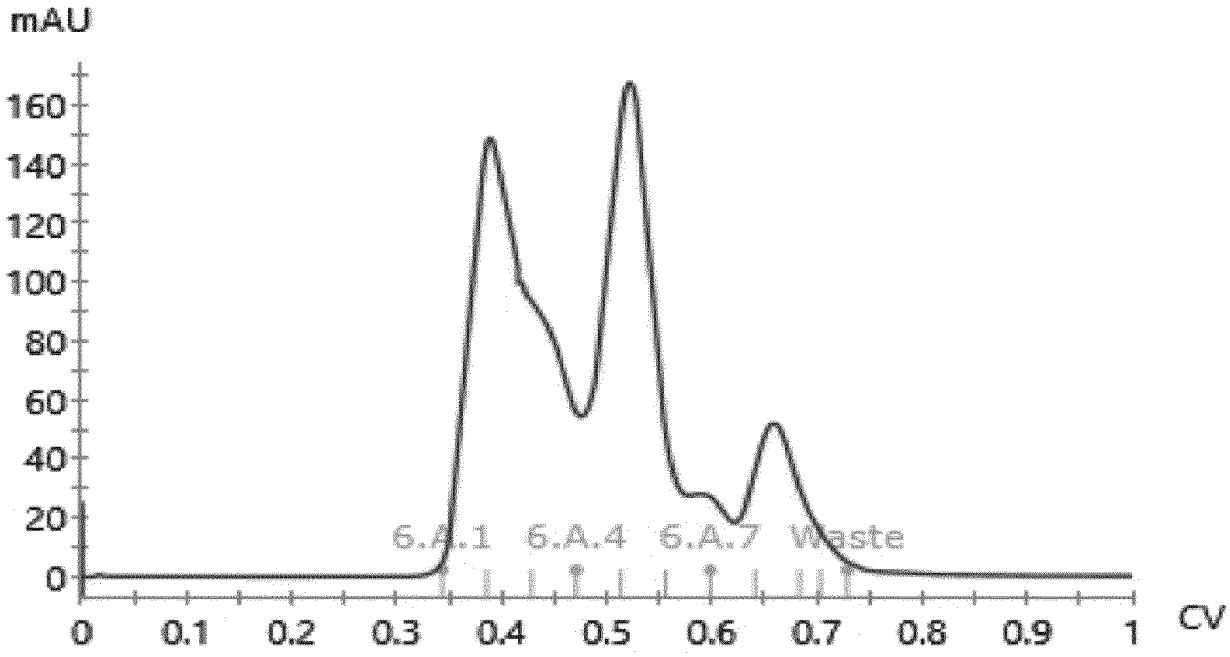

mAU
160
140
120
100
80
60
40
20
0
6.A.1
6.A.4
6.A.7
Waste
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
CV

Figure 5B

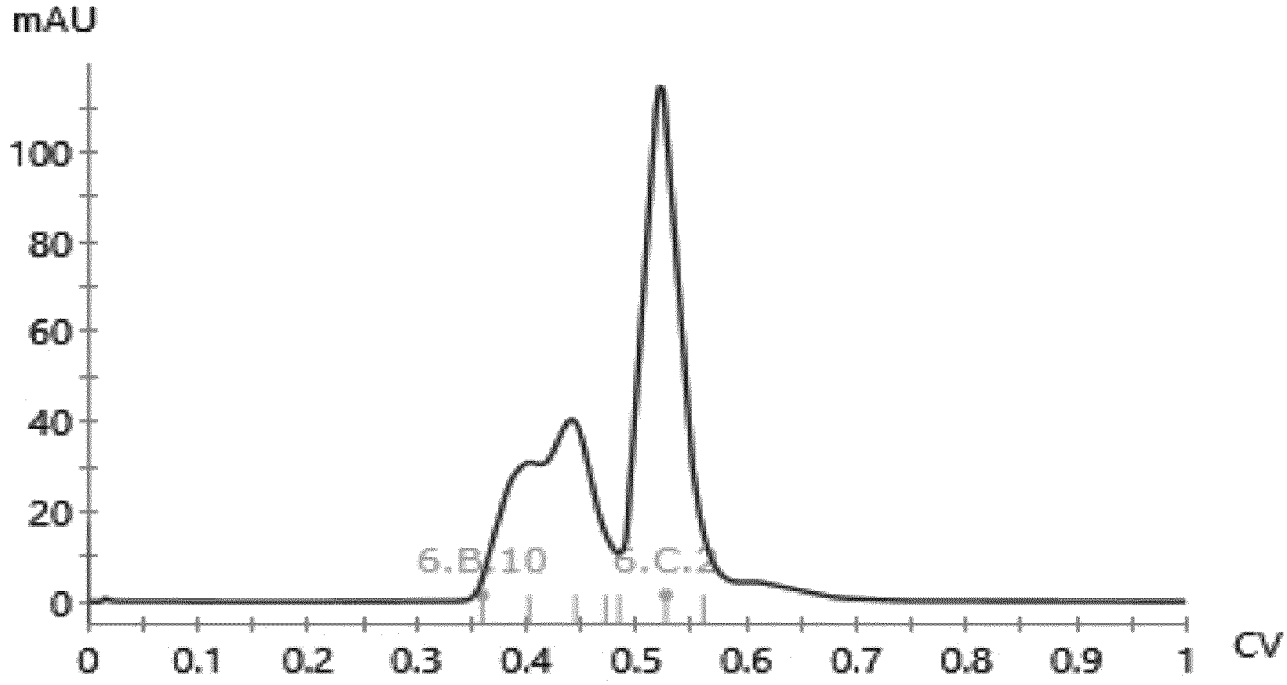


Figure 5C

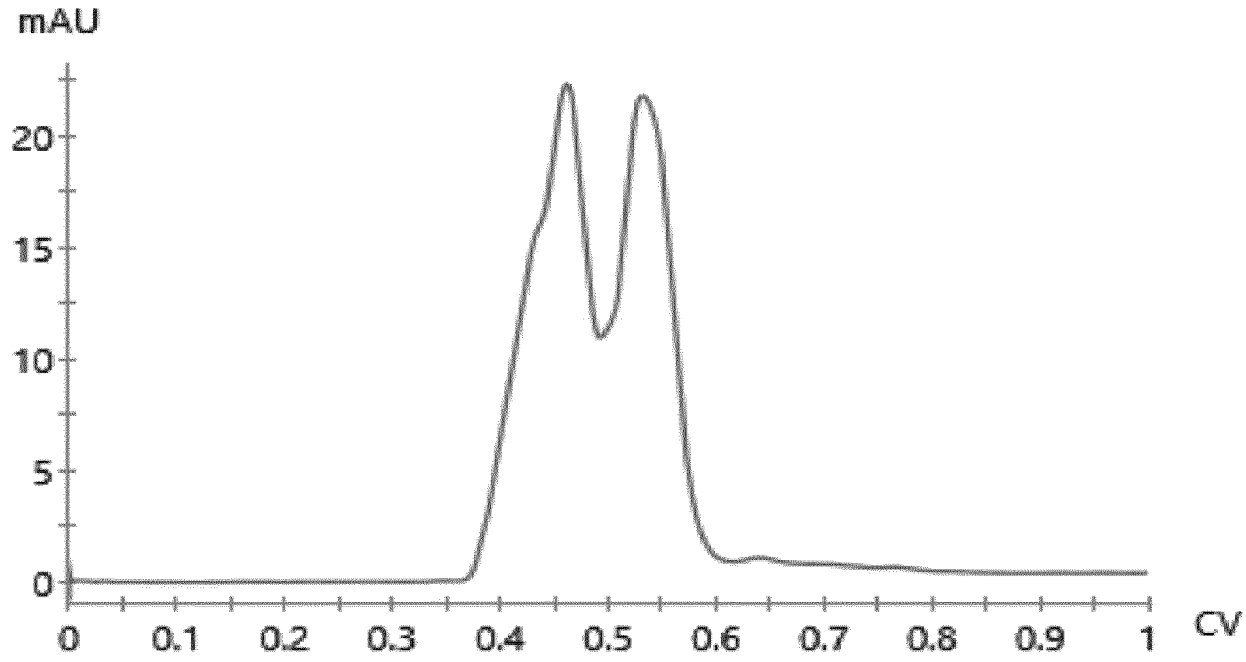


Figure 5D

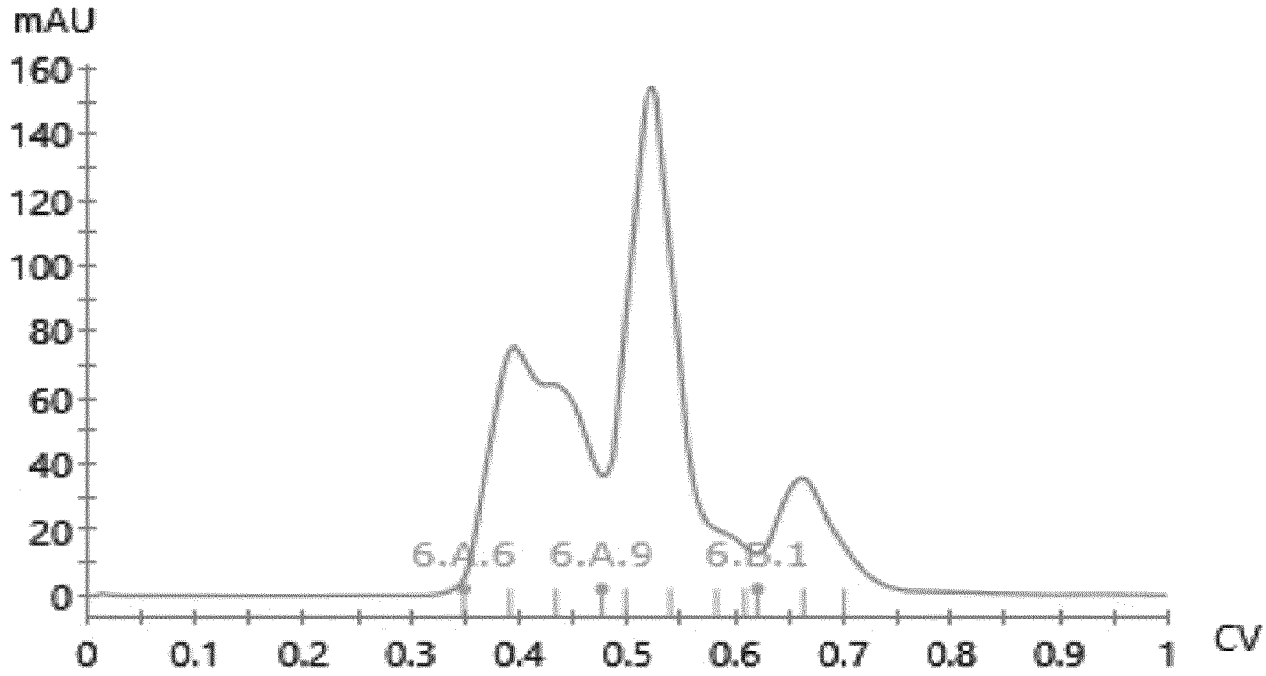

mAU
160
140
120
100
80
60
40
20
0
6.A.6
6.A.9
6.B.1
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
CV

Figure 5E

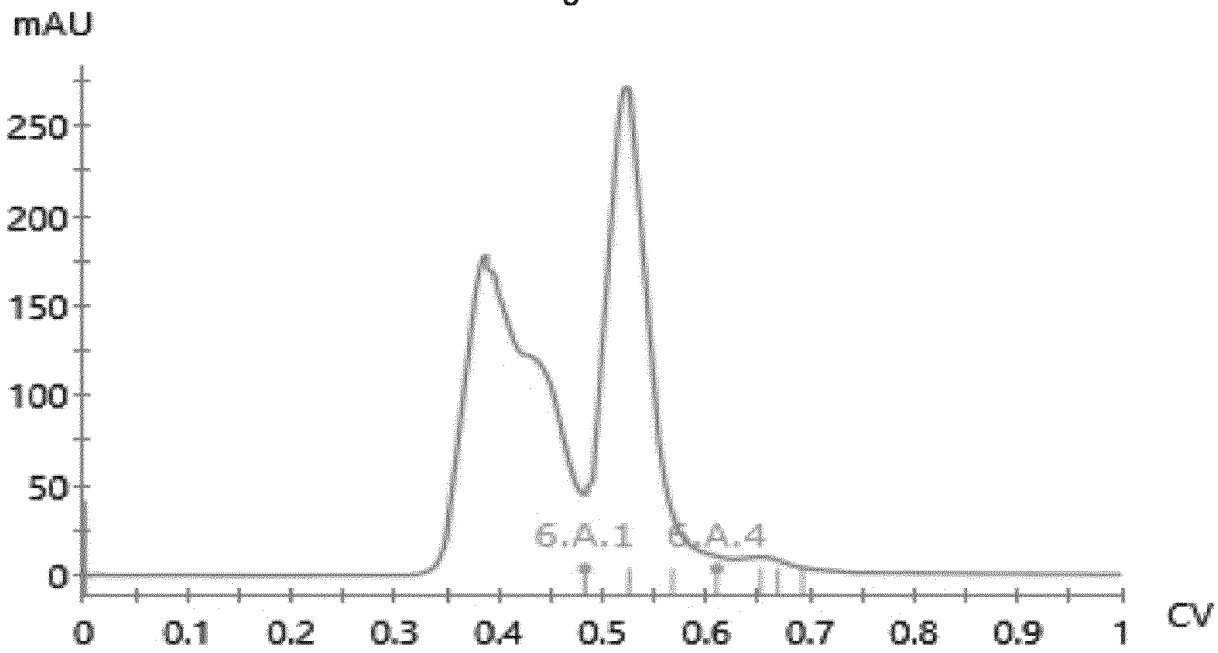


Figure 5F

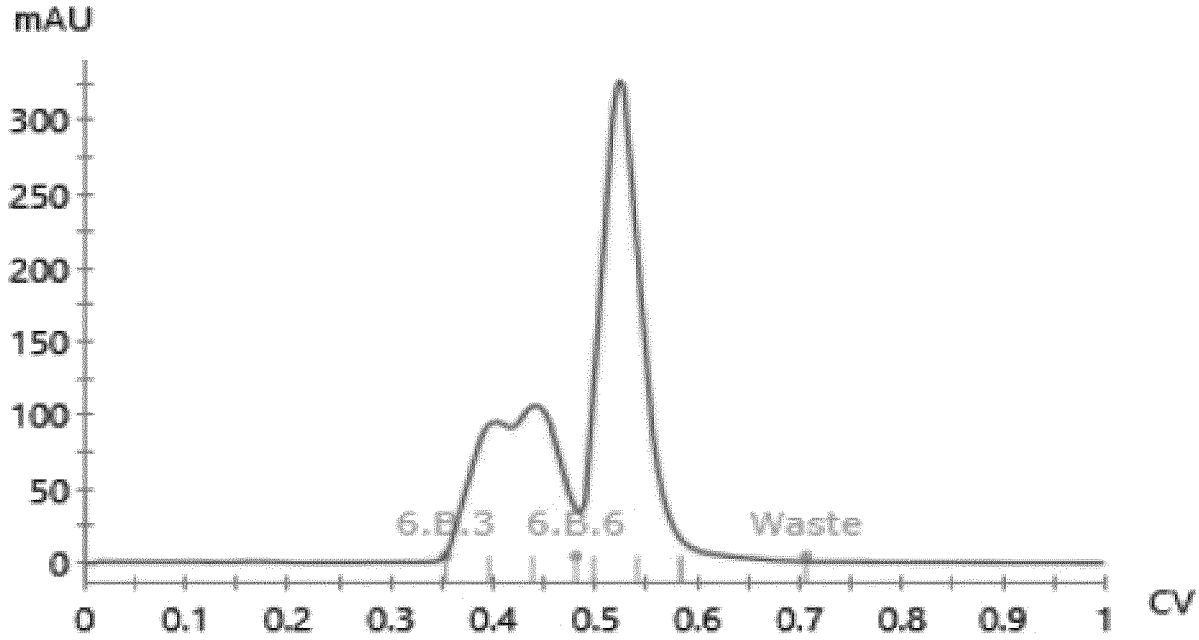

mAU
300
250
200
150
100
50
0
6.B.3
6.B.6
Waste
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
CV

Figure 5G

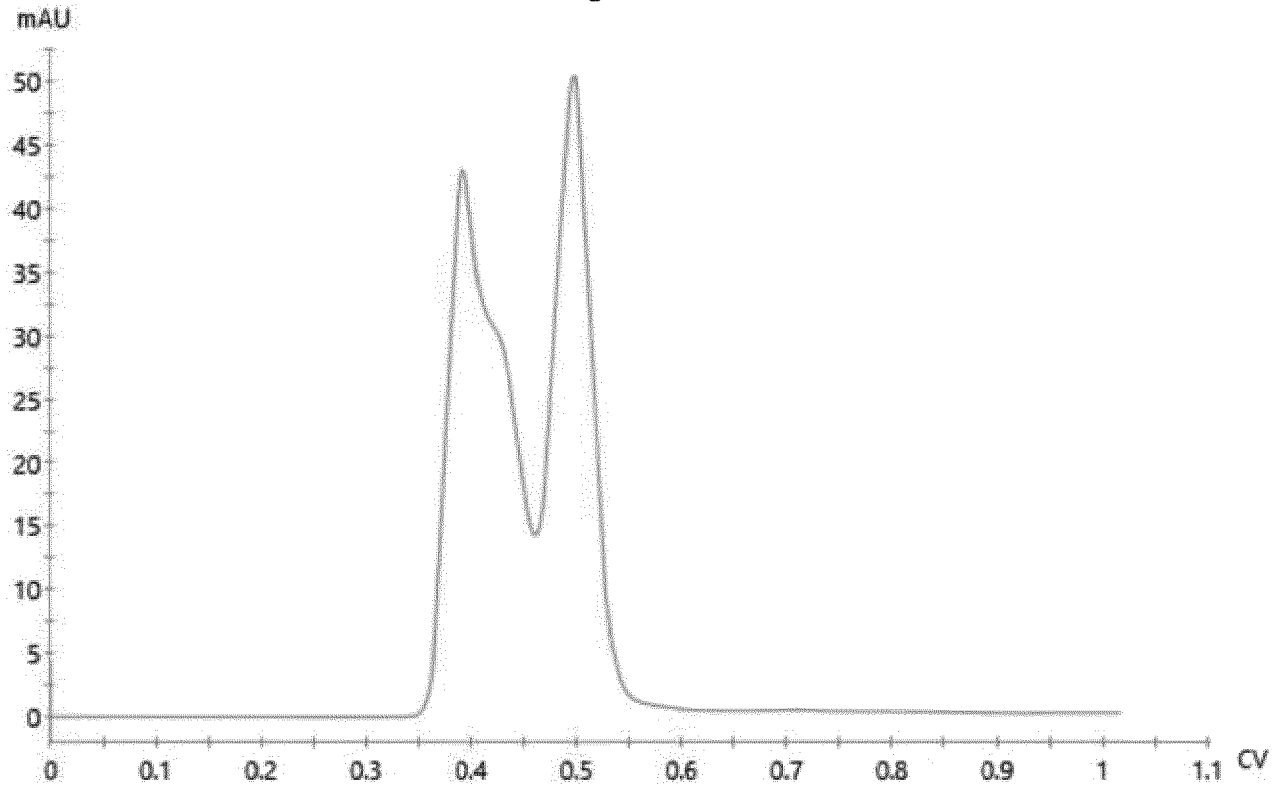


Figure 5H

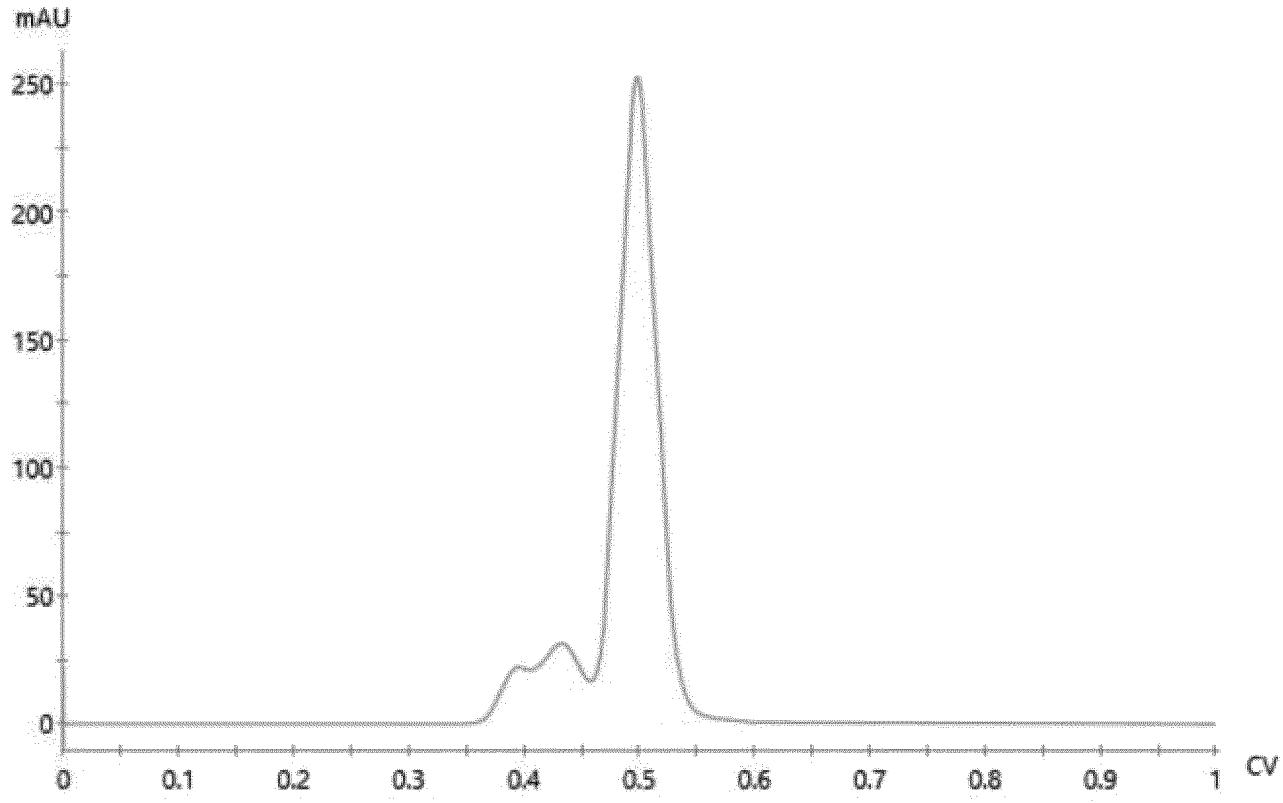


Figure 5l

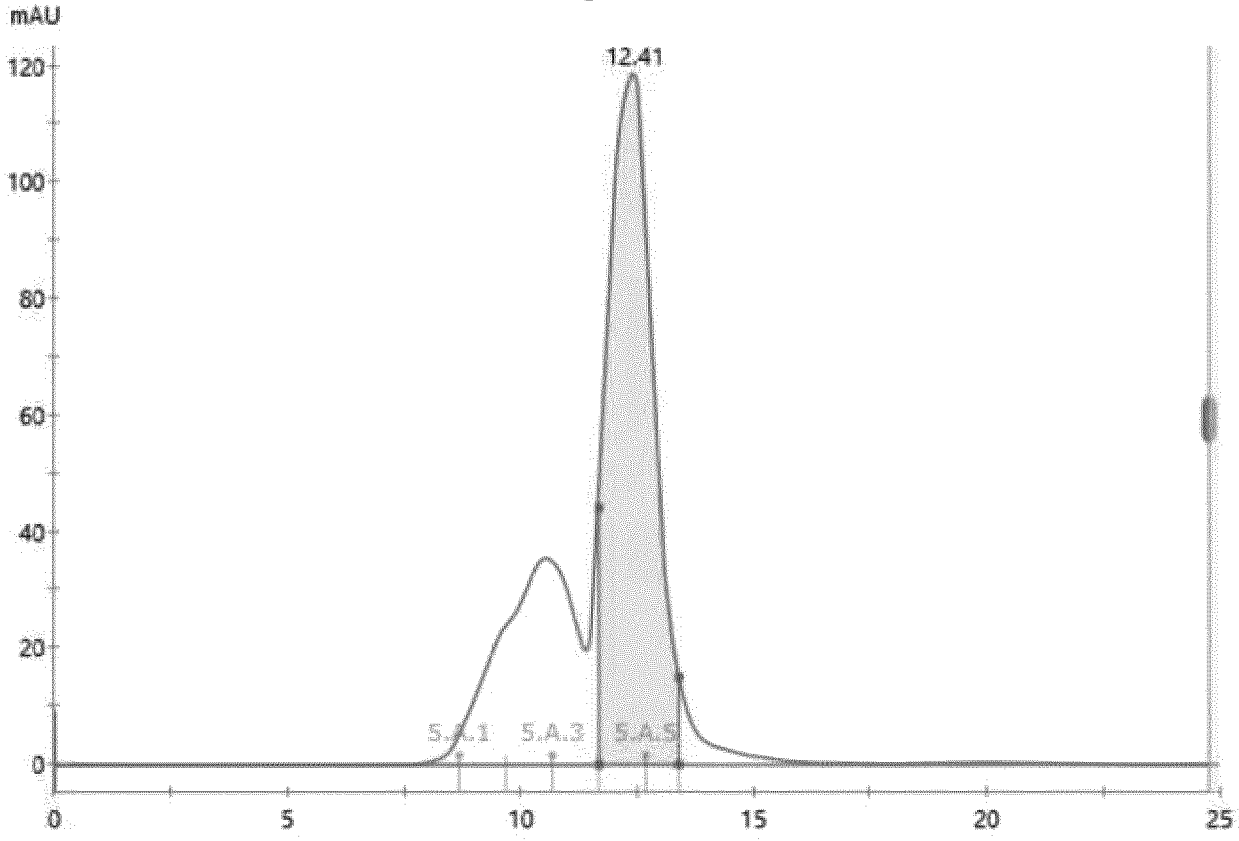


Figure 6A

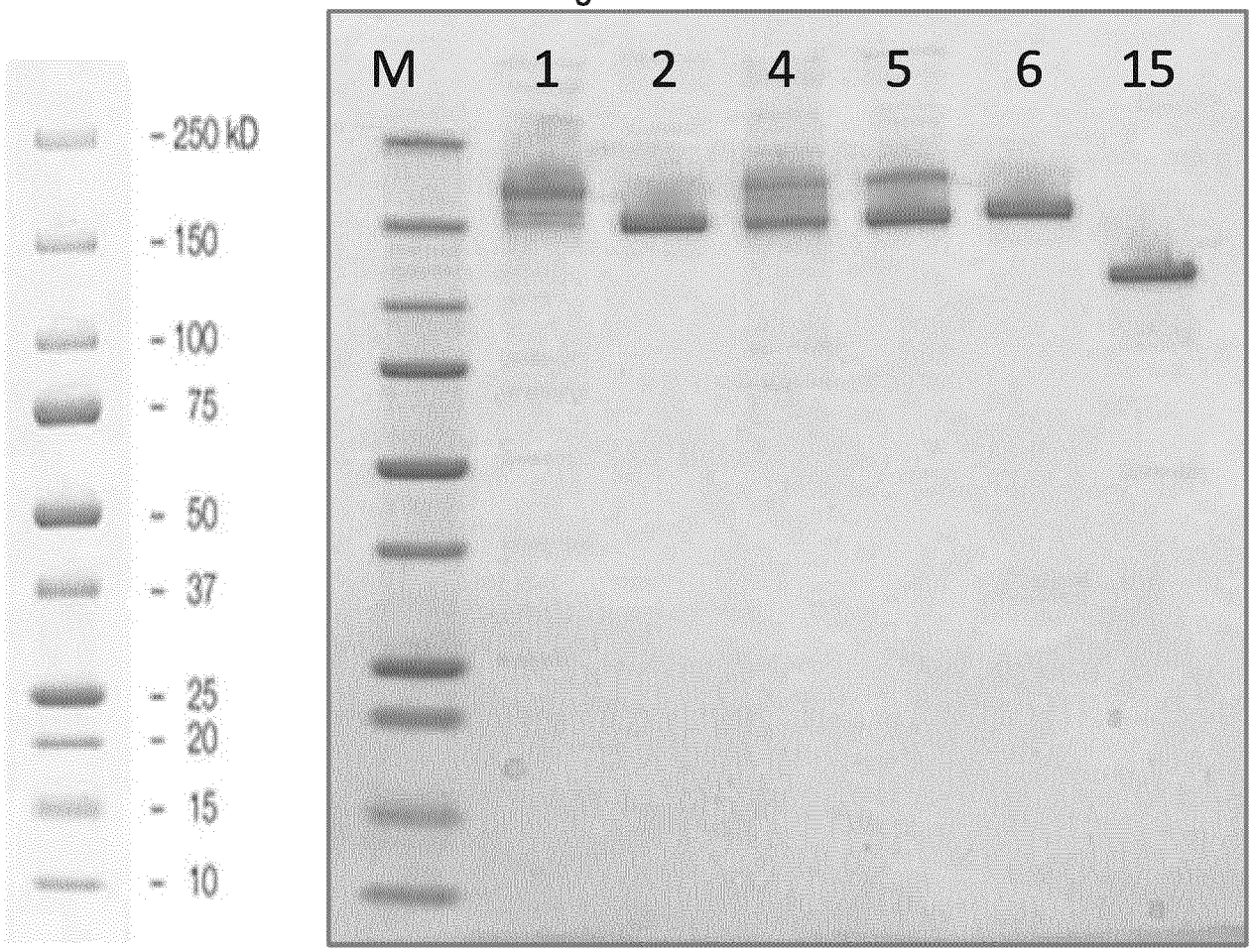


Figure 6B

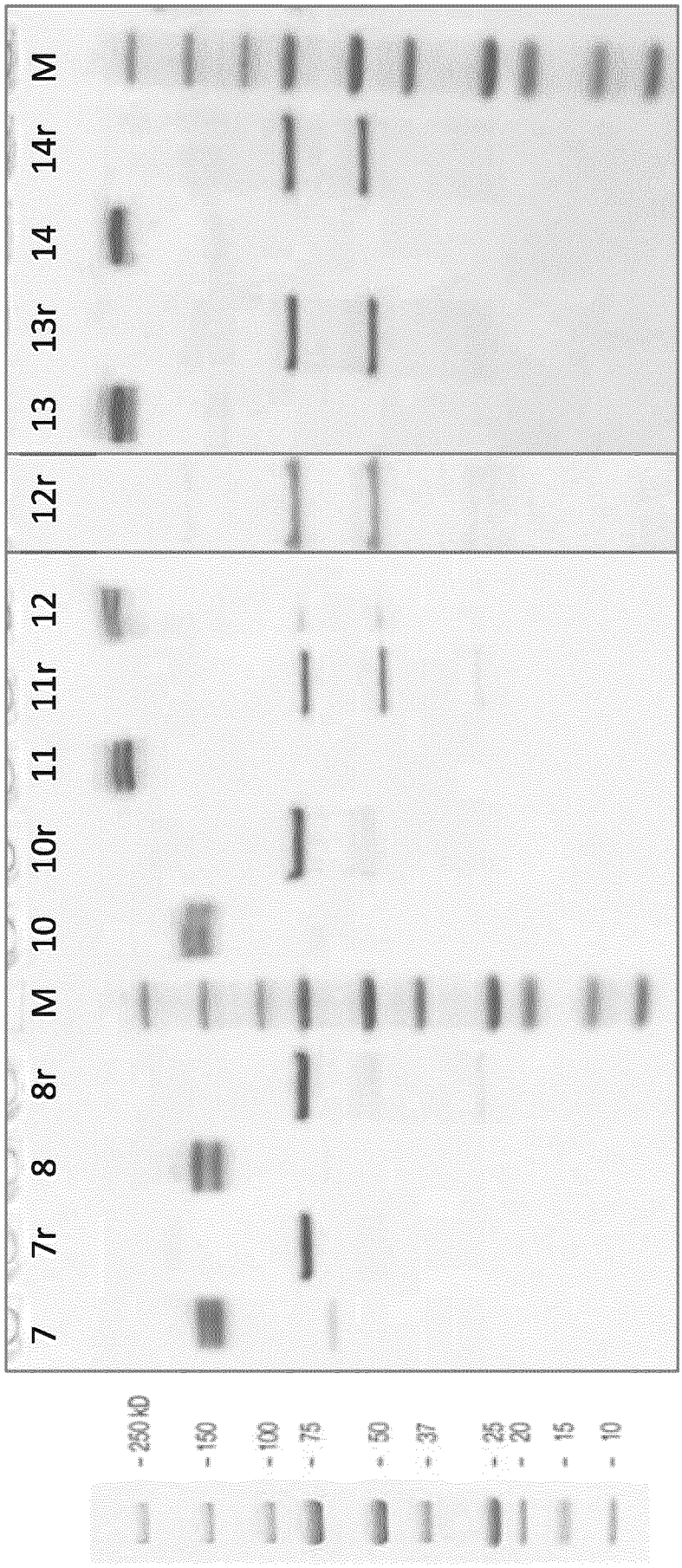

M
14r
14
13r
13
12r
12
11r
11
10r
10
M
8r
8
7r
7
250 kD
150
100
75
50
37
25
20
15
10

Figure 7A

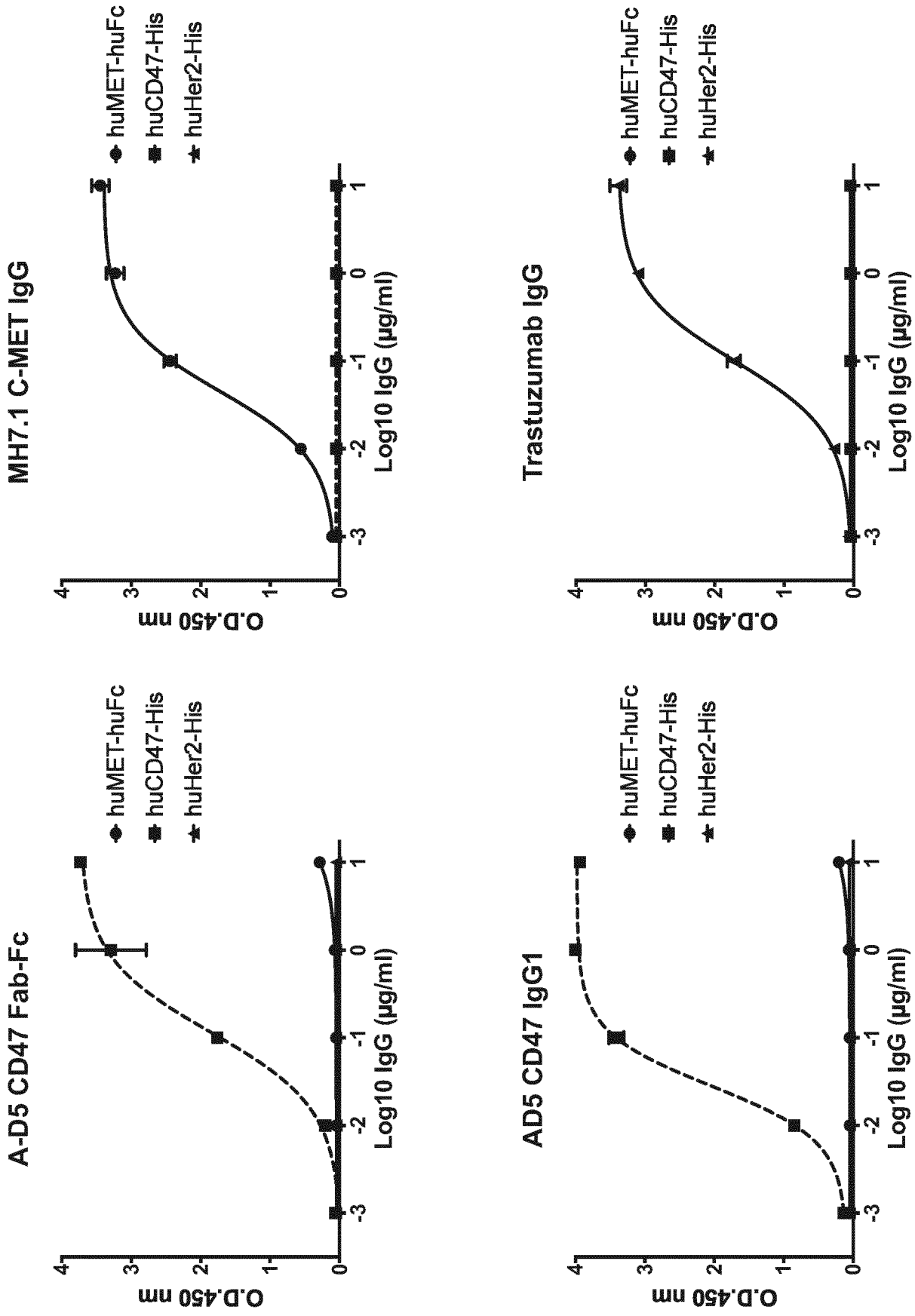

MH7.1 C-MET IgG
Trastuzumab IgG
A-D5 CD47 Fab-Fc
AD5 CD47 IgG1
huMET-huFc
huCD47-His
huHer2-His
O.D.450 nm
Log10 IgG (µg/ml)
0
1
2
3
4
-3
-2
-1
0
1

Figure 7B

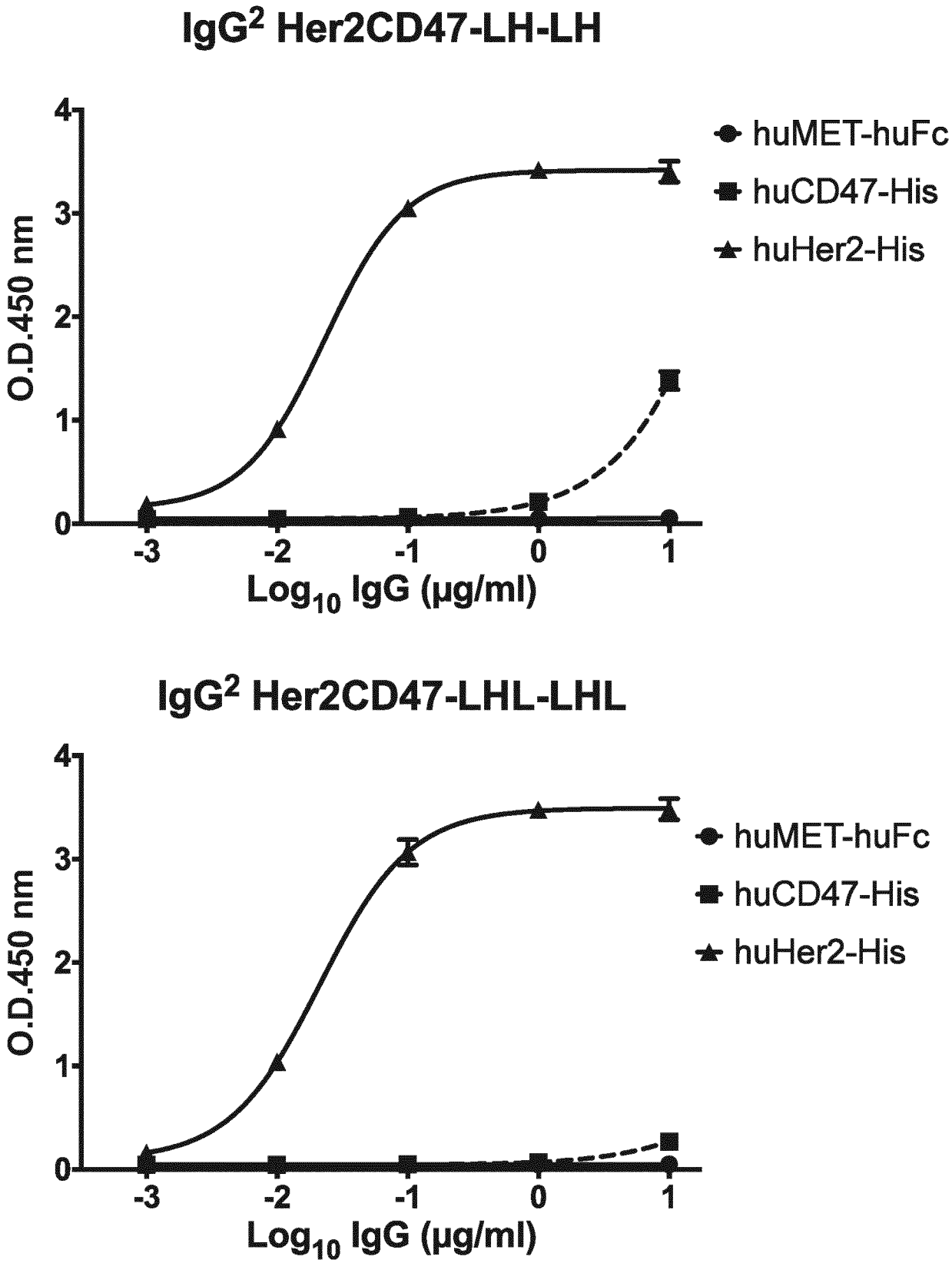

IgG2 Her2CD47-LH-LH
O.D.450 nm
4
3
2
1
0
-3
-2
-1
0
1
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His
IgG2 Her2CD47-LHL-LHL
O.D.450 nm
4
3
2
1
0
-3
-2
-1
0
1
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His

Figure 7C

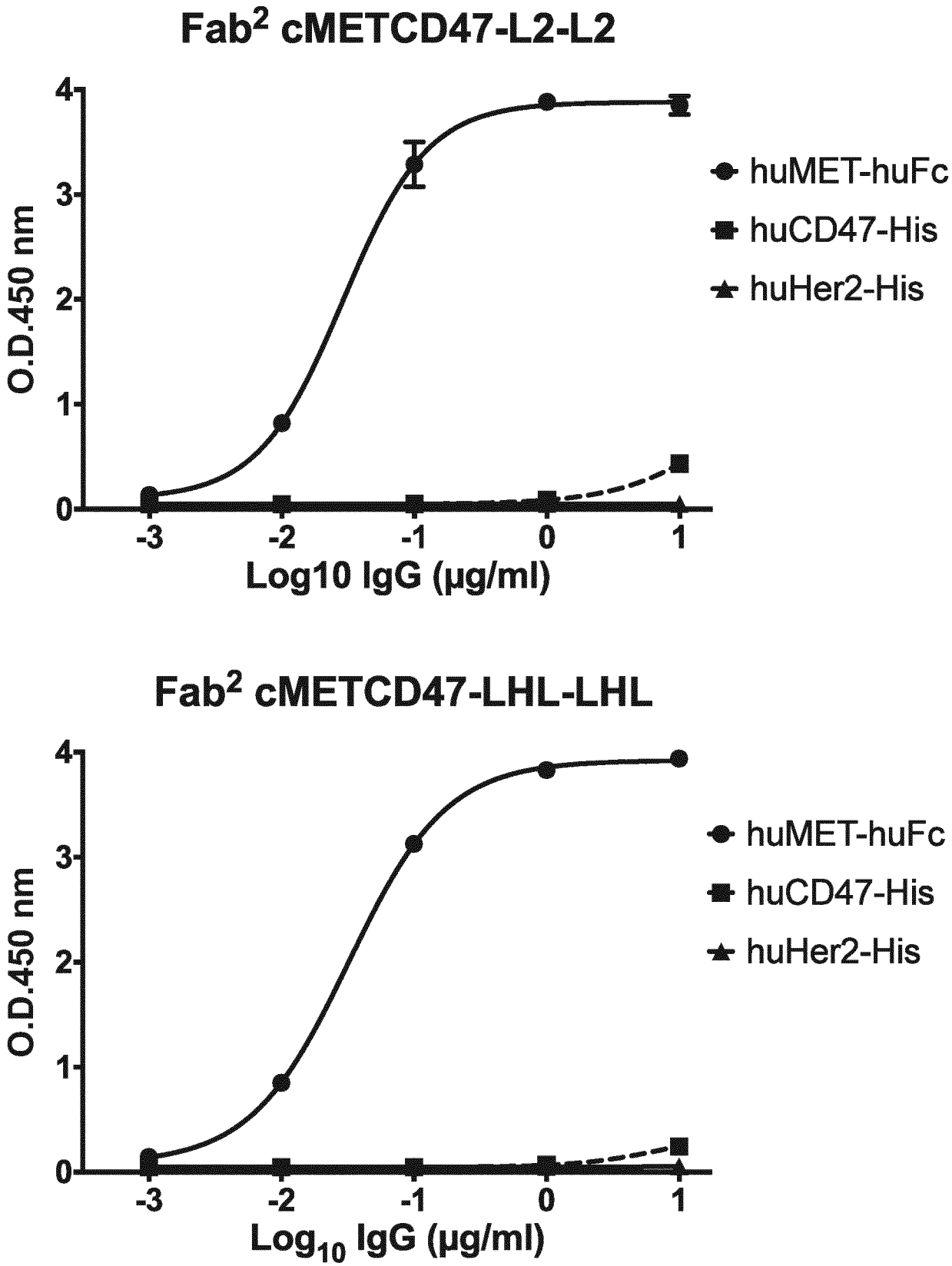

Fab2 cMETCD47-L2-L2
O.D.450 nm
0
1
2
3
4
-3
-2
-1
0
1
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His
Fab2 cMETCD47-LHL-LHL
O.D.450 nm
0
1
2
3
4
-3
-2
-1
0
1
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His

Figure 8A

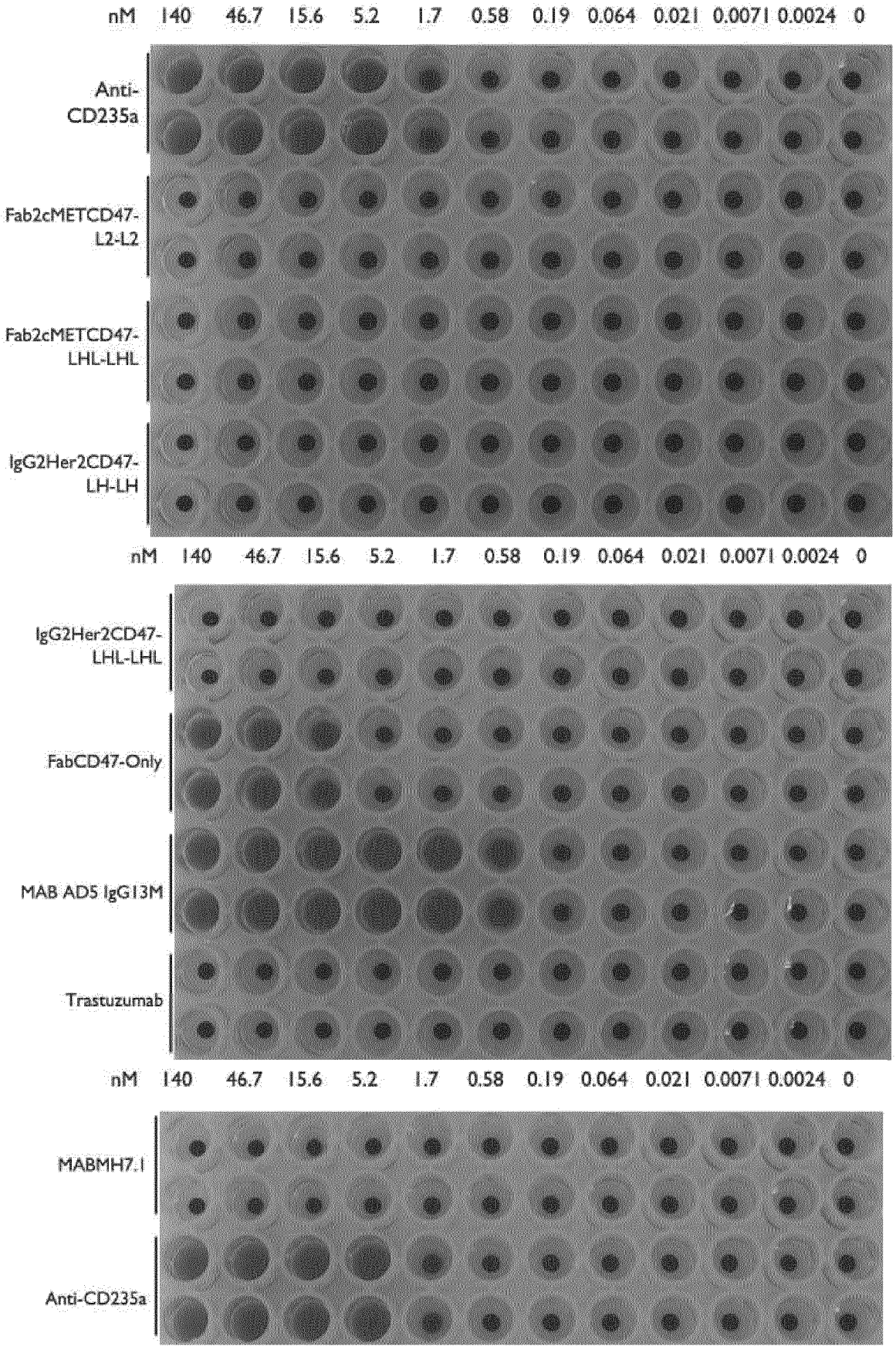

nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
Anti-CD235a
Fab2cMETCD47-L2-L2
Fab2cMETCD47-LHL-LHL
IgG2Her2CD47-LH-LH
nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
IgG2Her2CD47-LHL-LHL
FabCD47-Only
MAB AD5 IgG13M
Trastuzumab
nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
MABMH7.1
Anti-CD235a

Figure 8B

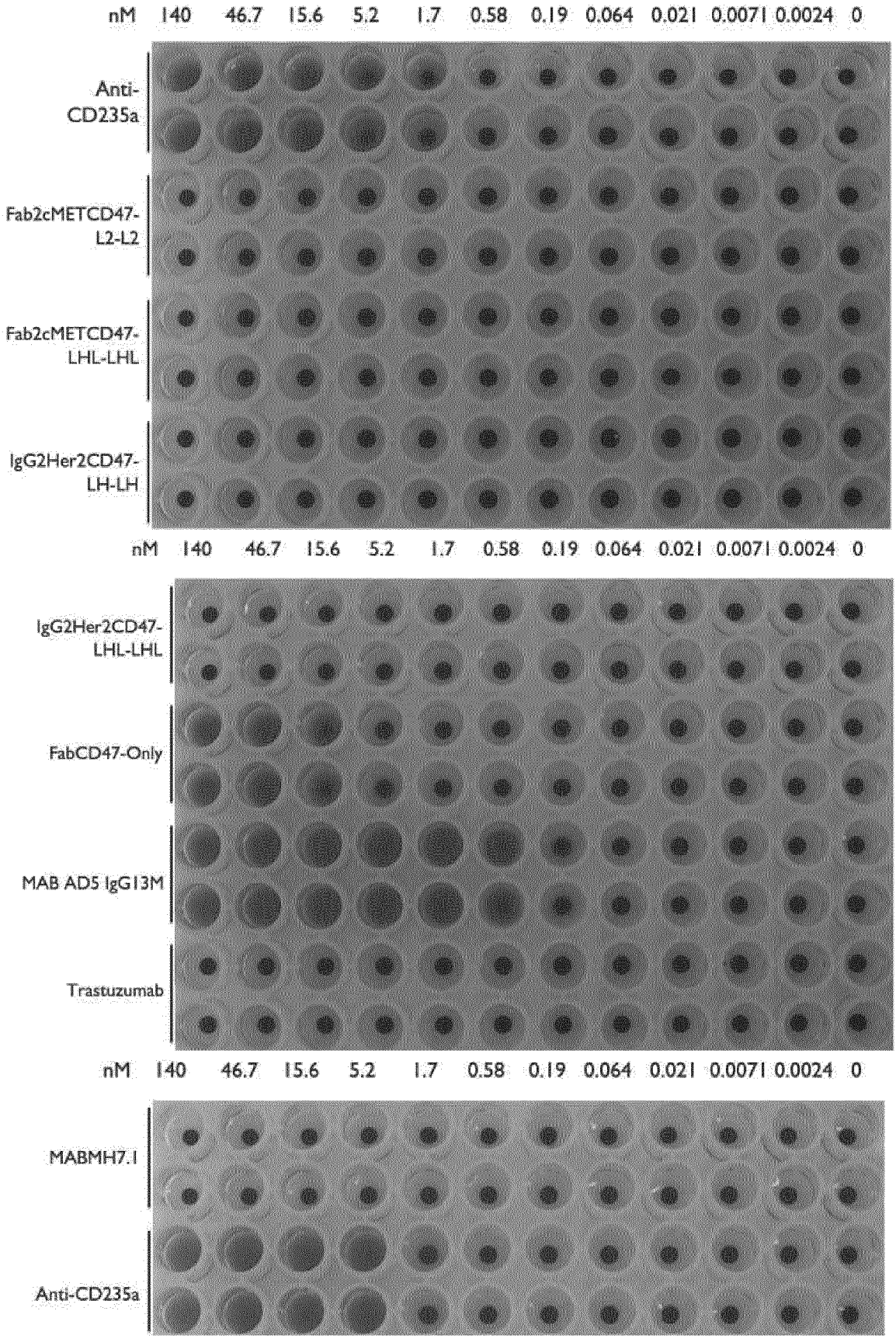

nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
Anti-CD235a
Fab2cMETCD47-L2-L2
Fab2cMETCD47-LHL-LHL
IgG2Her2CD47-LH-LH
nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
IgG2Her2CD47-LHL-LHL
FabCD47-Only
MAB AD5 IgG13M
Trastuzumab
nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
MABMH7.1
Anti-CD235a

Figure 8C

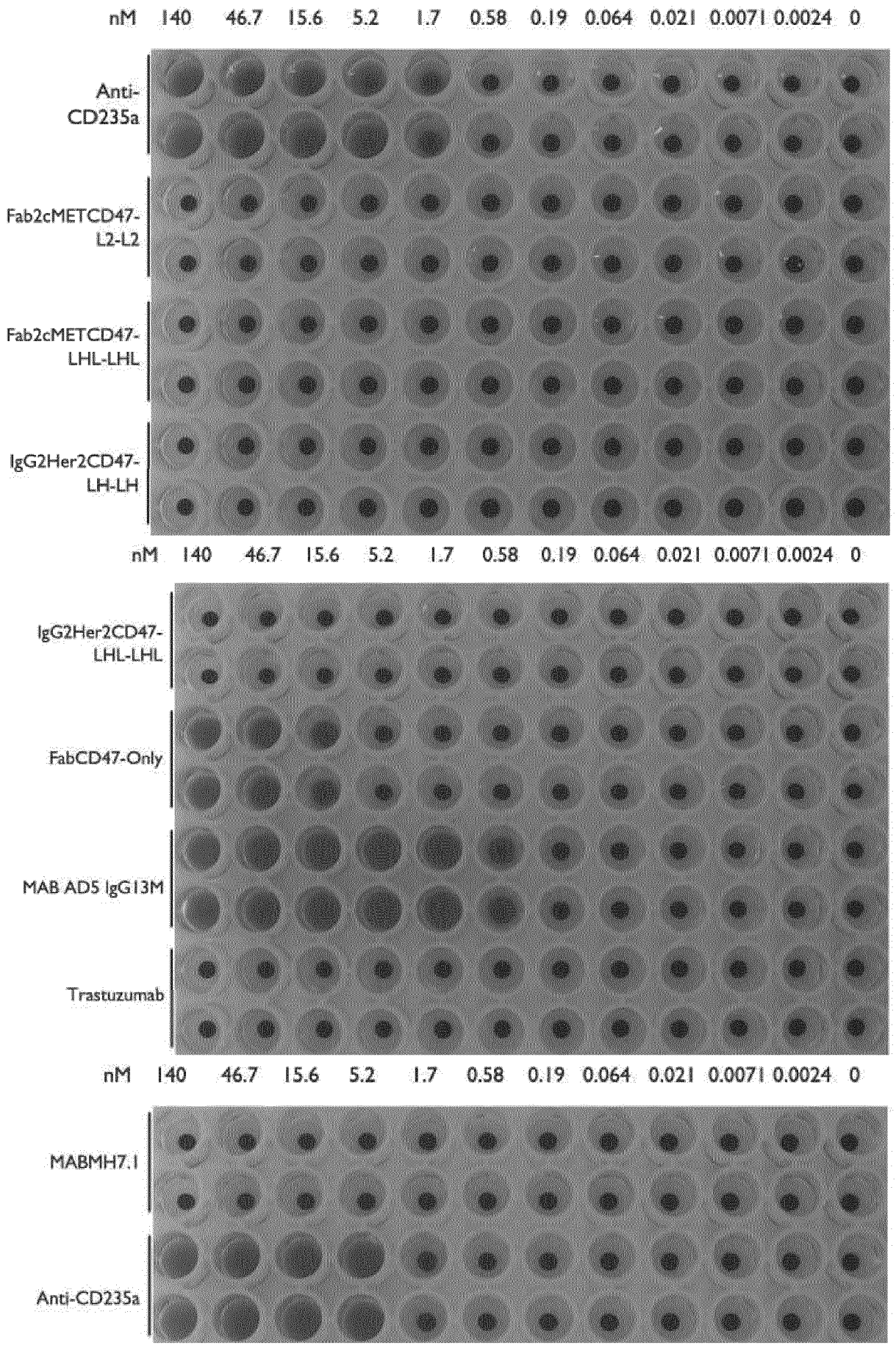

nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
Anti-CD235a
Fab2cMETCD47-L2-L2
Fab2cMETCD47-LHL-LHL
IgG2Her2CD47-LH-LH
nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
IgG2Her2CD47-LHL-LHL
FabCD47-Only
MAB AD5 IgG13M
Trastuzumab
nM 140 46.7 15.6 5.2 1.7 0.58 0.19 0.064 0.021 0.0071 0.0024 0
MABMH7.1
Anti-CD235a

Figure 9A

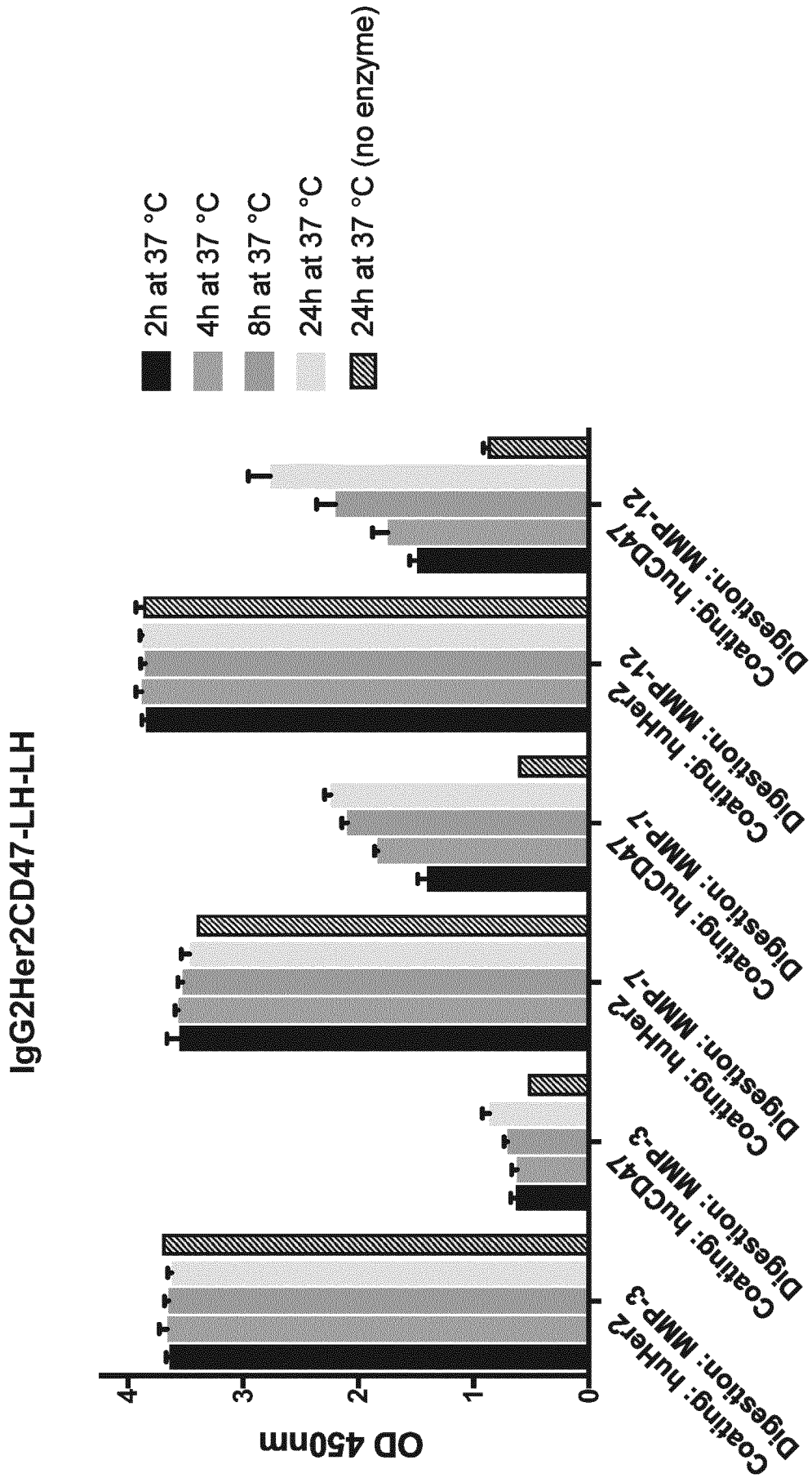

2h at 37 °C
4h at 37 °C
8h at 37 °C
24h at 37 °C
24h at 37 °C (no enzyme)
IgG2Her2CD47-LH-LH
OD 450nm
0
1
2
3
4
Coating: huHer2
Digestion: MMP-3
Coating: huCD47
Digestion: MMP-3
Coating: huHer2
Digestion: MMP-7
Coating: huCD47
Digestion: MMP-7
Coating: huHer2
Digestion: MMP-12
Coating: huCD47
Digestion: MMP-12

Figure 9B

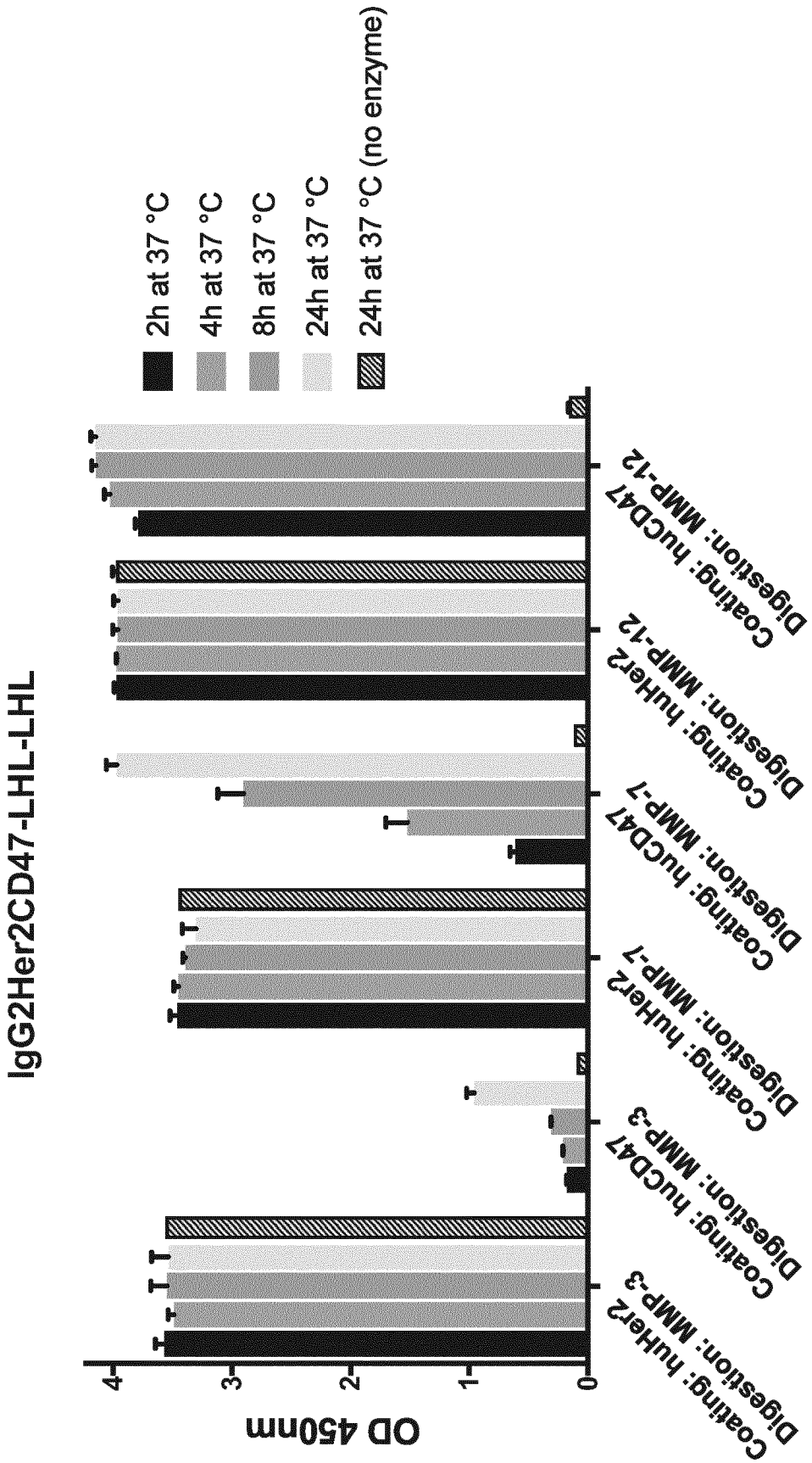

IgG2Her2CD47-LHL-LHL
OD 450nm
0
1
2
3
4
2h at 37 °C
4h at 37 °C
8h at 37 °C
24h at 37 °C
24h at 37 °C (no enzyme)
Coating: huCD47
Digestion: MMP-12
Coating: huHer2
Digestion: MMP-12
Coating: huCD47
Digestion: MMP-7
Coating: huHer2
Digestion: MMP-7
Coating: huCD47
Digestion: MMP-3
Coating: huHer2
Digestion: MMP-3

Figure 9C

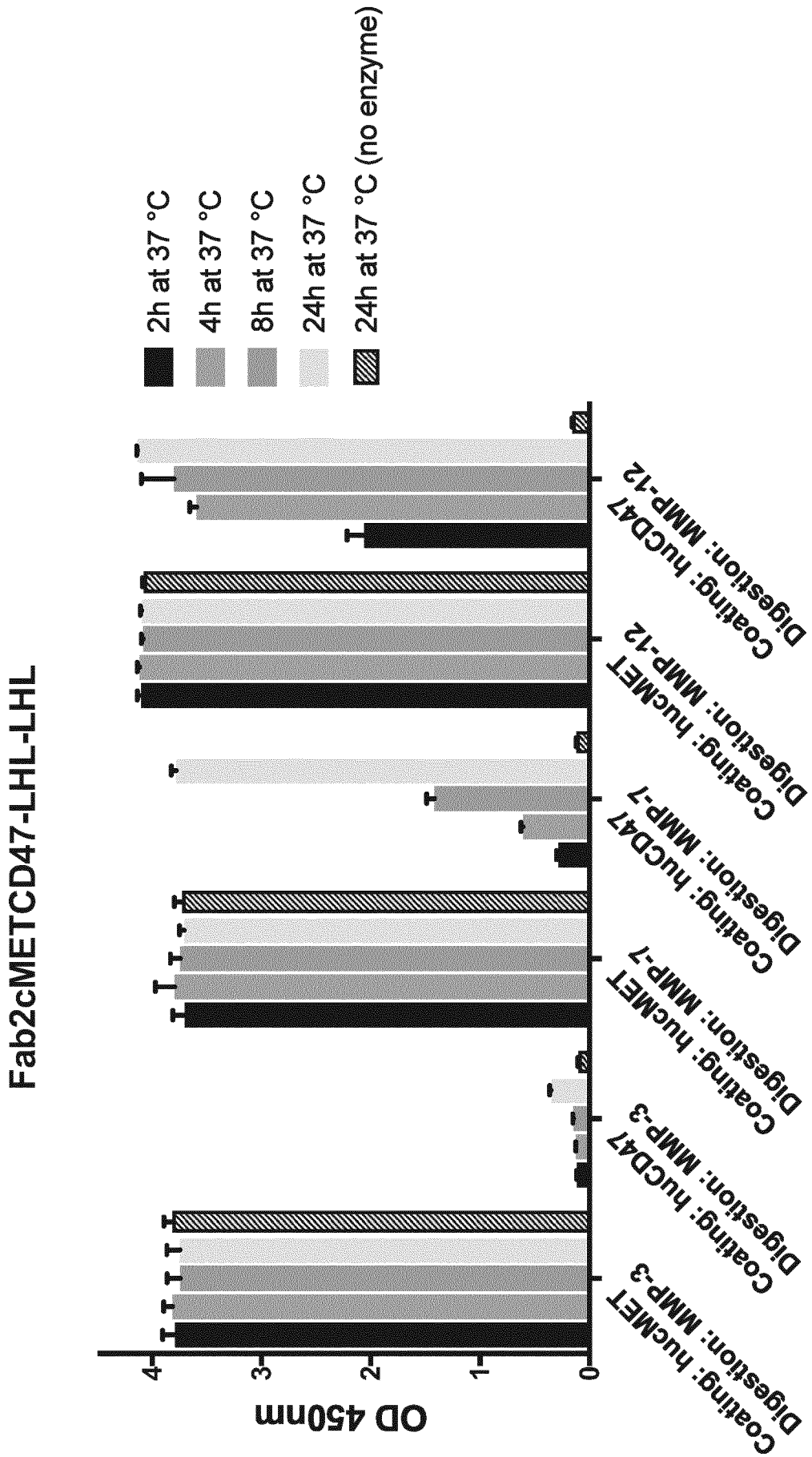

Fab2cMETCD47-LHL-LHL
OD 450nm
0
1
2
3
4
2h at 37 °C
4h at 37 °C
8h at 37 °C
24h at 37 °C
24h at 37 °C (no enzyme)
Coating: huCMET
Digestion: MMP-3
Coating: huCD47
Digestion: MMP-3
Coating: huCMET
Digestion: MMP-7
Coating: huCD47
Digestion: MMP-7
Coating: huCMET
Digestion: MMP-12
Coating: huCD47
Digestion: MMP-12

Figure 10A

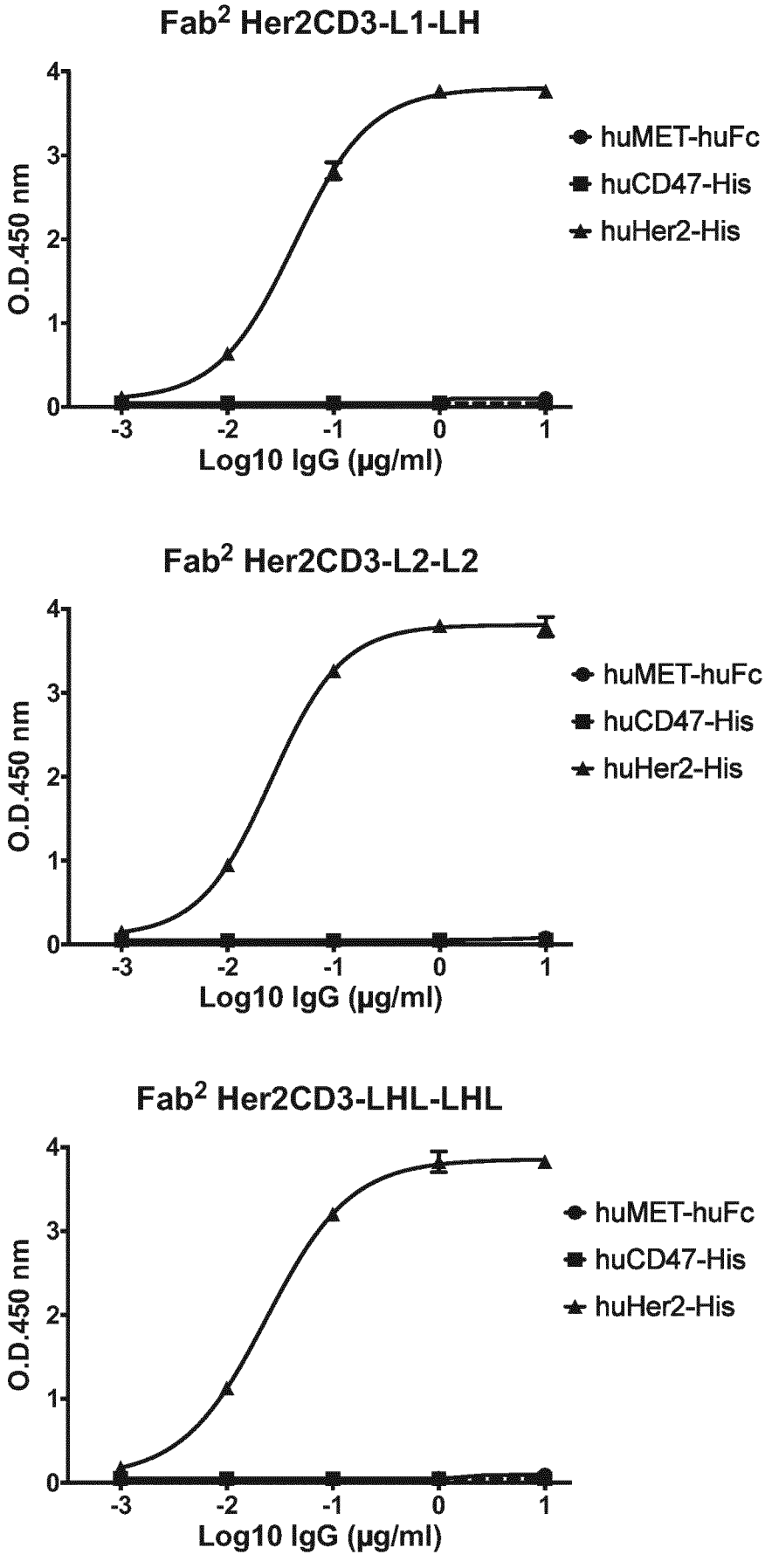

Fab2 Her2CD3-L1-LH
O.D.450 nm
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His
Fab2 Her2CD3-L2-L2
O.D.450 nm
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His
Fab2 Her2CD3-LHL-LHL
O.D.450 nm
Log10 IgG (µg/ml)
huMET-huFc
huCD47-His
huHer2-His

Figure 10B

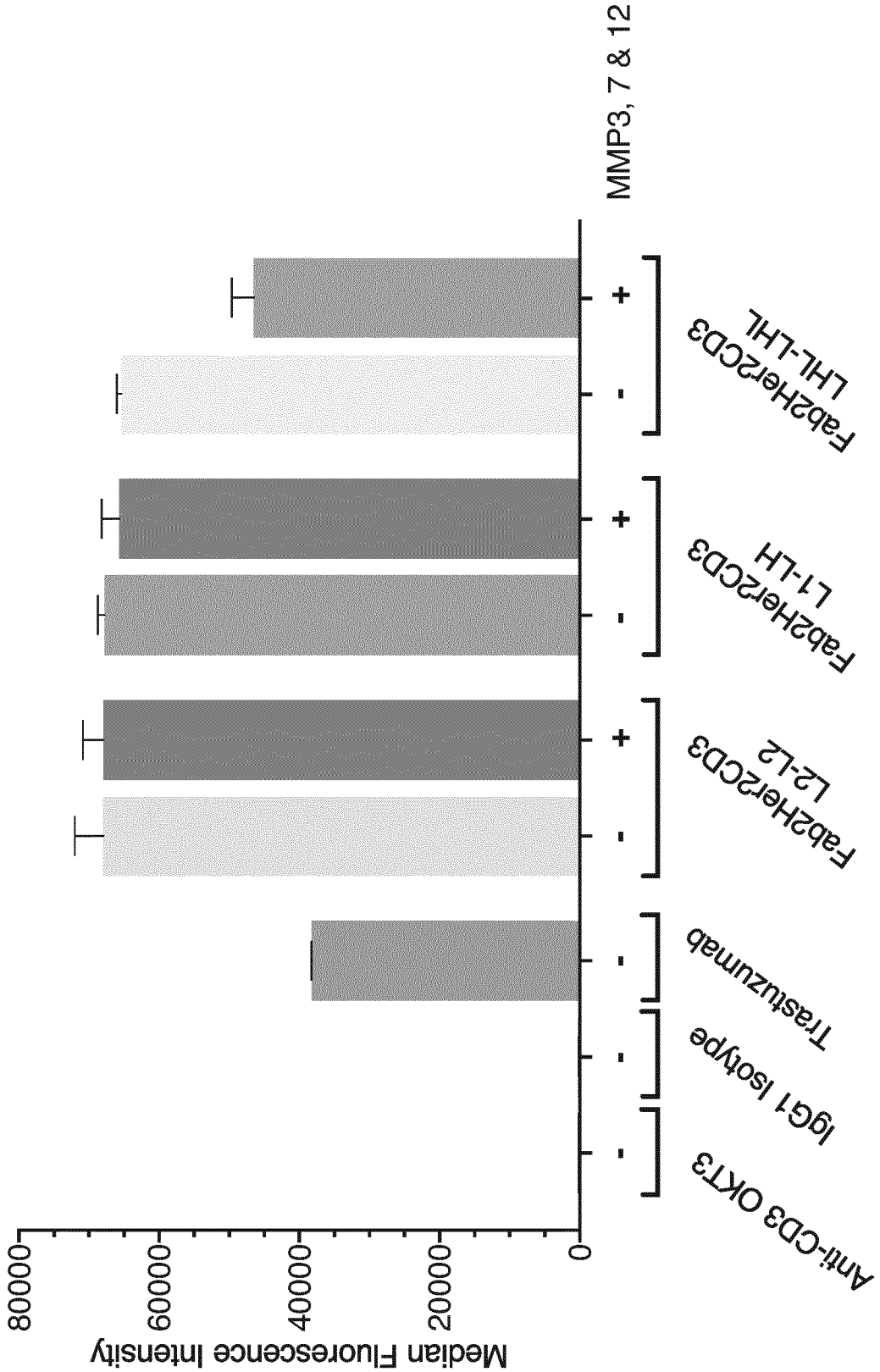

MMP3, 7 & 12
Median Fluorescence Intensity
80000
60000
40000
20000
0
Anti-CD3 OKT3
IgG1 isotype
Trastuzumab
Fab2Her2CD3 L2-L2
Fab2Her2CD3 L1-LH
Fab2Her2CD3 LHL-LHL
+
-

Figure 10C

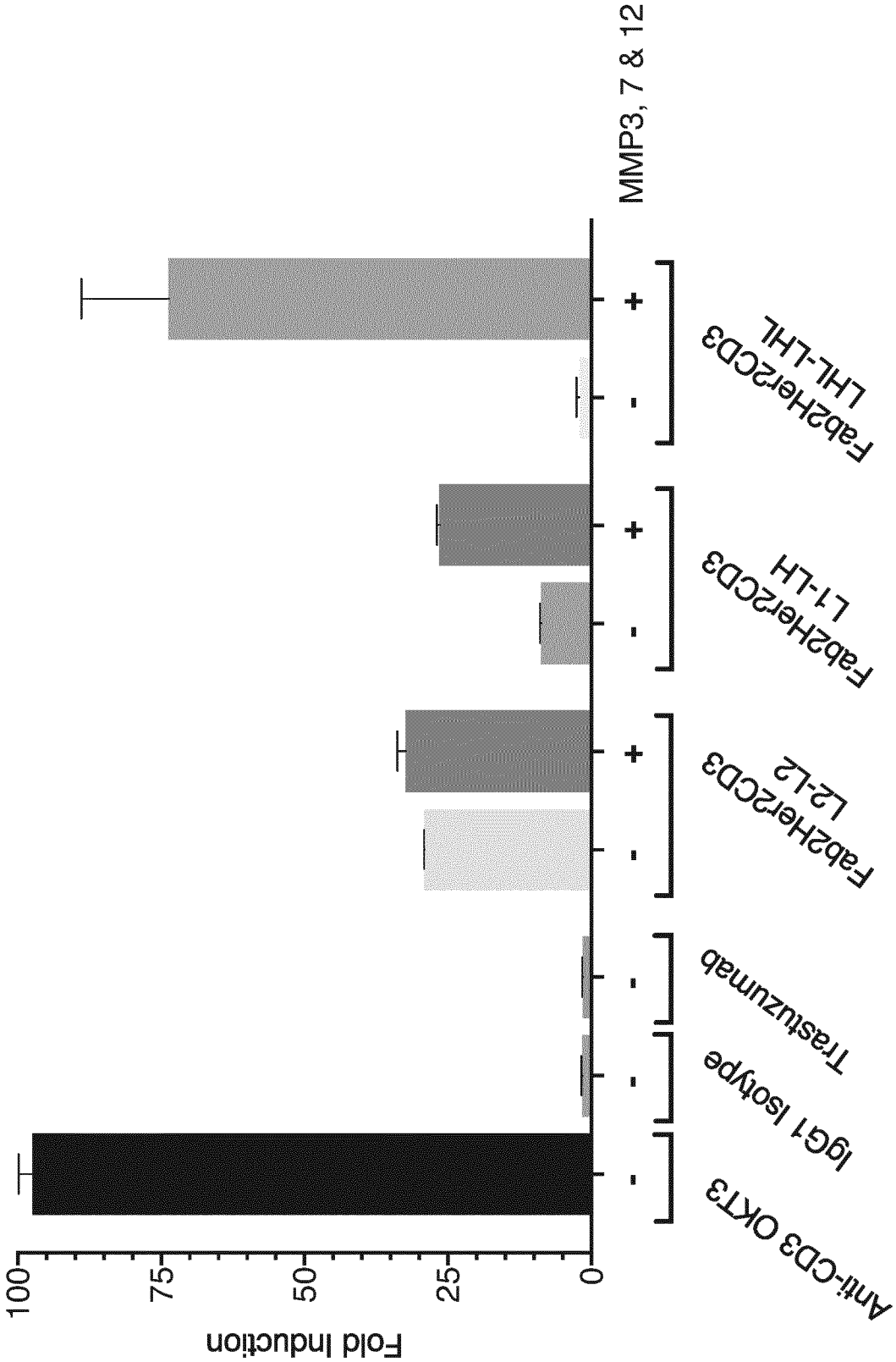
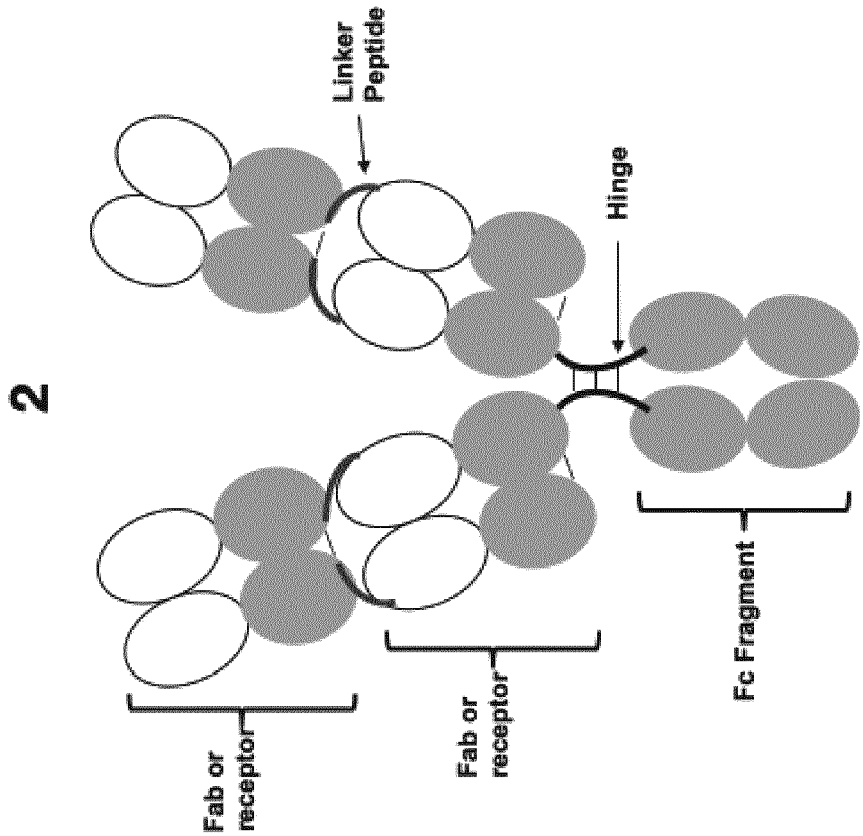

MMP3, 7 & 12
Fold Induction
0
25
50
75
100
Anti-CD3 OKT3
IgG1 Isotype
Trastuzumab
Fab2Her2CD3 L2-L2
Fab2Her2CD3 L1-LH
Fab2Her2CD3 LHL-LHL
-
+

Figure 11


2
Linker Peptide
Hinge
Fab or receptor
Fab or receptor
Fc Fragment

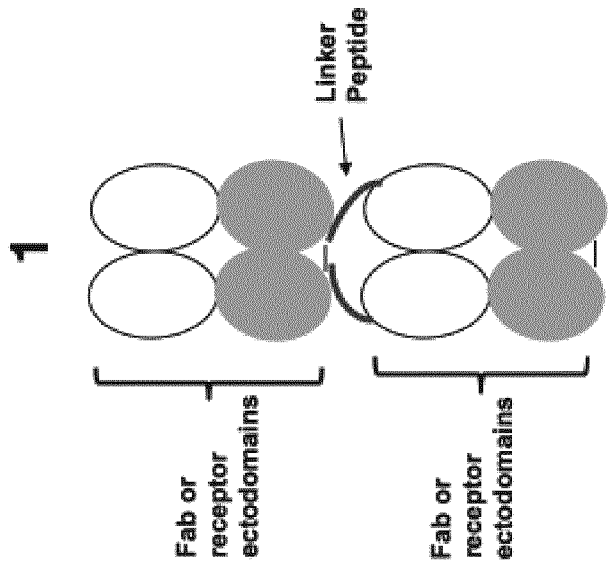

1
Linker Peptide
Fab or receptor ectodomains
Fab or receptor ectodomains

Figure 11

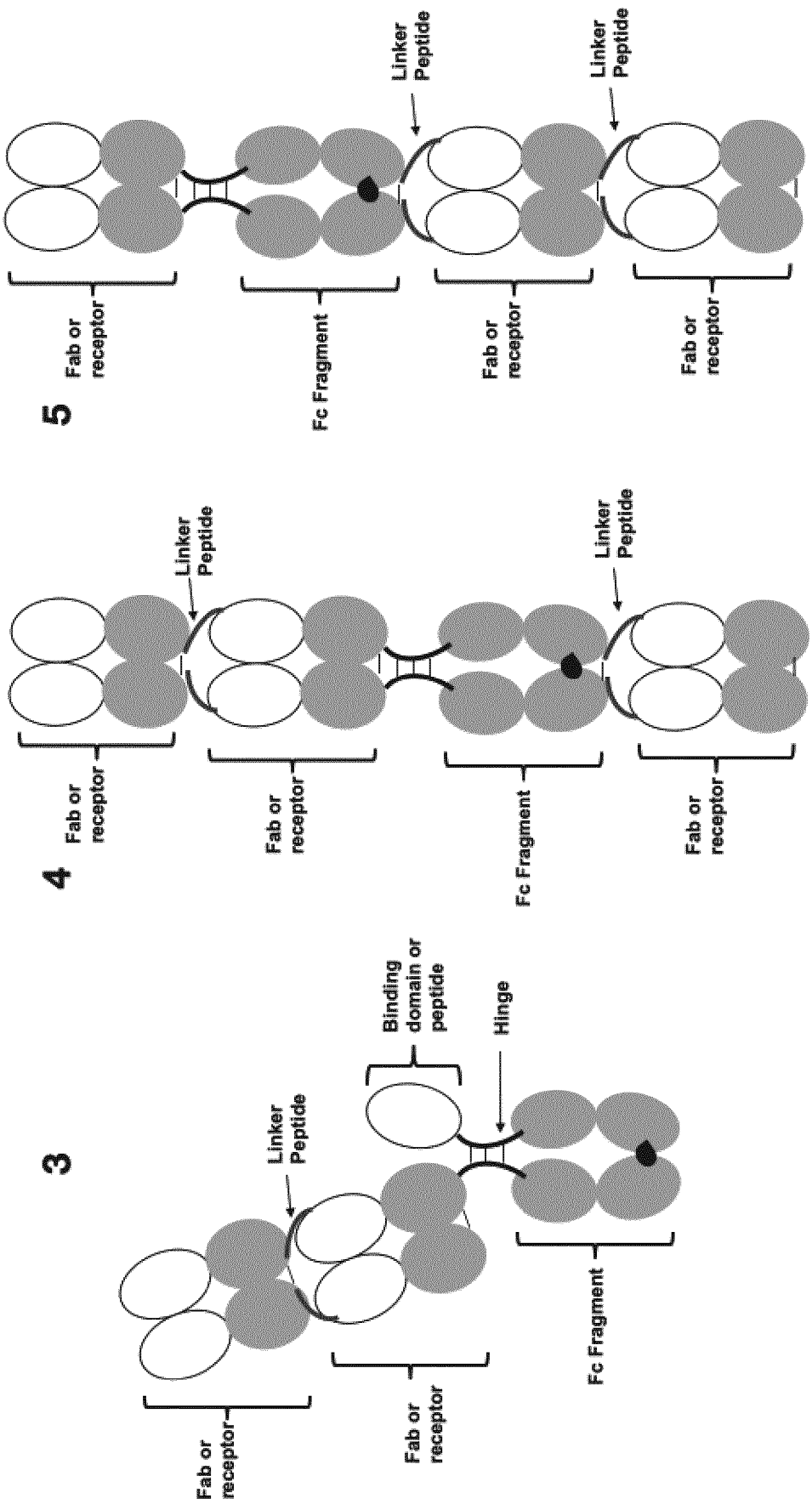

5
Fab or receptor
Fc Fragment
Fab or receptor
Fab or receptor
Linker Peptide
Linker Peptide
4
Fab or receptor
Fab or receptor
Fc Fragment
Fab or receptor
Linker Peptide
Linker Peptide
3
Fab or receptor
Fab or receptor
Fc Fragment
Linker Peptide
Binding domain or peptide
Hinge

Figure 12

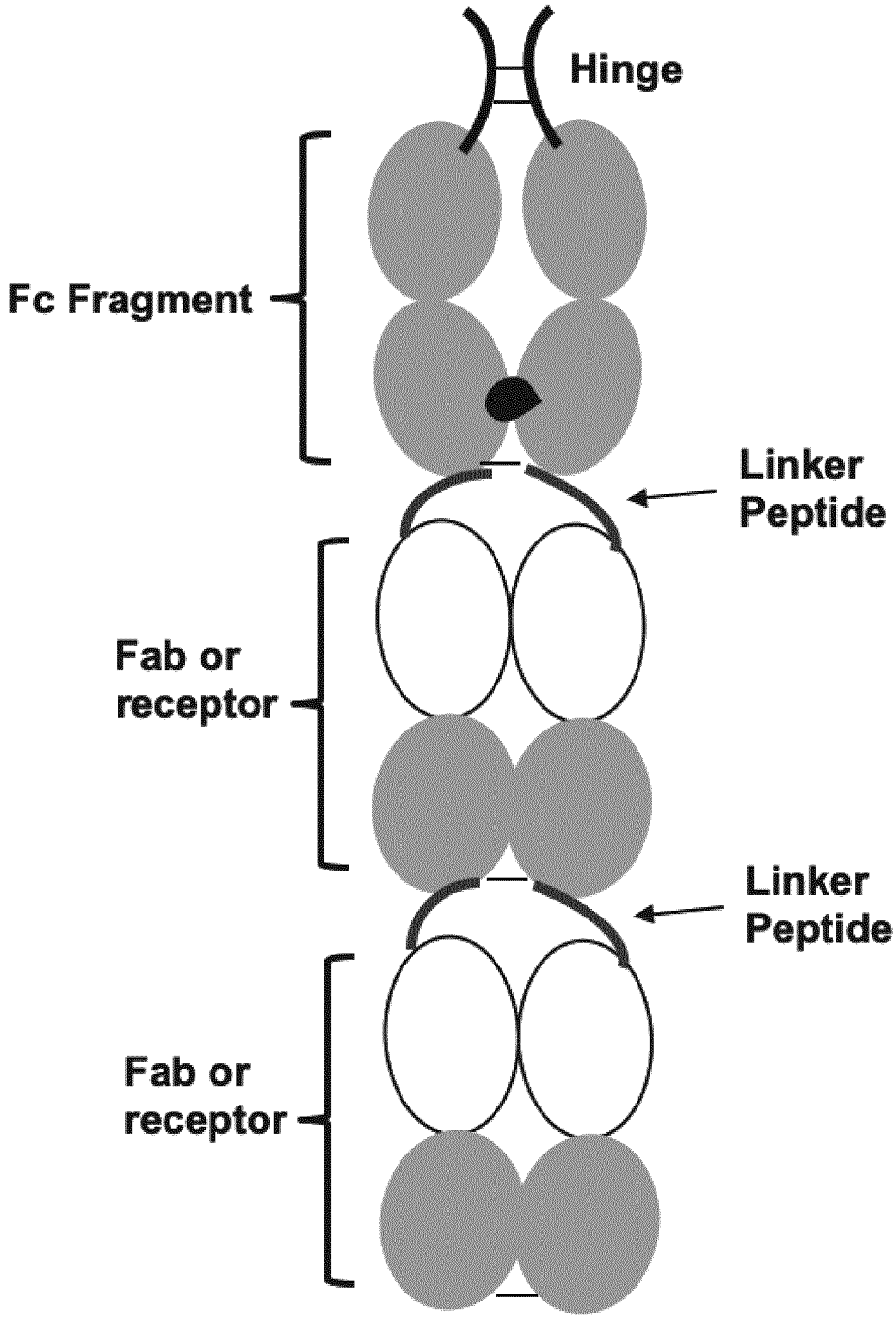

Hinge
Fc Fragment
Linker Peptide
Fab or receptor
Linker Peptide
Fab or receptor

Figure 13

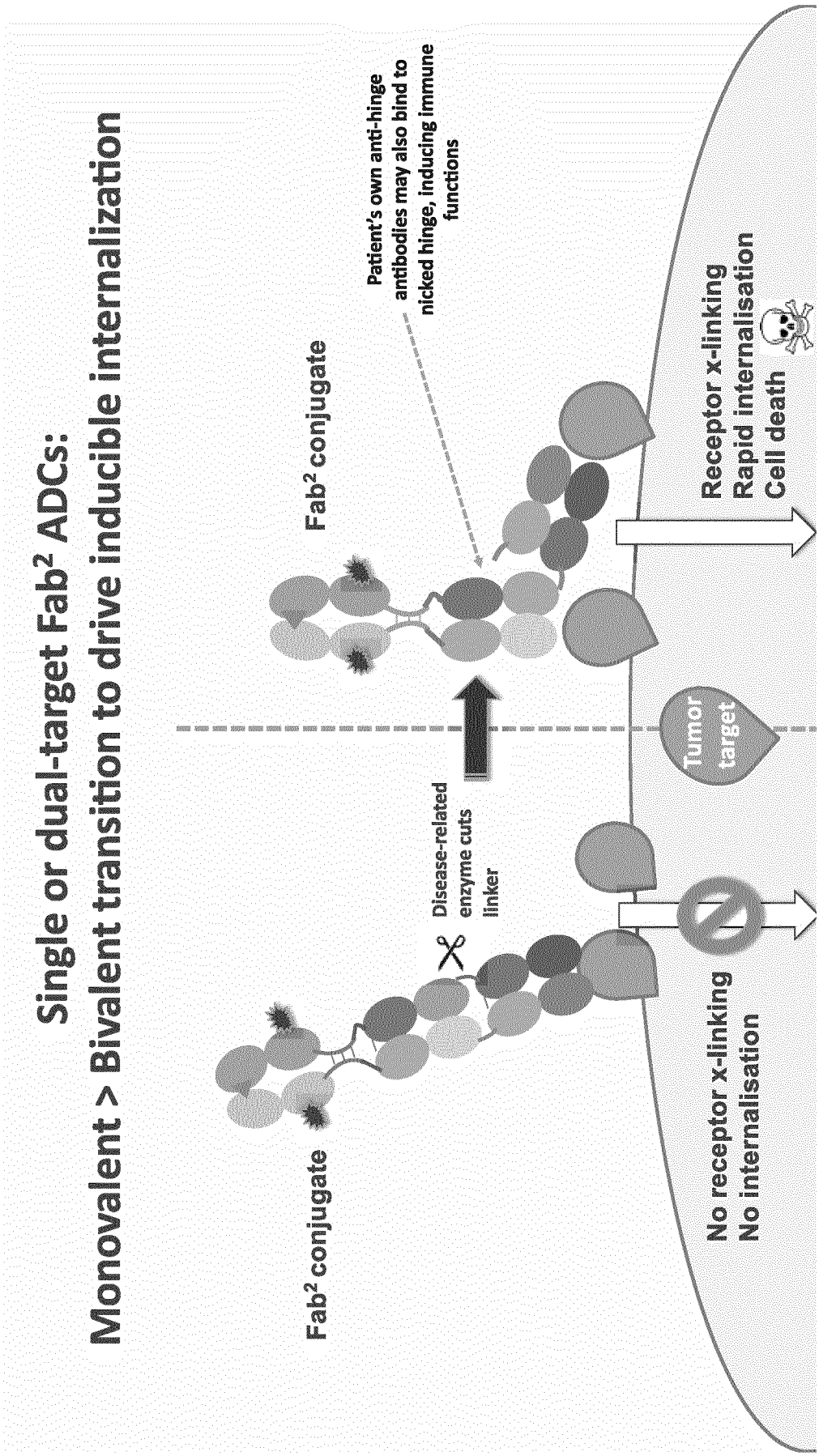

Single or dual-target Fab² ADCs:
Monovalent > Bivalent transition to drive inducible internalization
Fab² conjugate
Patient's own anti-hinge antibodies may also bind to nicked hinge, inducing immune functions
Receptor x-linking
Rapid internalisation
Cell death
Tumor target
Disease-related enzyme cuts linker
Fab² conjugate
No receptor x-linking
No internalisation

Figure 14

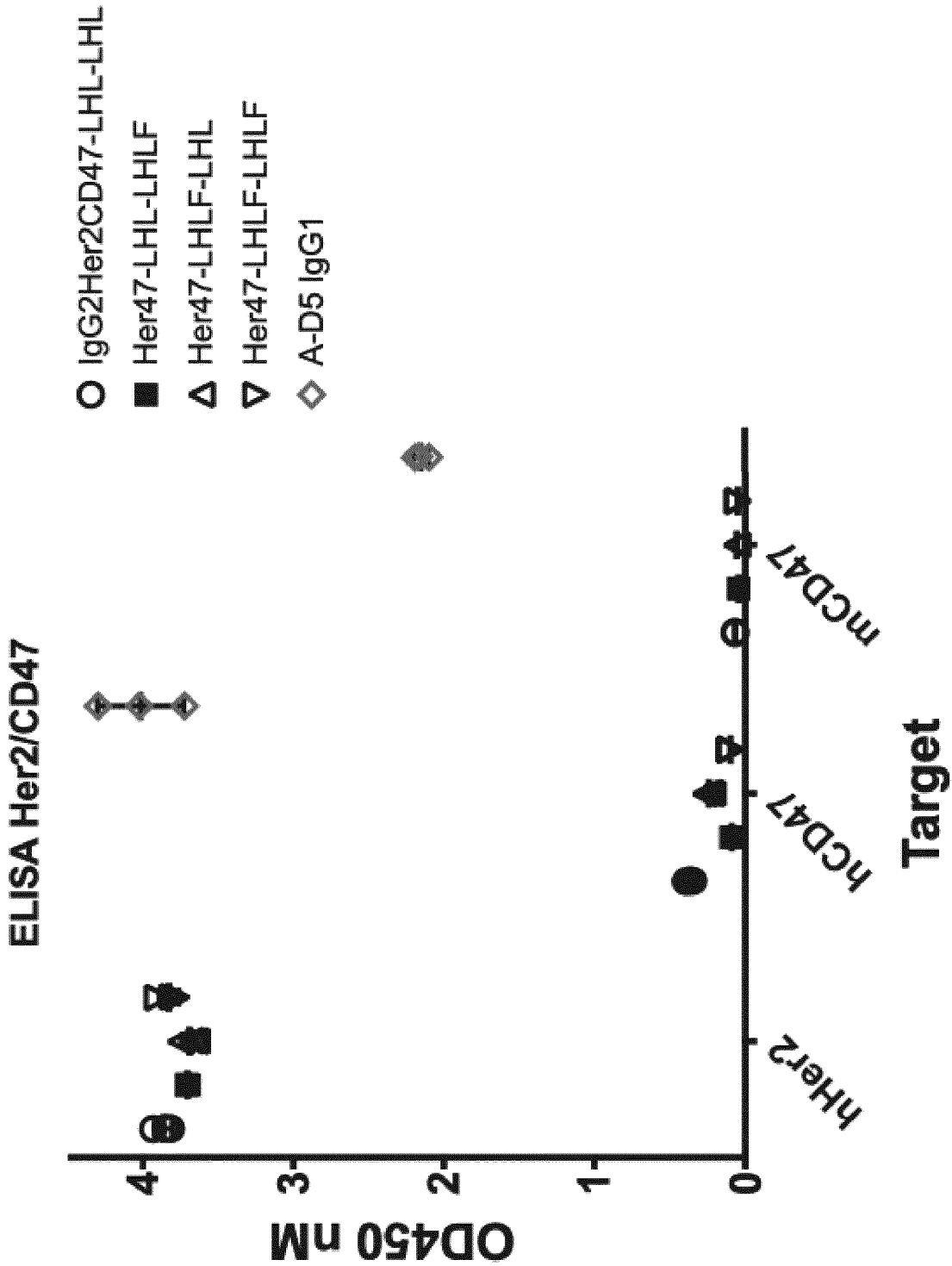

ELISA Her2/CD47
IgG2Her2CD47-LHL-LHL
Her47-LHL-LHLF
Her47-LHLF-LHL
Her47-LHLF-LHLF
A-D5 IgG1
OD450 nM
0
1
2
3
4
hHer2
hCD47
mCD47
Target

Figure 15A

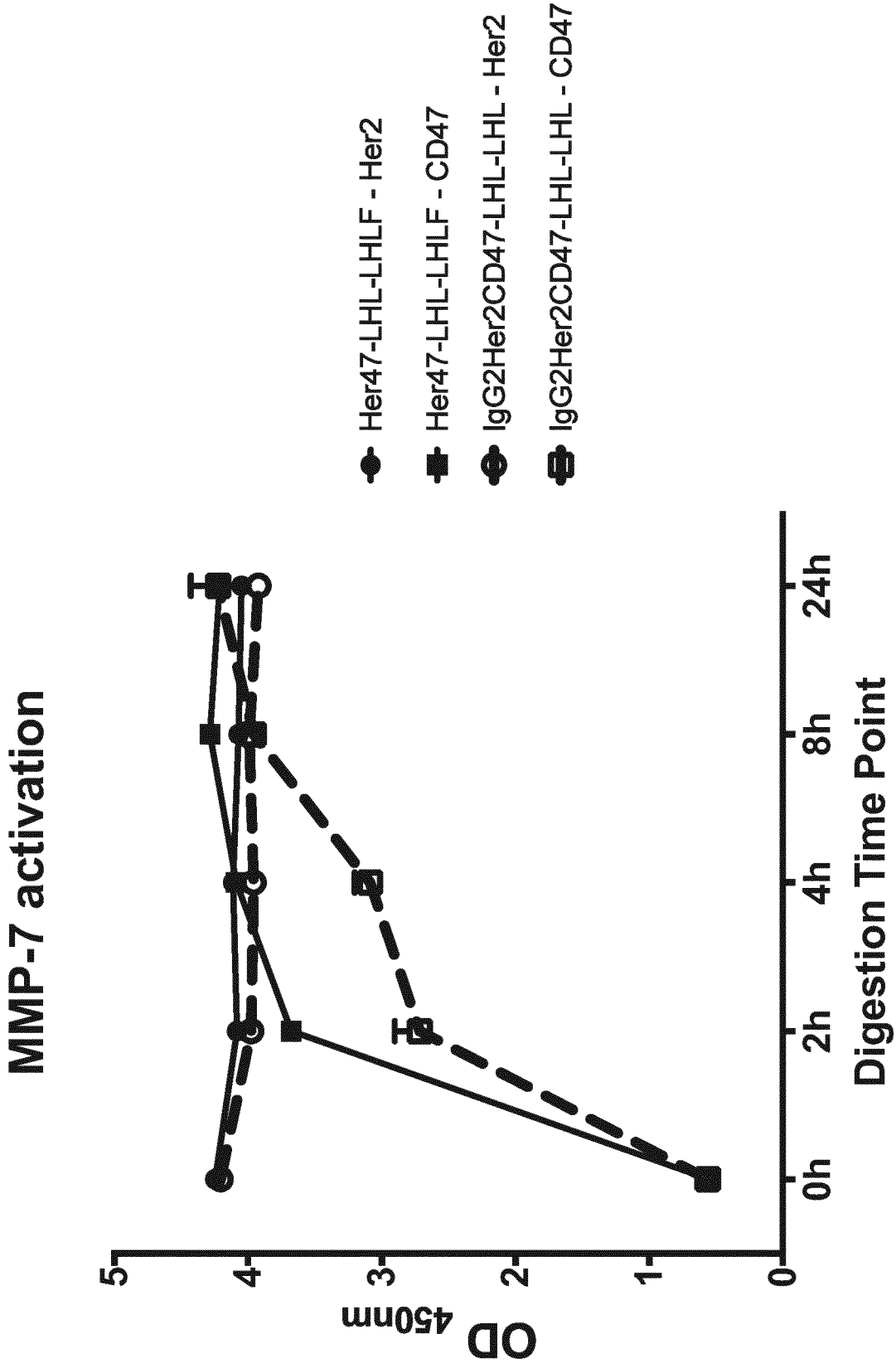

MMP-7 activation
Her47-LHL-LHLF - Her2
Her47-LHL-LHLF - CD47
IgG2Her2CD47-LHL-LHL - Her2
IgG2Her2CD47-LHL-LHL - CD47
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point

Figure 15B

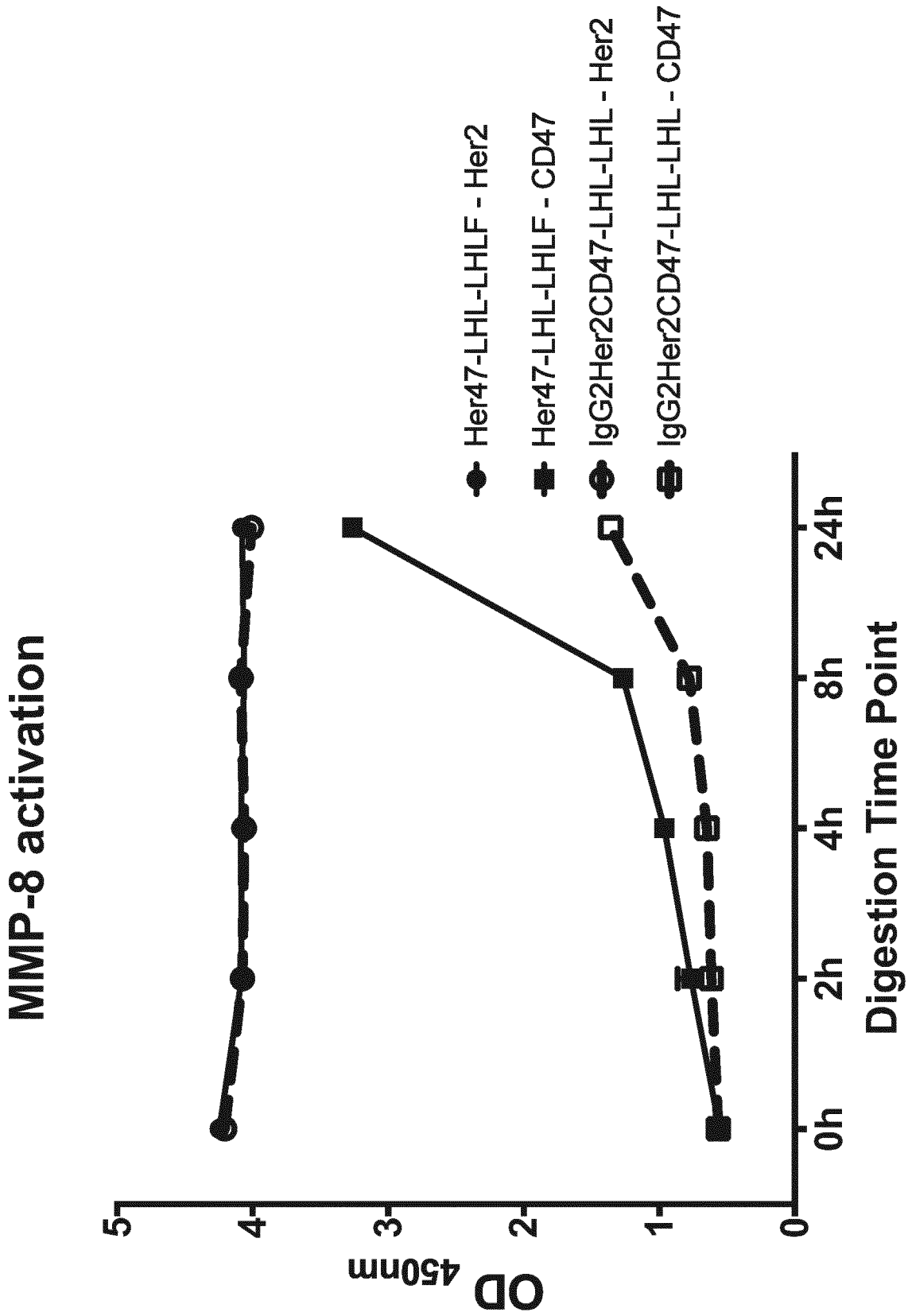

MMP-8 activation
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF - Her2
Her47-LHL-LHLF - CD47
IgG2Her2CD47-LHL-LHL - Her2
IgG2Her2CD47-LHL-LHL - CD47

Figure 15C

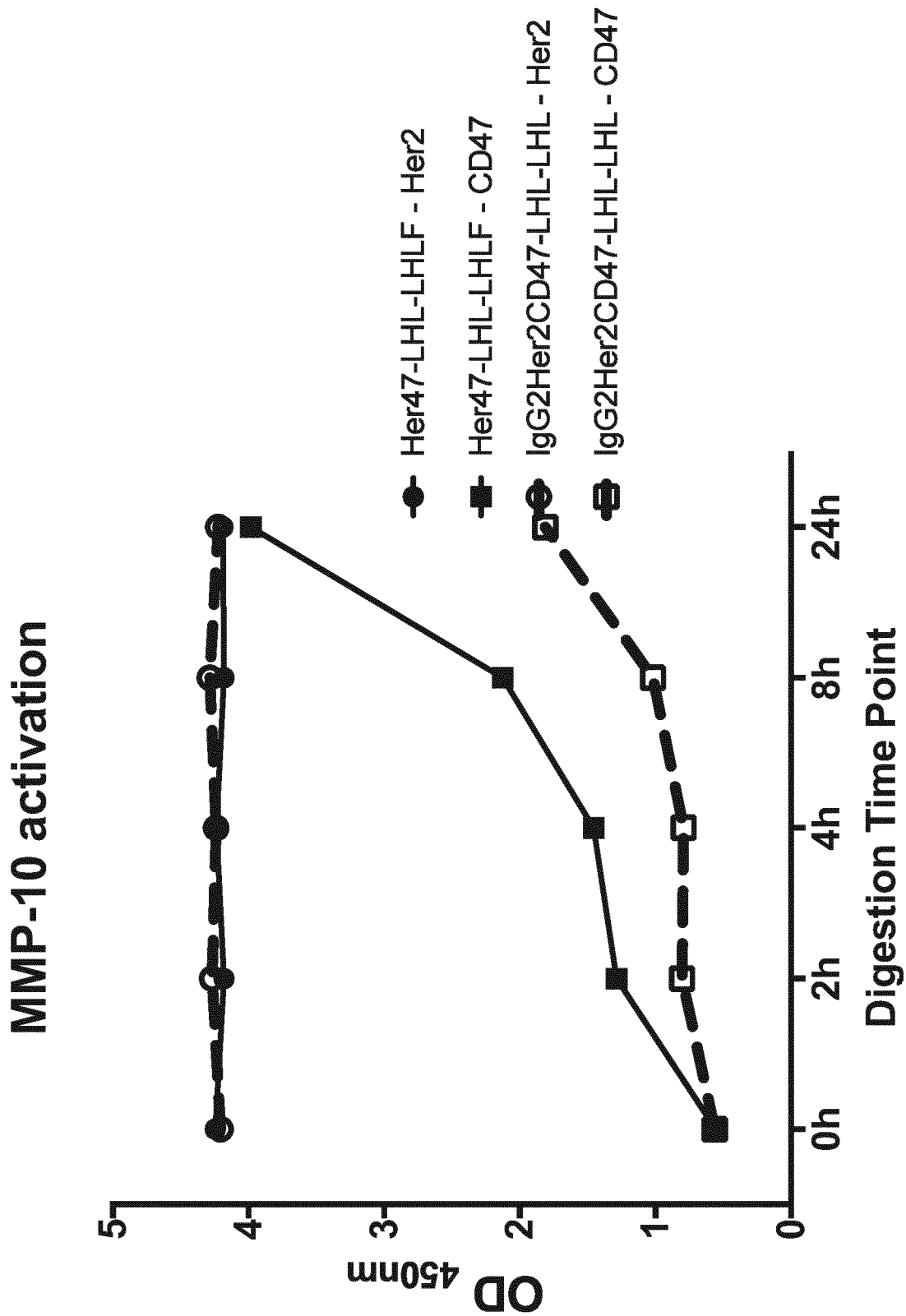

MMP-10 activation
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF - Her2
Her47-LHL-LHLF - CD47
IgG2Her2CD47-LHL-LHL - Her2
IgG2Her2CD47-LHL-LHL - CD47

Figure 15D

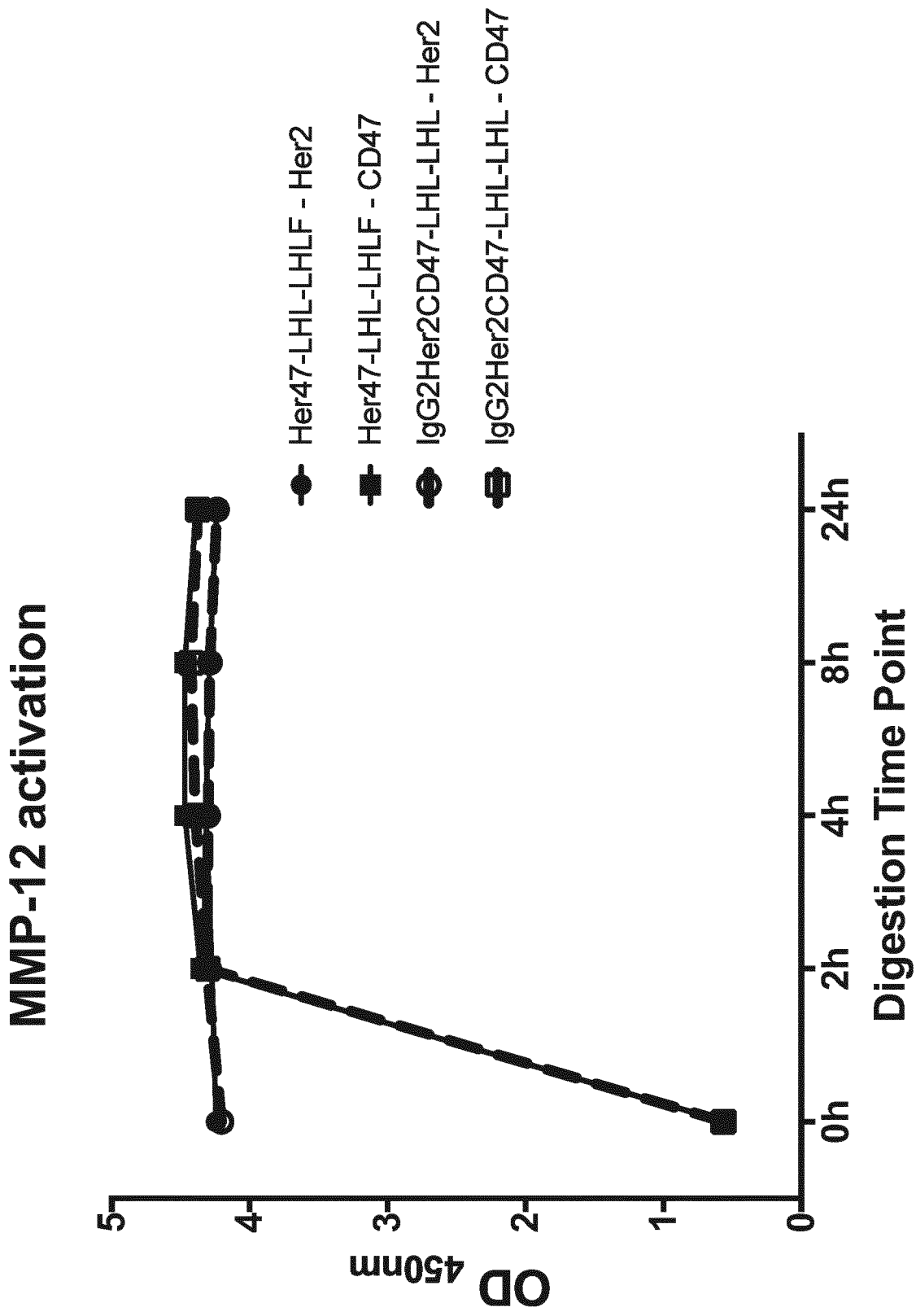

MMP-12 activation
Her47-LHL-LHLF - Her2
Her47-LHL-LHLF - CD47
IgG2Her2CD47-LHL-LHL - Her2
IgG2Her2CD47-LHL-LHL - CD47
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point

Figure 15E

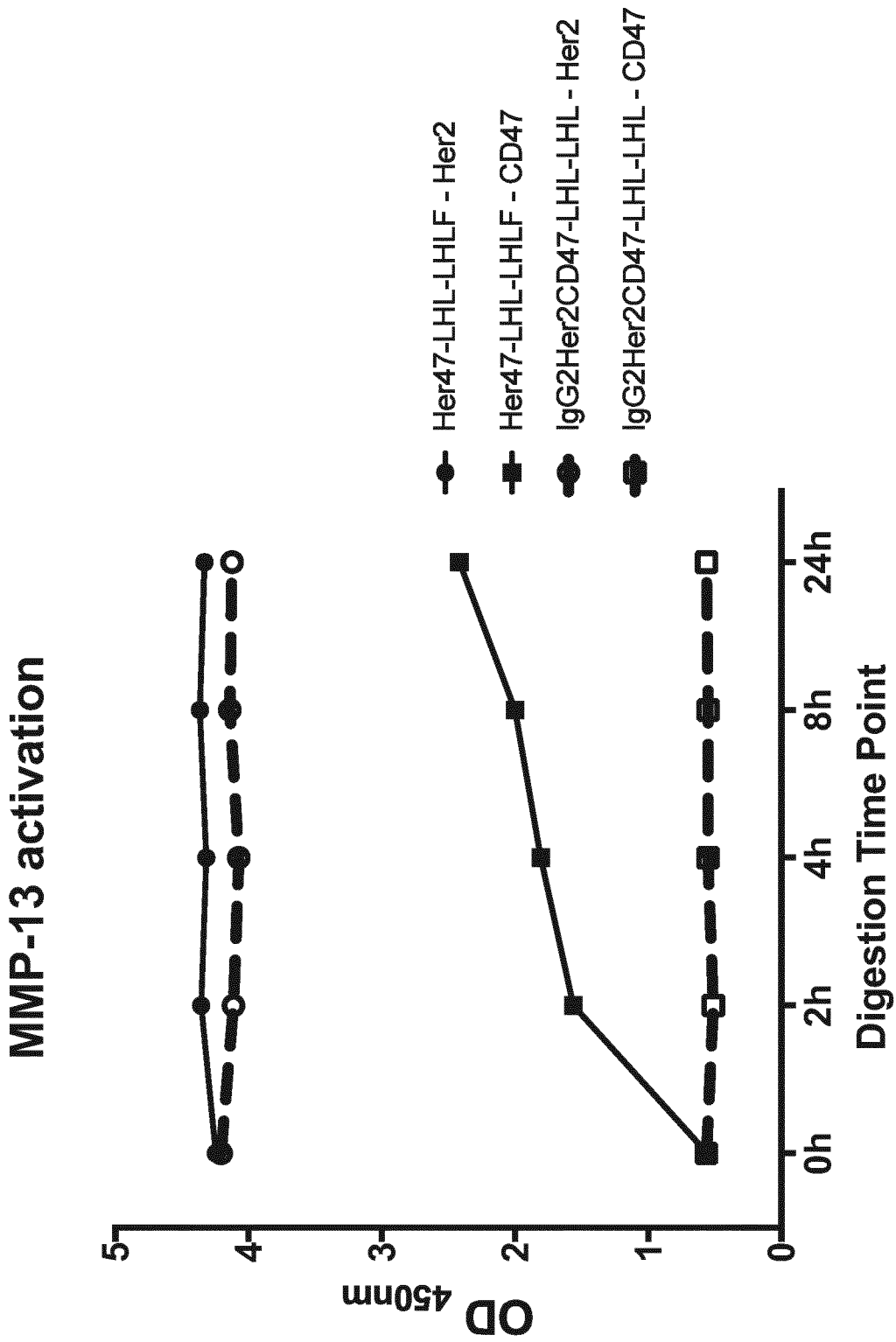

MMP-13 activation
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF - Her2
Her47-LHL-LHLF - CD47
IgG2Her2CD47-LHL-LHL - Her2
IgG2Her2CD47-LHL-LHL - CD47

Figure 15F

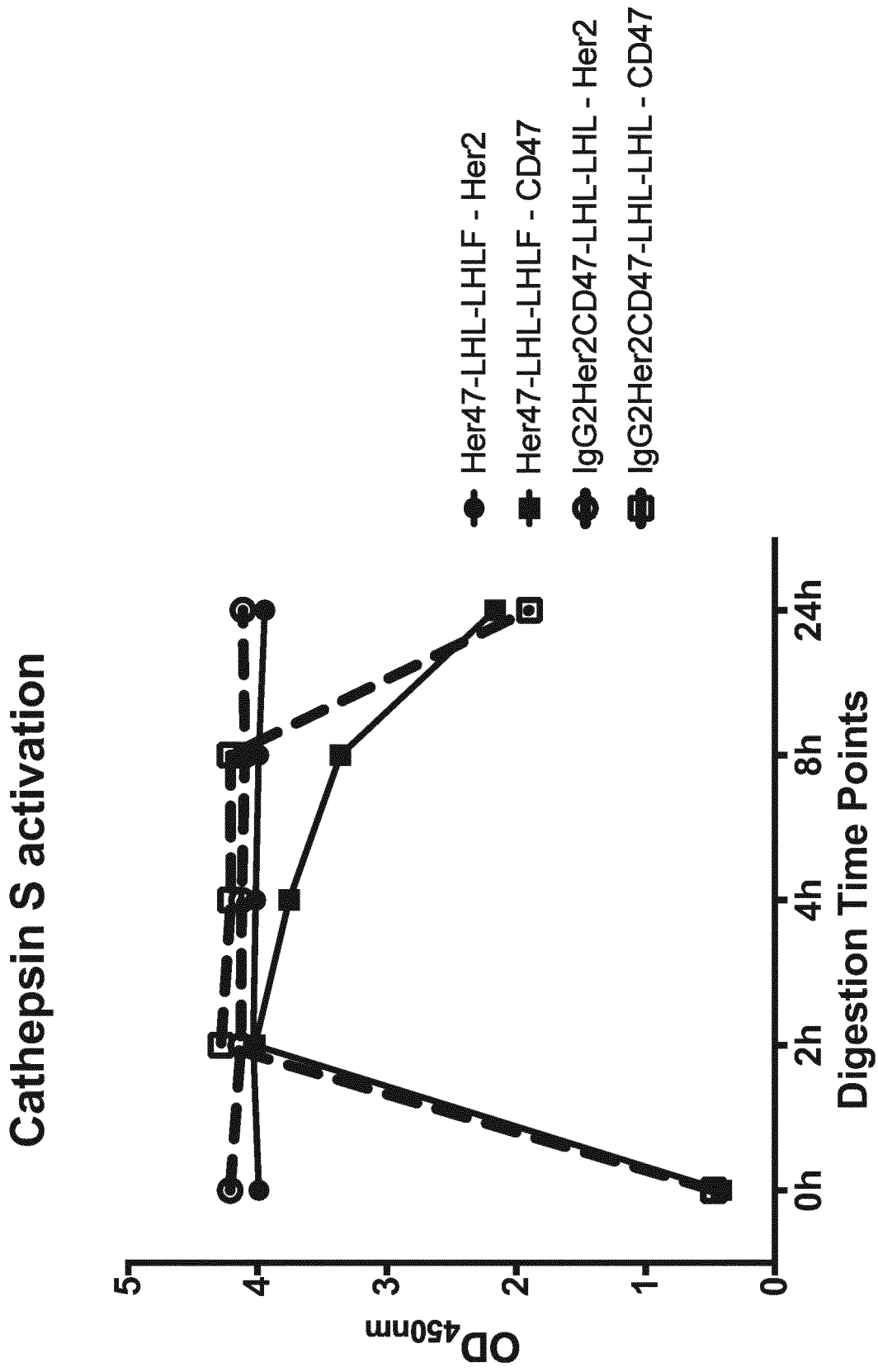

Cathepsin S activation
OD450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF - Her2
Her47-LHL-LHLF - CD47
IgG2Her2CD47-LHL-LHL - Her2
IgG2Her2CD47-LHL-LHL - CD47

Figure 16

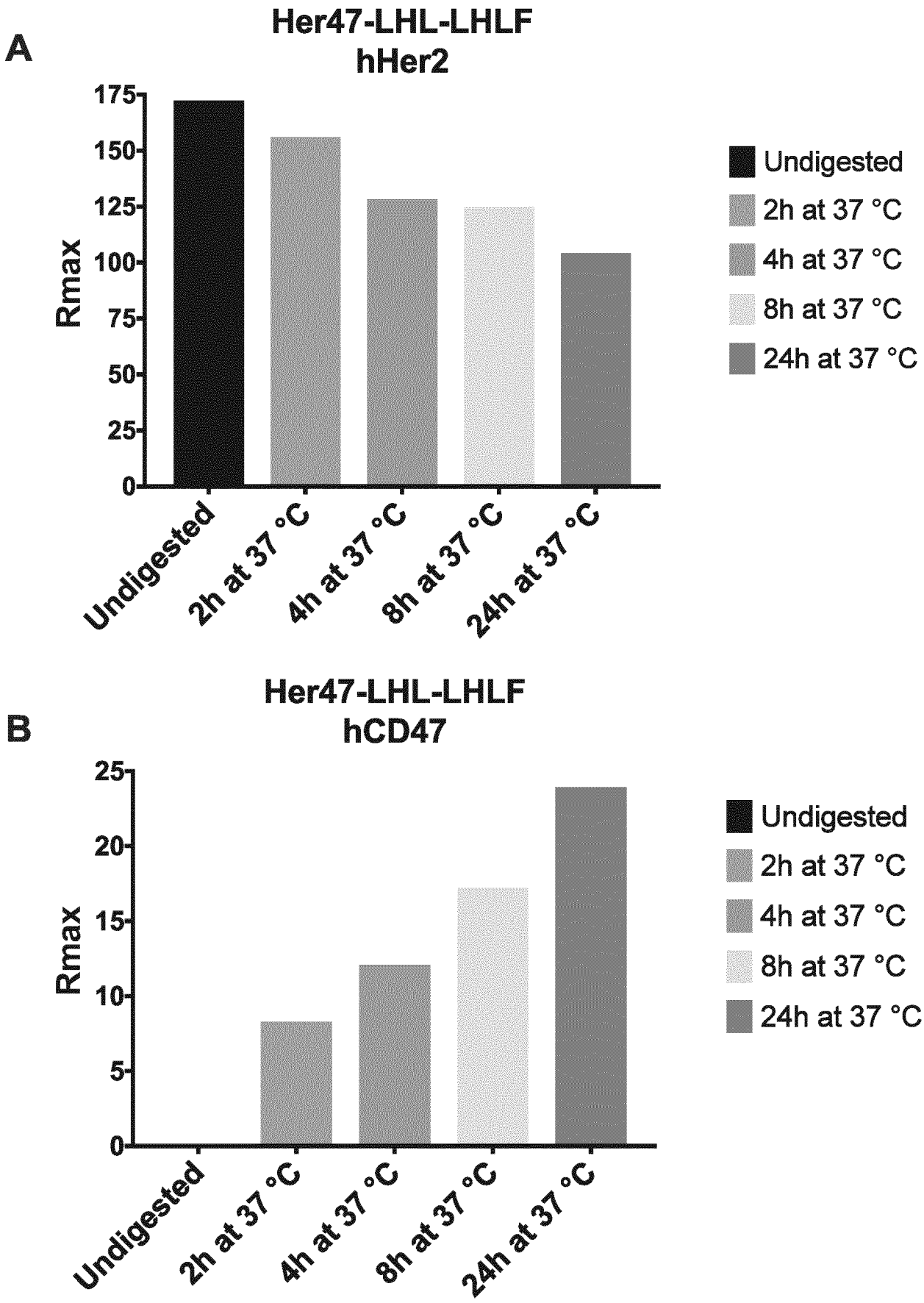
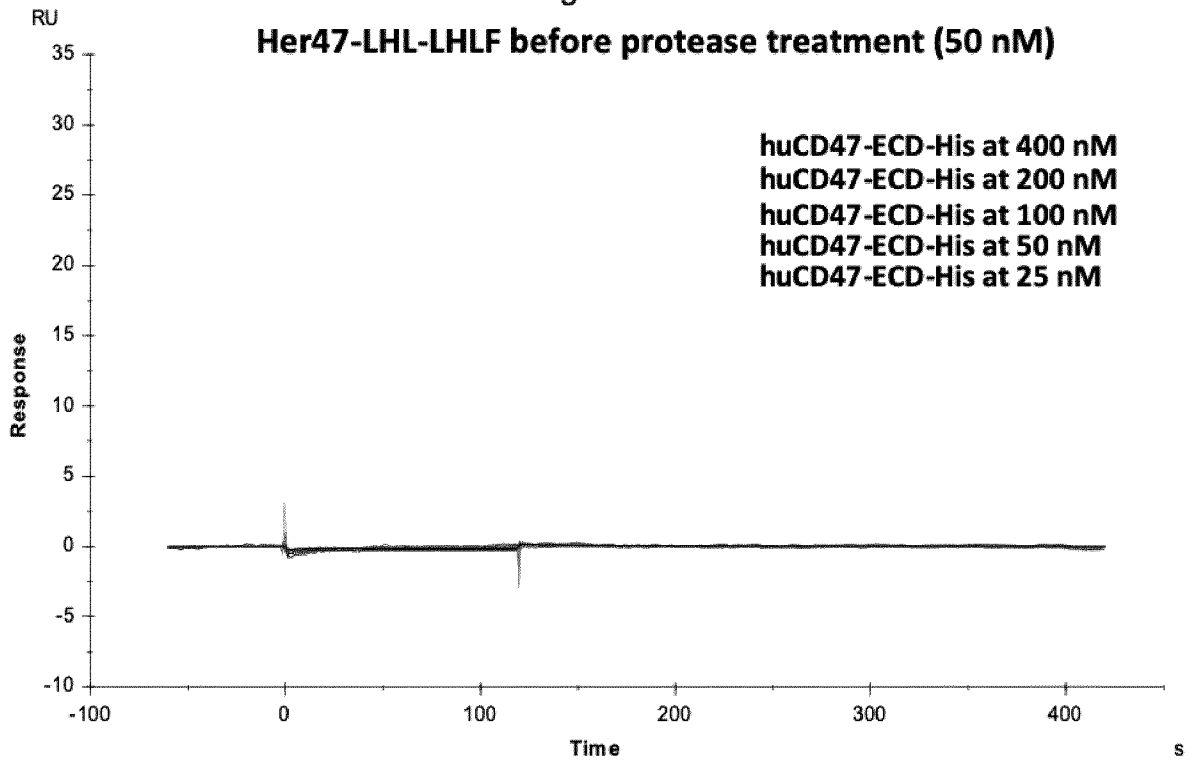

A
Her47-LHL-LHLF
hHer2
Rmax
175
150
125
100
75
50
25
0
Undigested
2h at 37 °C
4h at 37 °C
8h at 37 °C
24h at 37 °C
B
Her47-LHL-LHLF
hCD47
Rmax
25
20
15
10
5
0
Undigested
2h at 37 °C
4h at 37 °C
8h at 37 °C
24h at 37 °C

Figure 17


Her47-LHL-LHLF before protease treatment (50 nM)
huCD47-ECD-His at 400 nM
huCD47-ECD-His at 200 nM
huCD47-ECD-His at 100 nM
huCD47-ECD-His at 50 nM
huCD47-ECD-His at 25 nM
RU
Response
Time
s

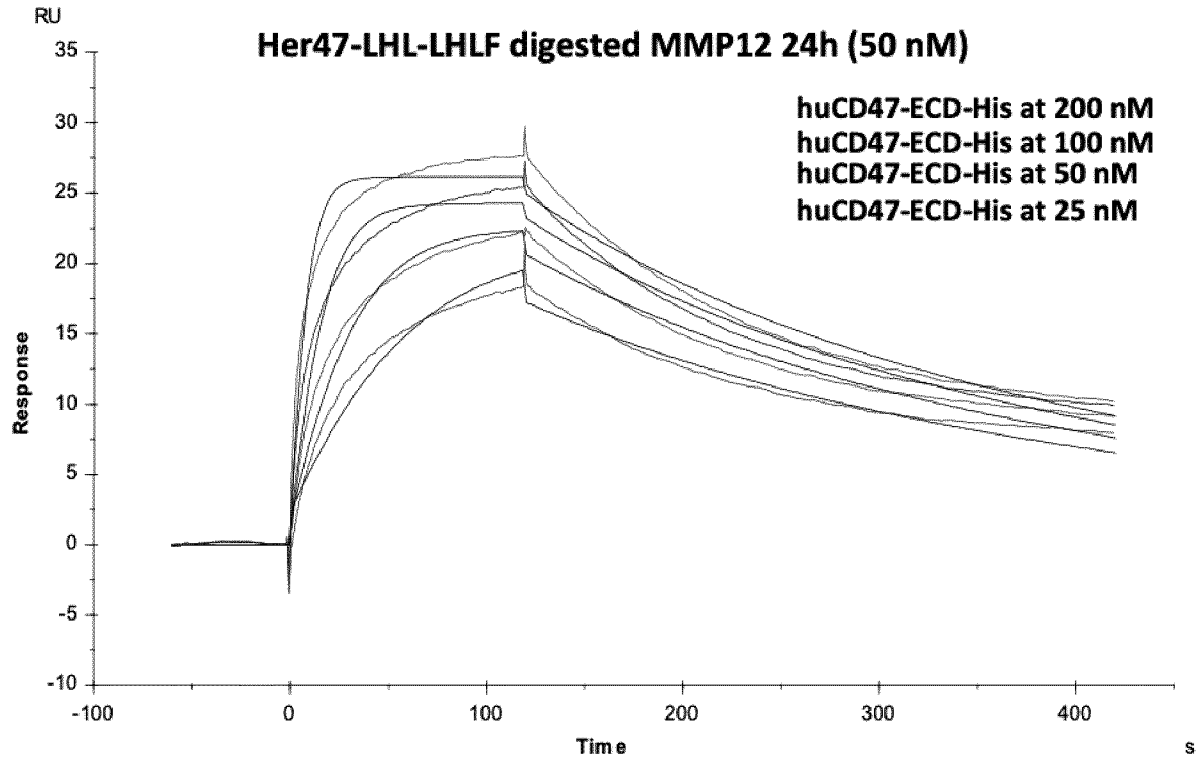

Her47-LHL-LHLF digested MMP12 24h (50 nM)
huCD47-ECD-His at 200 nM
huCD47-ECD-His at 100 nM
huCD47-ECD-His at 50 nM
huCD47-ECD-His at 25 nM
RU
Response
Time
s

Fig. 18A

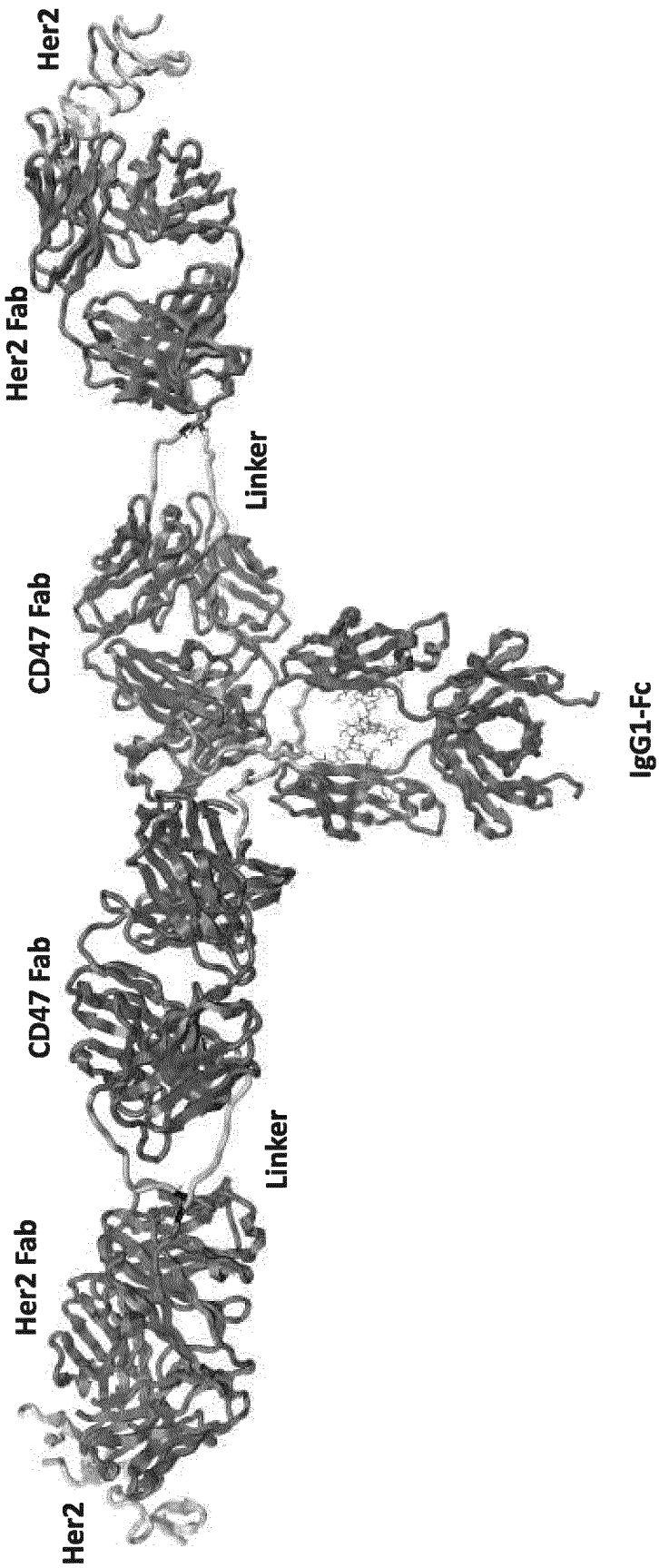

Her2
Her2 Fab
Linker
CD47 Fab
IgG1-Fc
CD47 Fab
Linker
Her2 Fab
Her2

Figure 18B

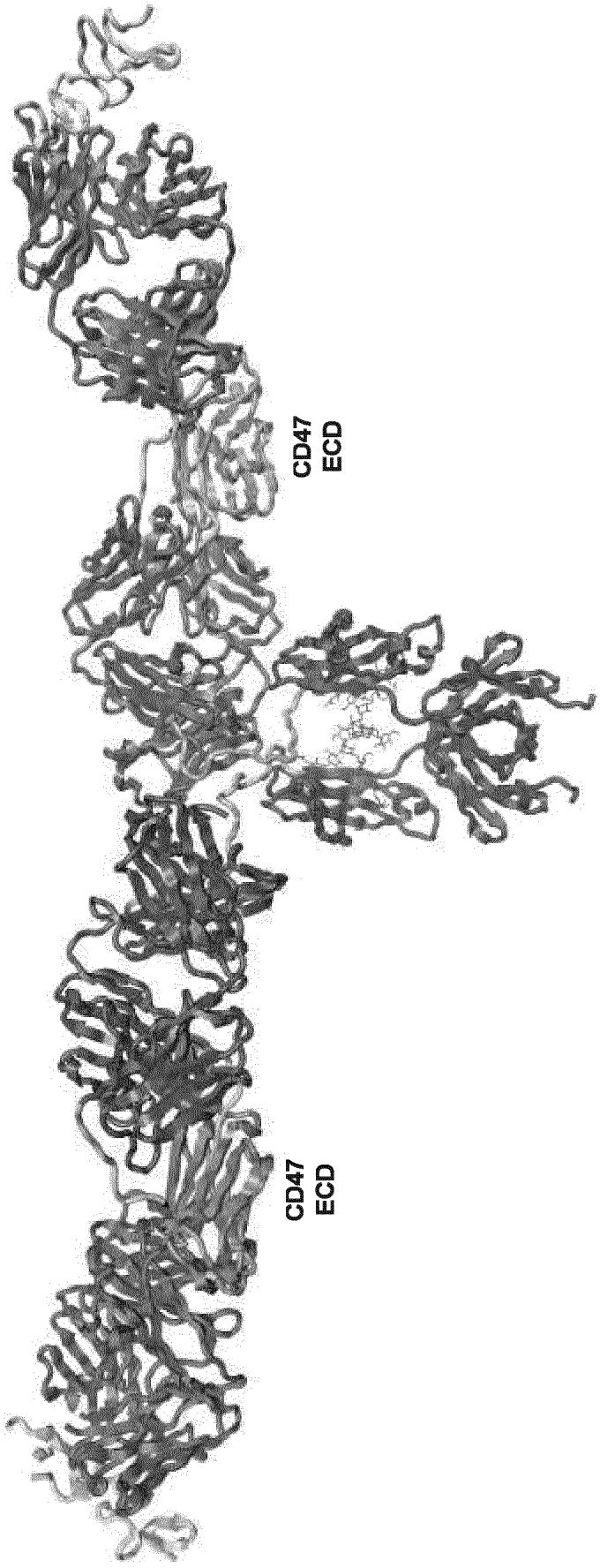


Figure 19

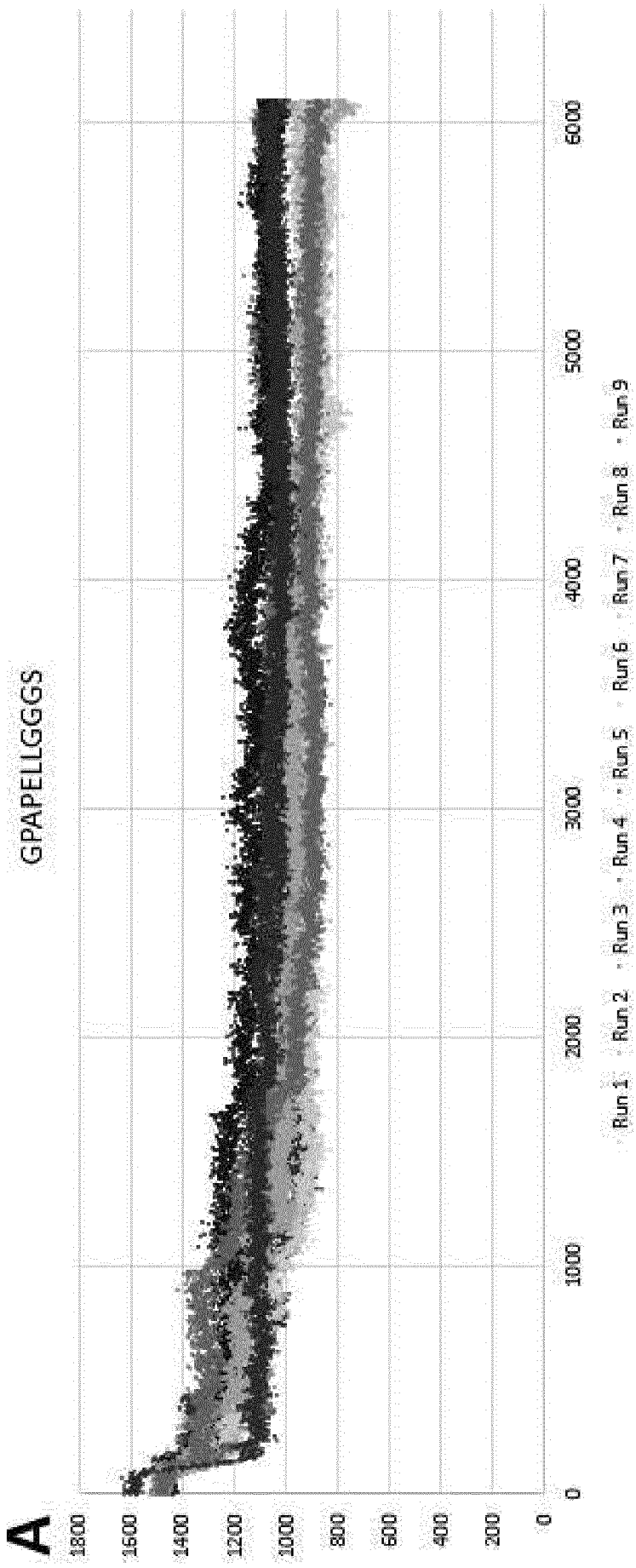

A
GPAPELLGGGS
1800
1600
1400
1200
1000
800
600
400
200
0
0
1000
2000
3000
4000
5000
6000
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9

Figure 19

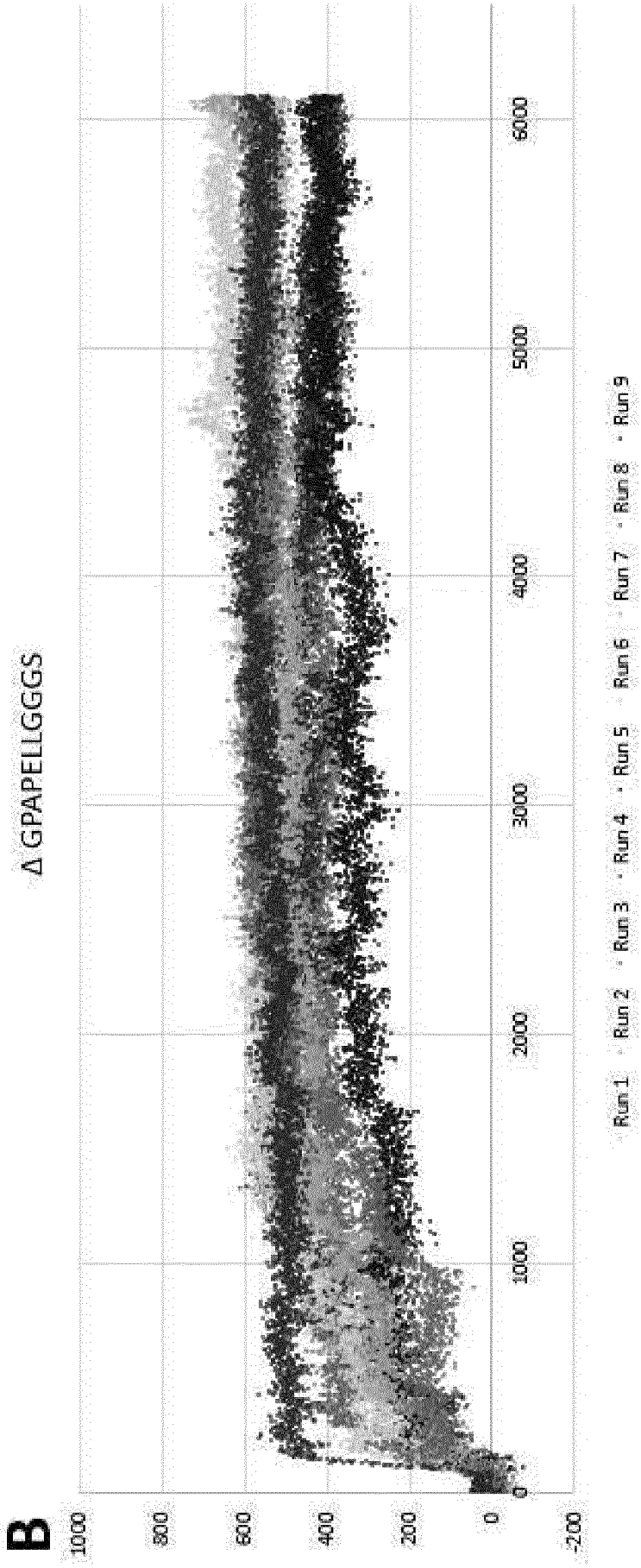

B
Δ GPAPELLGGGS
1000
800
600
400
200
0
-200
0
1000
2000
3000
4000
5000
6000
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9

Figure 19

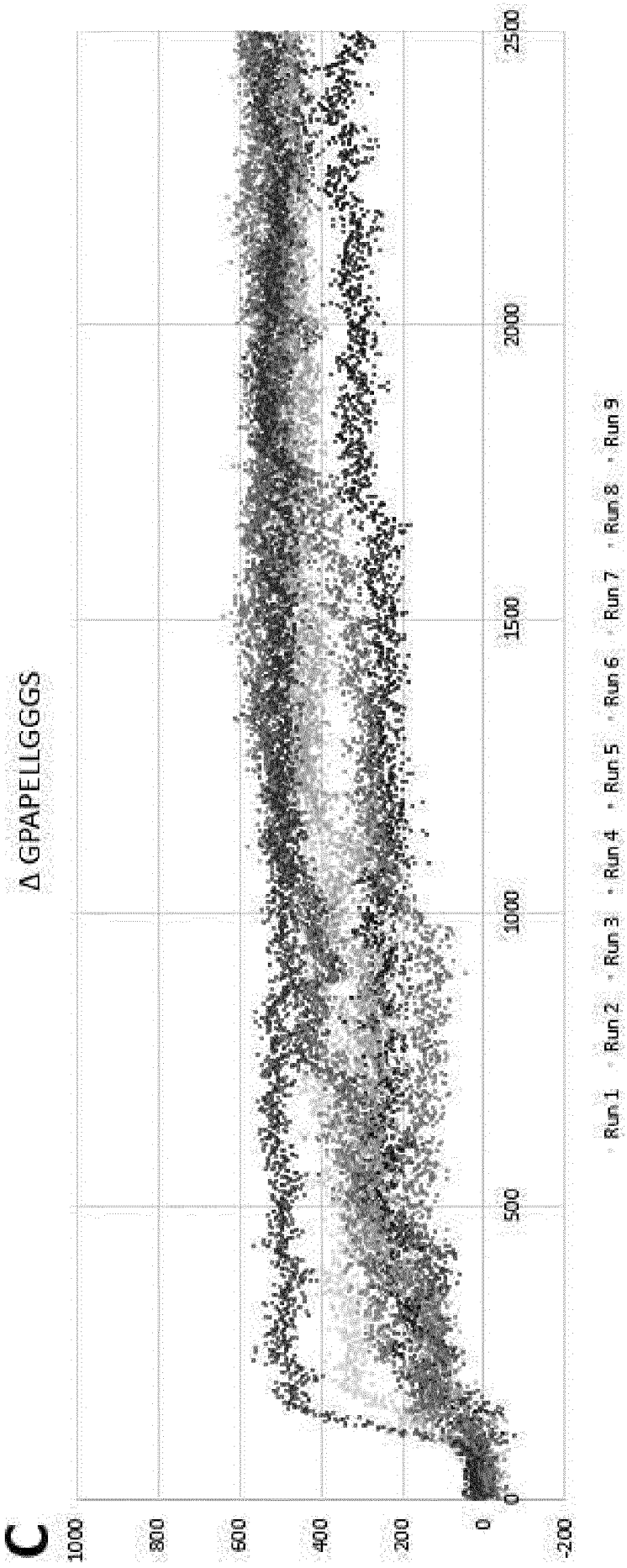

C
Δ GPAPELLGGGS
1000
800
600
400
200
0
-200
0
500
1000
1500
2000
2500
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9

Figure 19

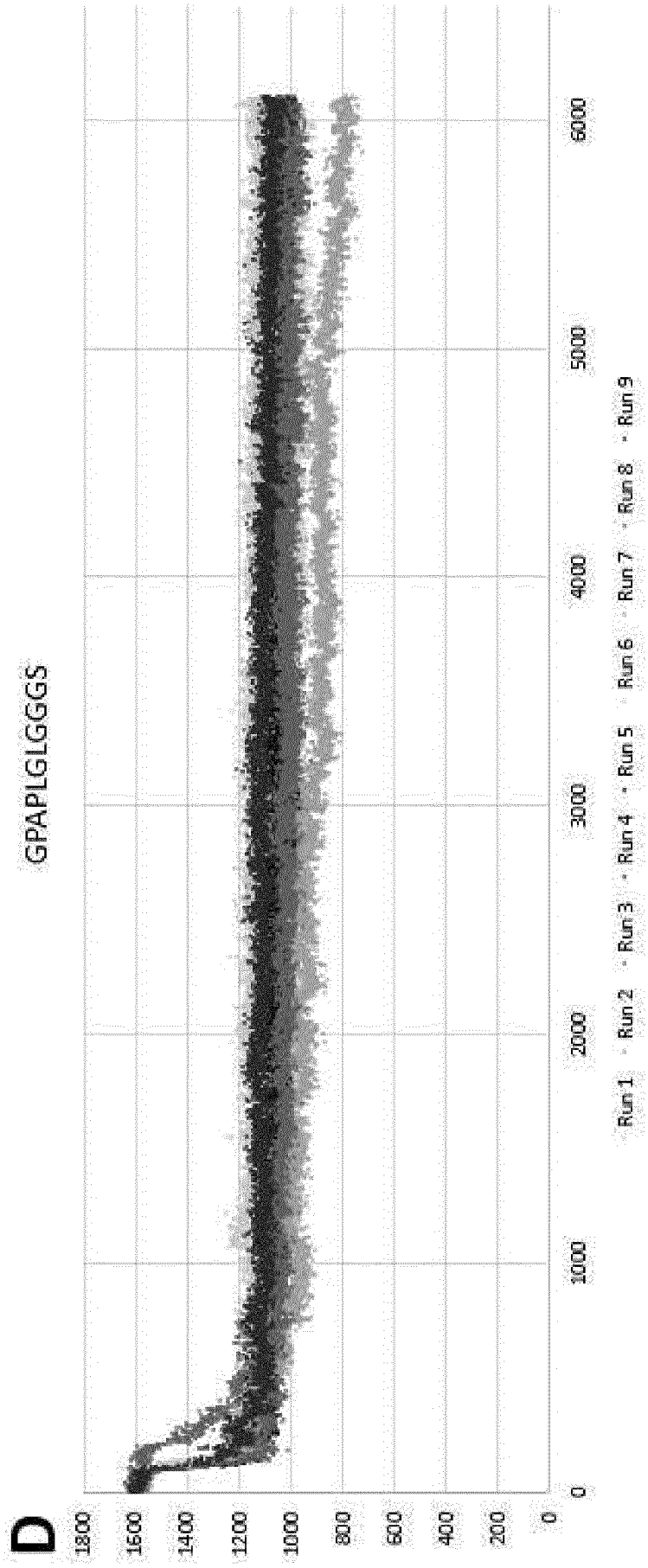

D
GPAPLGLGGGS
1800
1600
1400
1200
1000
800
600
400
200
0
0
1000
2000
3000
4000
5000
6000
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9

Figure 19

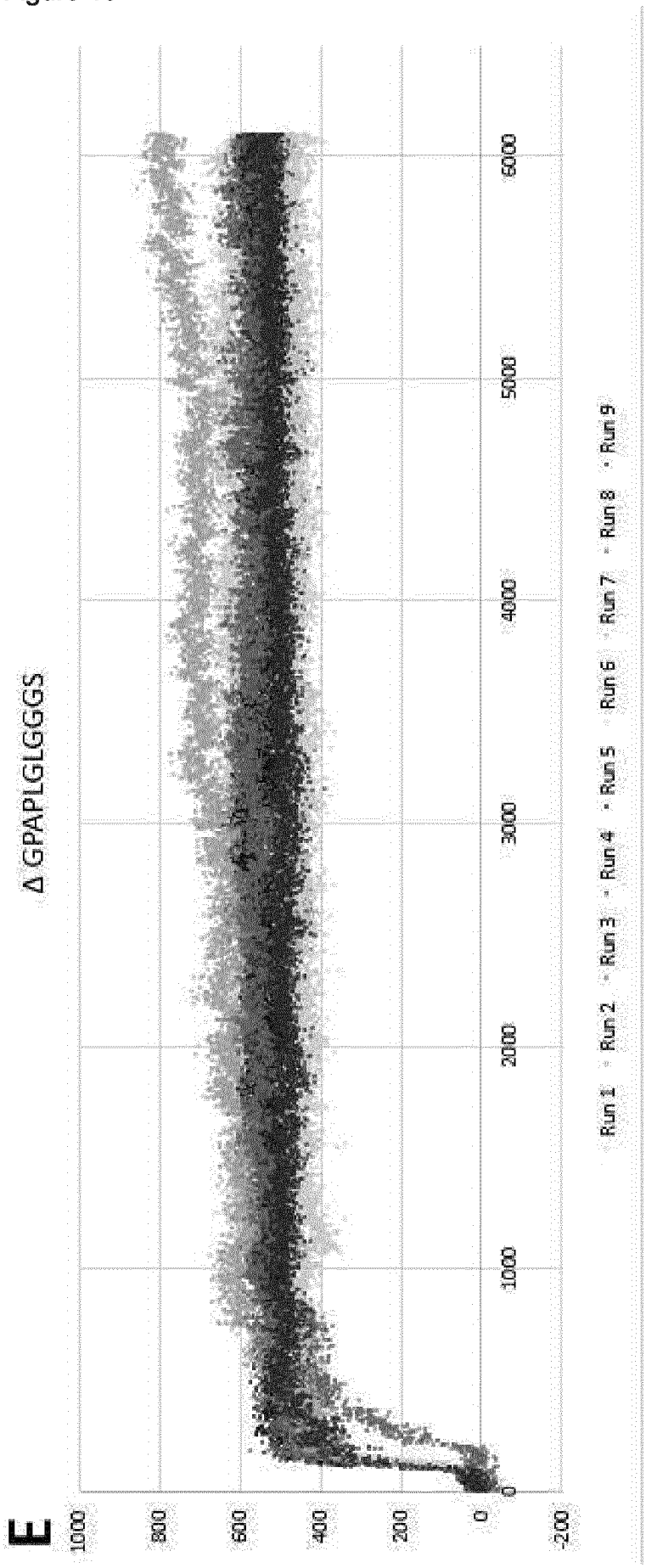

E
Δ GPAPLGLGGGS
1000
800
600
400
200
0
-200
1000
2000
3000
4000
5000
6000
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9

Figure 19

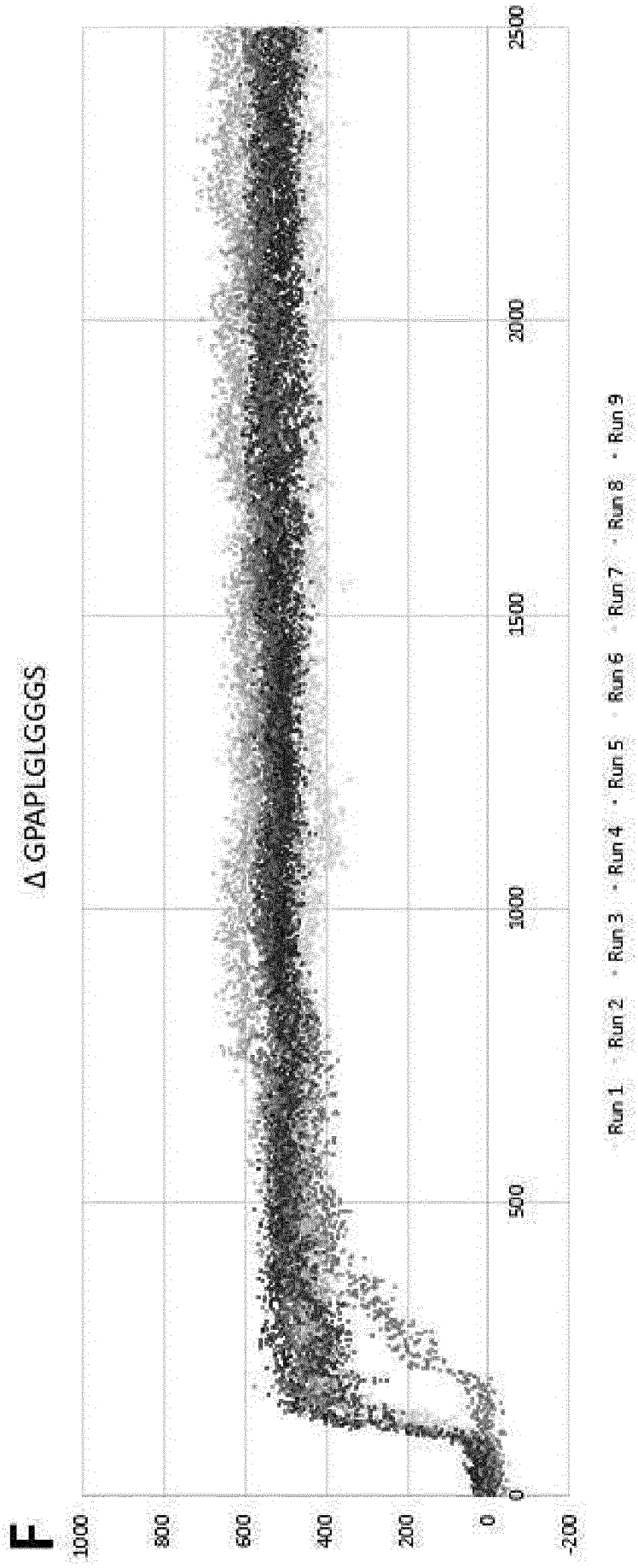

F
Δ GPAPLGLGGGS
1000
800
600
400
200
0
-200
500
1000
1500
2000
2500
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9

Figure 19

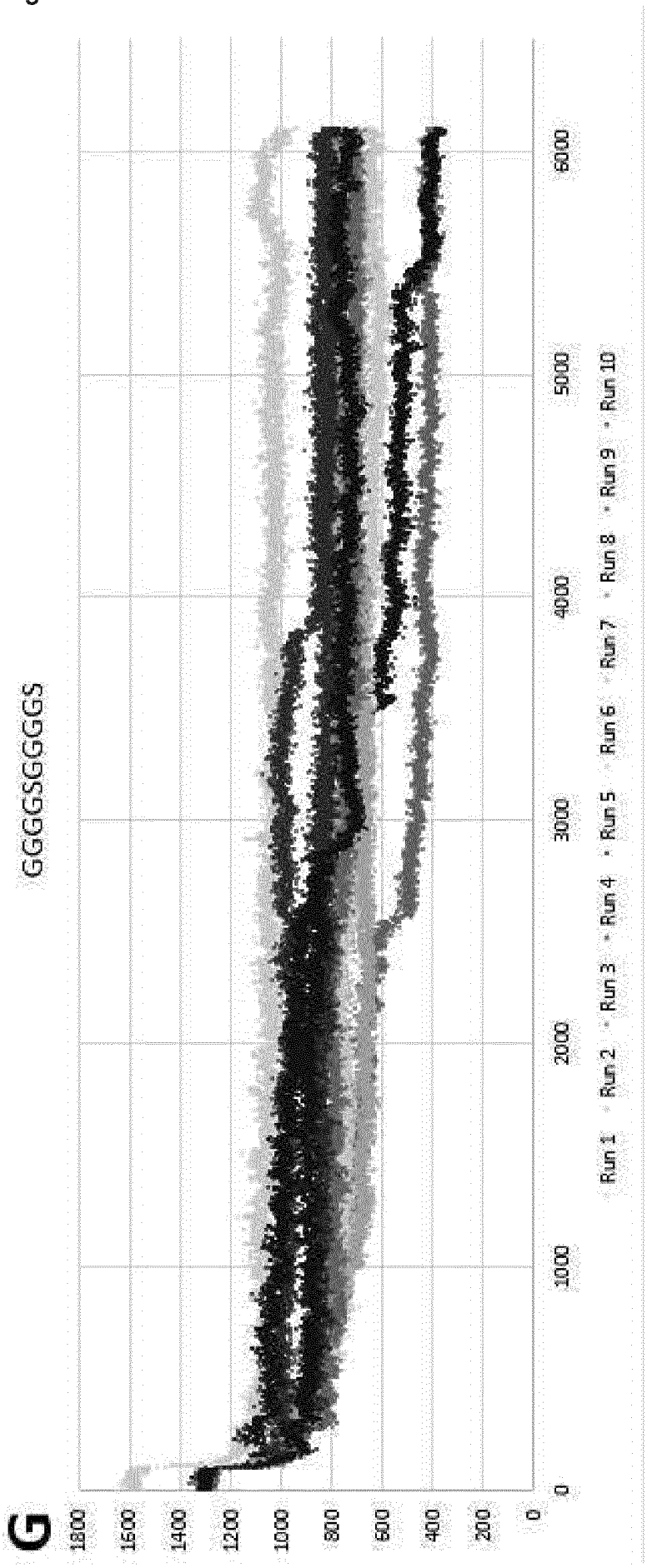

GGGGSGGGGS
G
1800
1600
1400
1200
1000
800
600
400
200
0
0
1000
2000
3000
4000
5000
6000
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9
Run 10

Figure 19

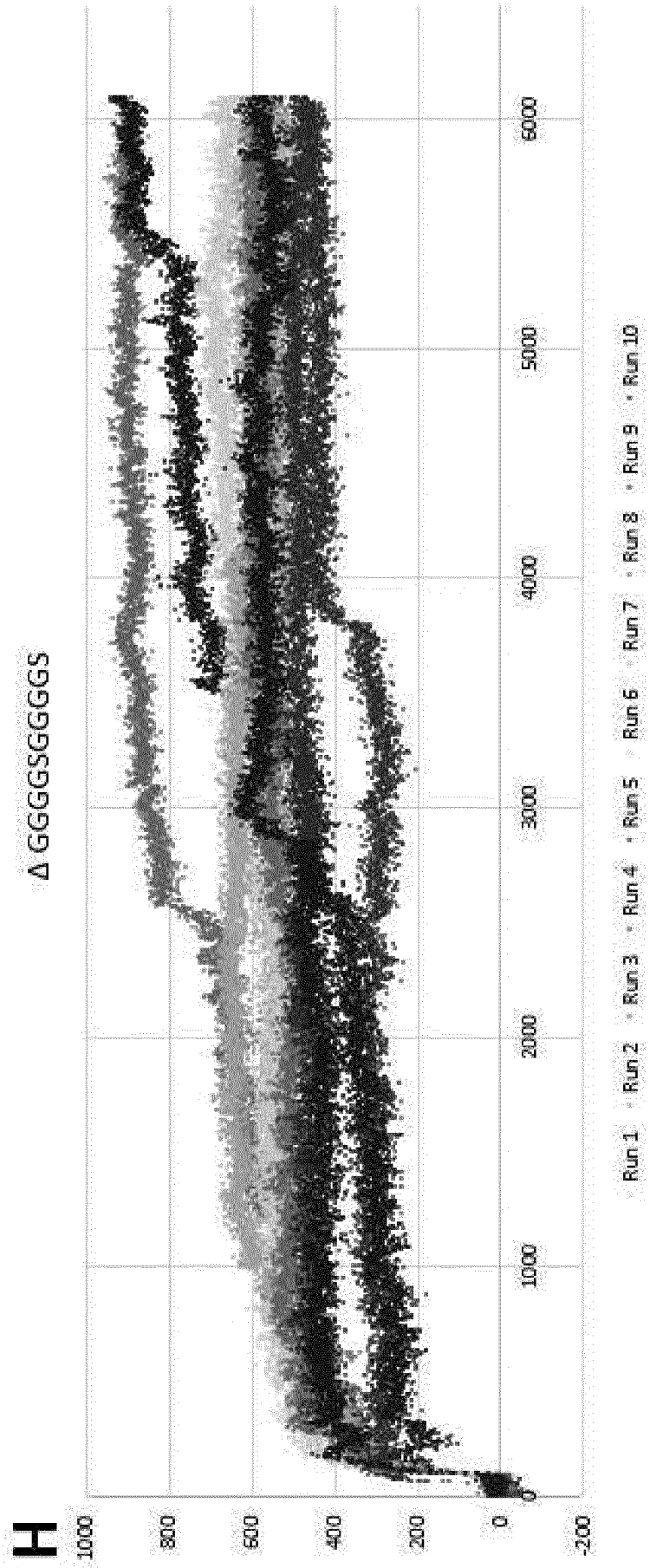

Δ GGGGSGGGGS
H
1000
800
600
400
200
0
-200
1000
2000
3000
4000
5000
6000
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9
Run 10

Figure 19

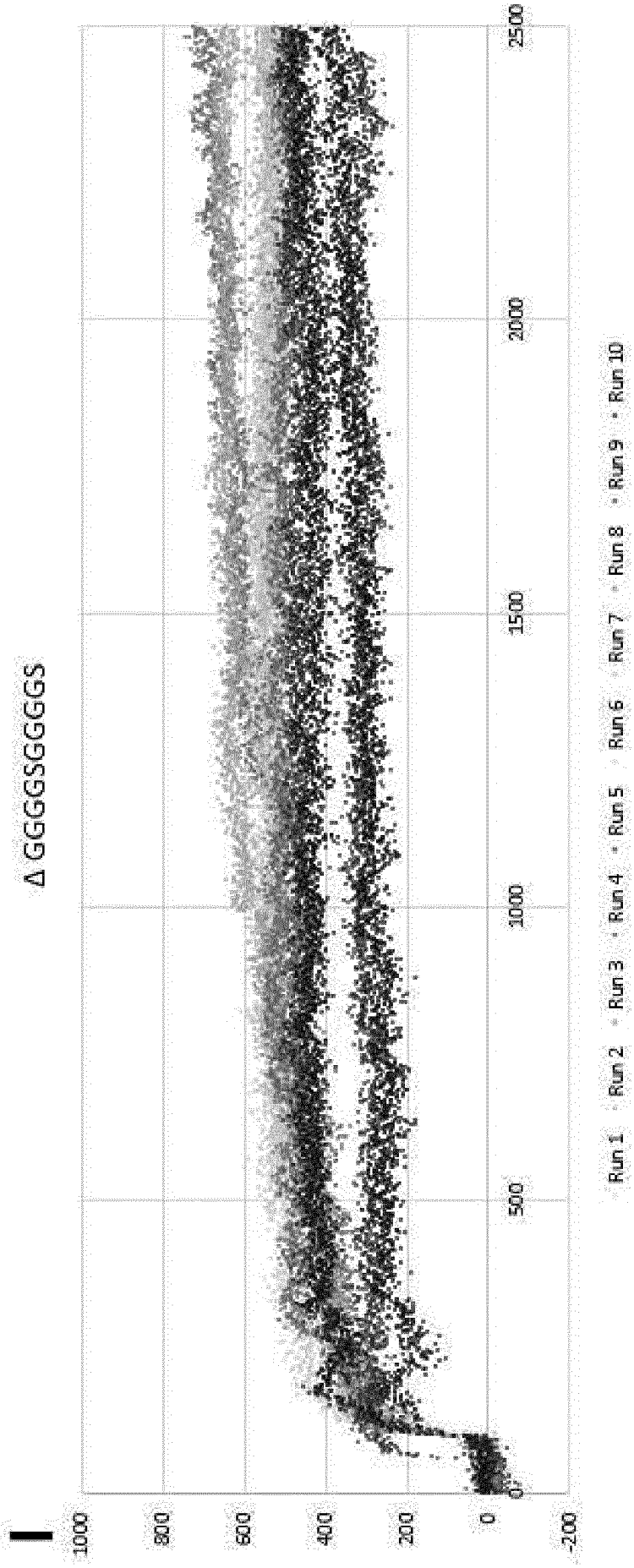

Δ GGGGSGGGGS
1000
800
600
400
200
0
-200
500
1000
1500
2000
2500
Run 1
Run 2
Run 3
Run 4
Run 5
Run 6
Run 7
Run 8
Run 9
Run 10

Figure 20A

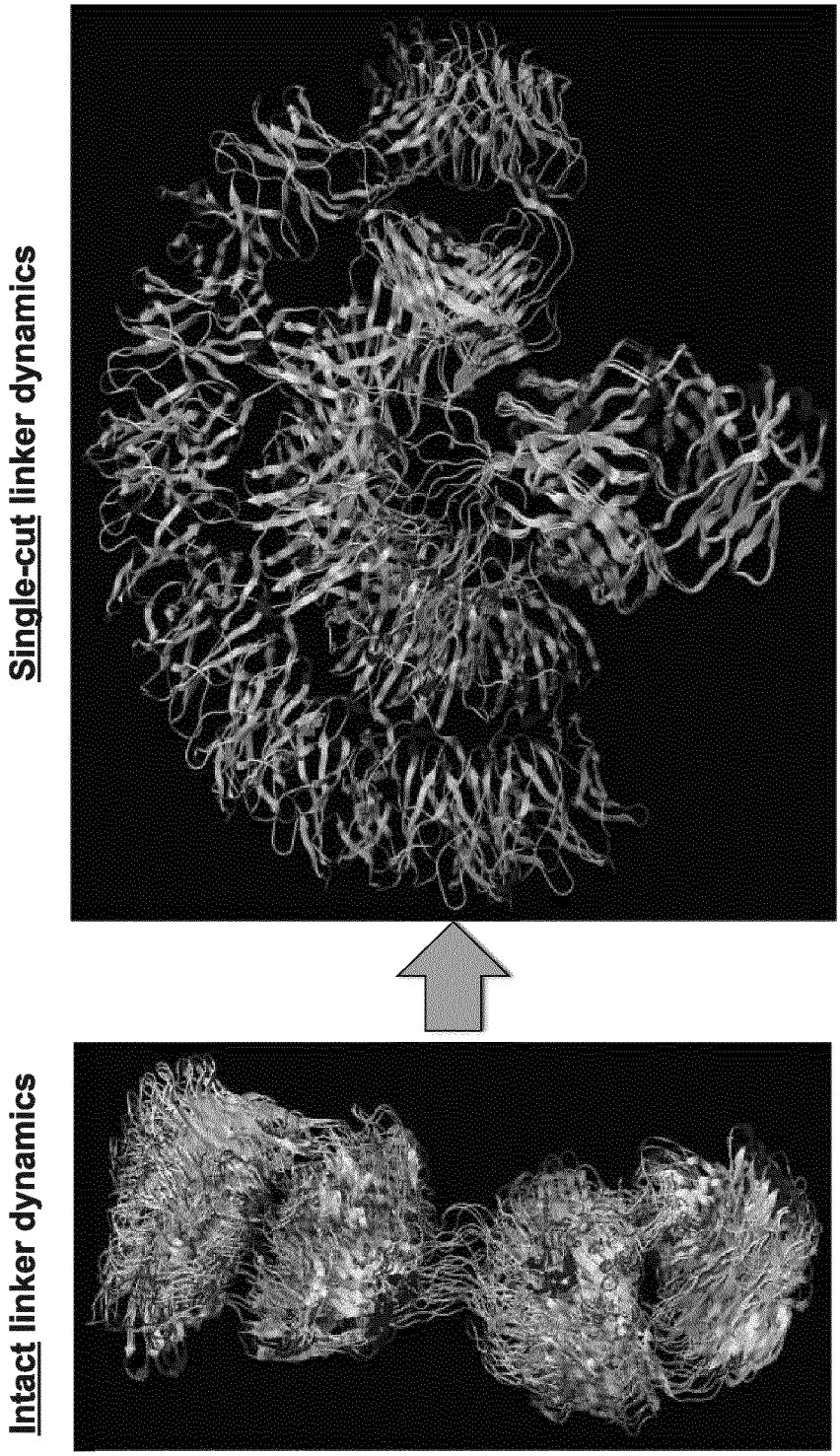


Figure 20B



FIG. 21

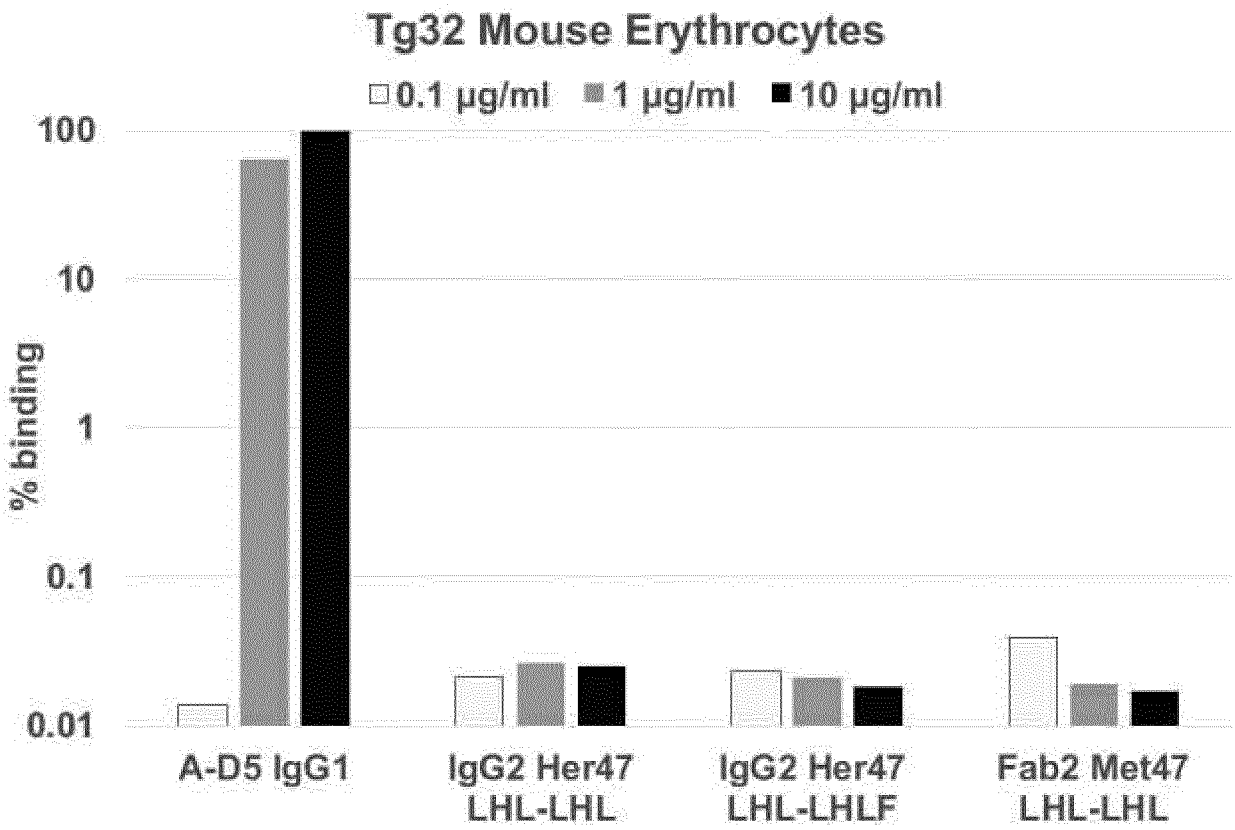

Tg32 Mouse Erythrocytes
0.1 µg/ml
1 µg/ml
10 µg/ml
100
10
1
0.1
0.01
% binding
A-D5 IgG1
IgG2 Her47 LHL-LHL
IgG2 Her47 LHL-LHLF
Fab2 Met47 LHL-LHL

Figure 22

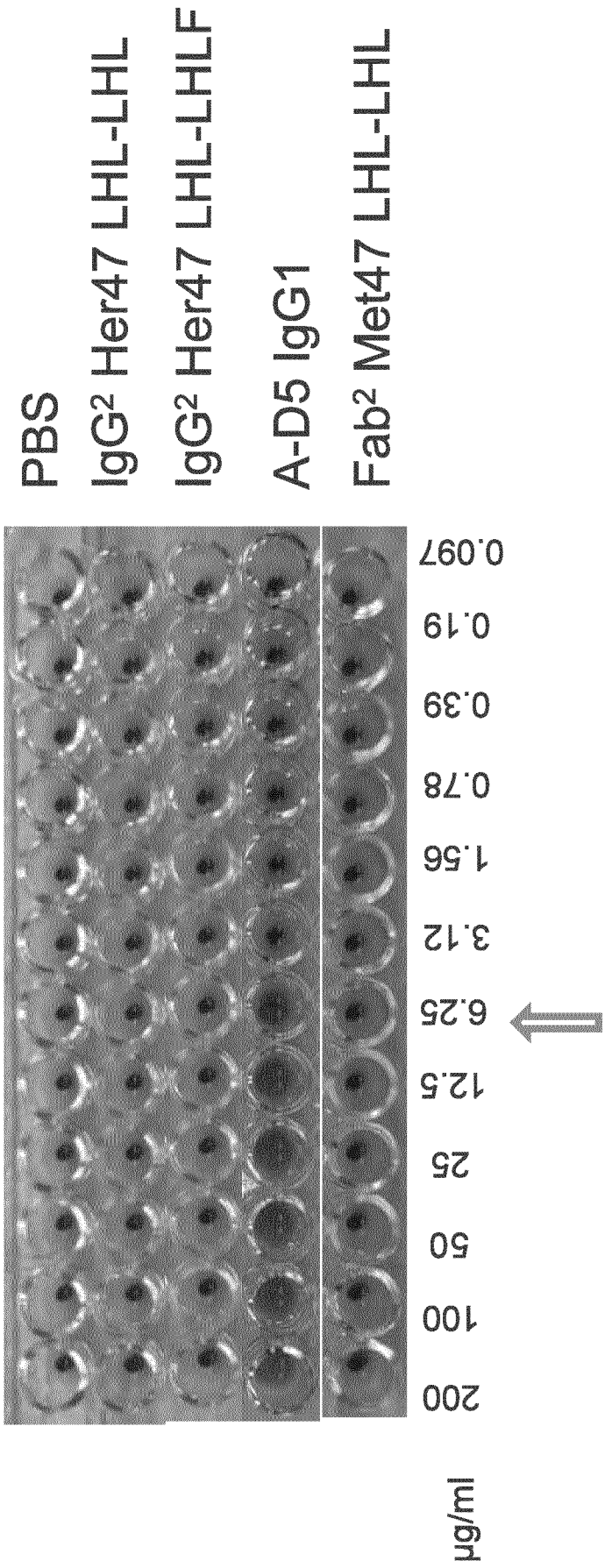

PBS
IgG² Her47 LHL-LHL
IgG² Her47 LHL-LHLF
A-D5 IgG1
Fab² Met47 LHL-LHL
0.097
0.19
0.39
0.78
1.56
3.12
6.25
12.5
25
50
100
200
µg/ml

Figure 23

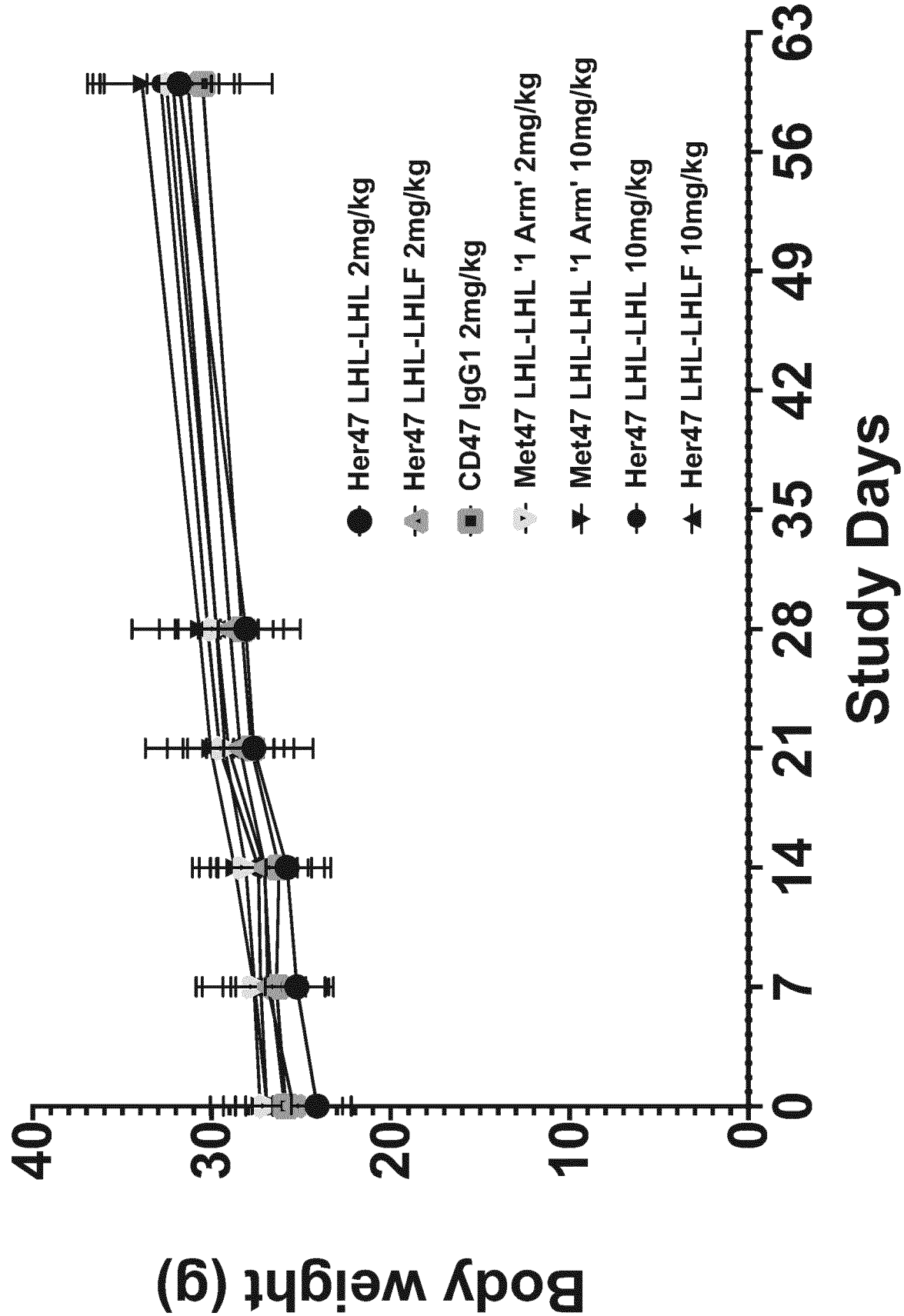

Body weight (g)
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
Study Days
Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg

Figure 24

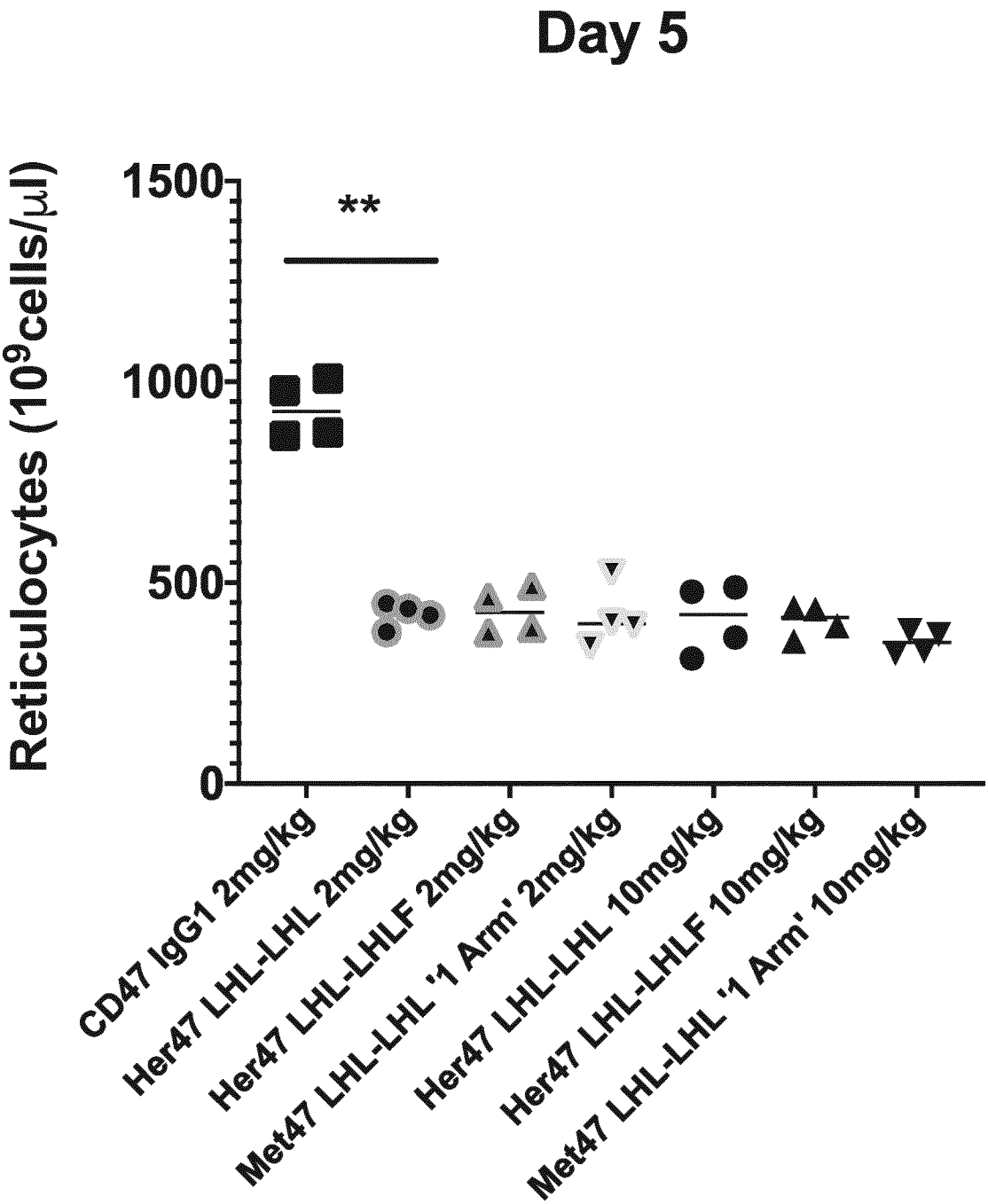

Day 5
Reticulocytes (10^9cells/μl)
1500
1000
500
0
**
CD47 IgG1 2mg/kg
Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg

Figure 25A

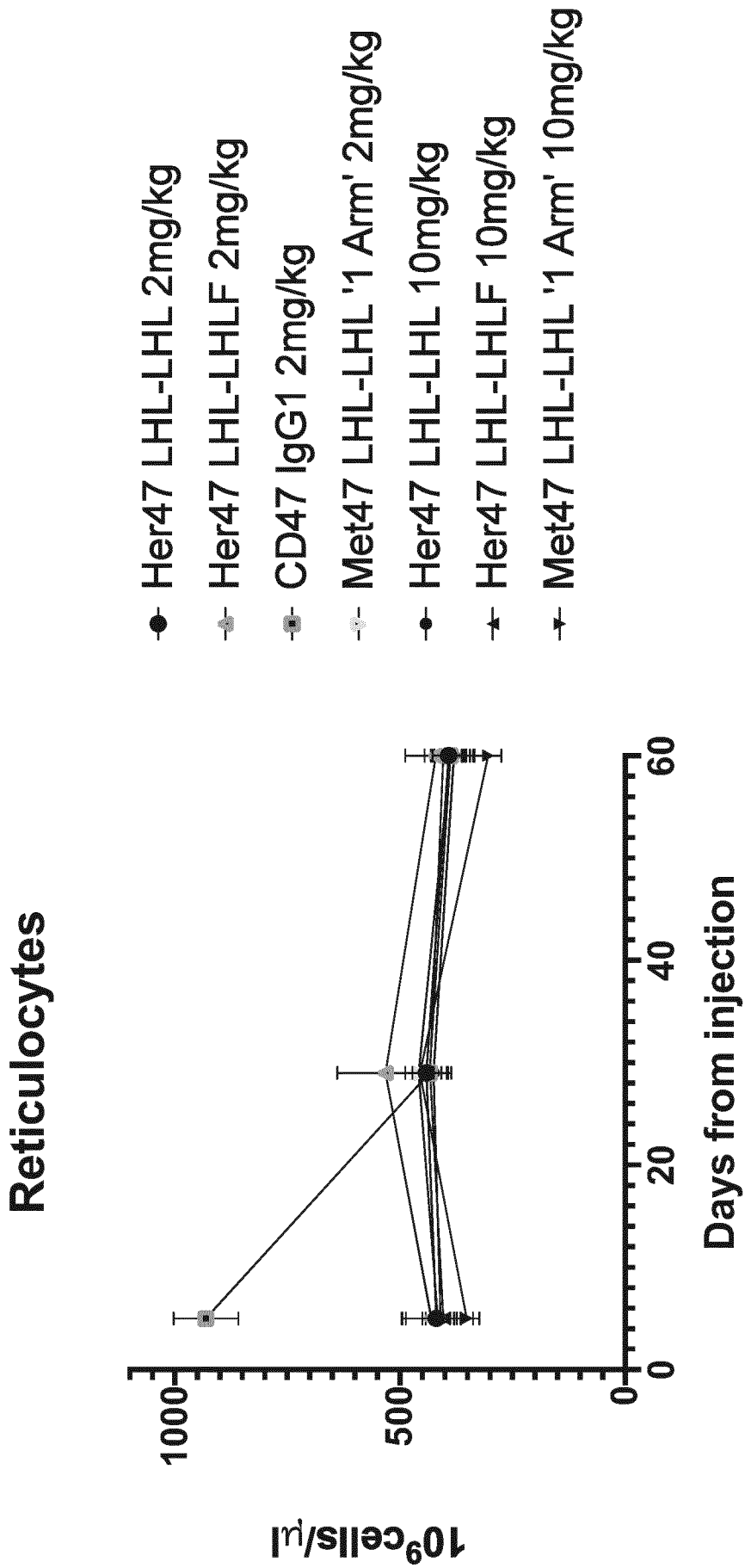

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Reticulocytes
10^9cells/µl
1000
500
0
0
20
40
60
Days from injection

Figure 25B

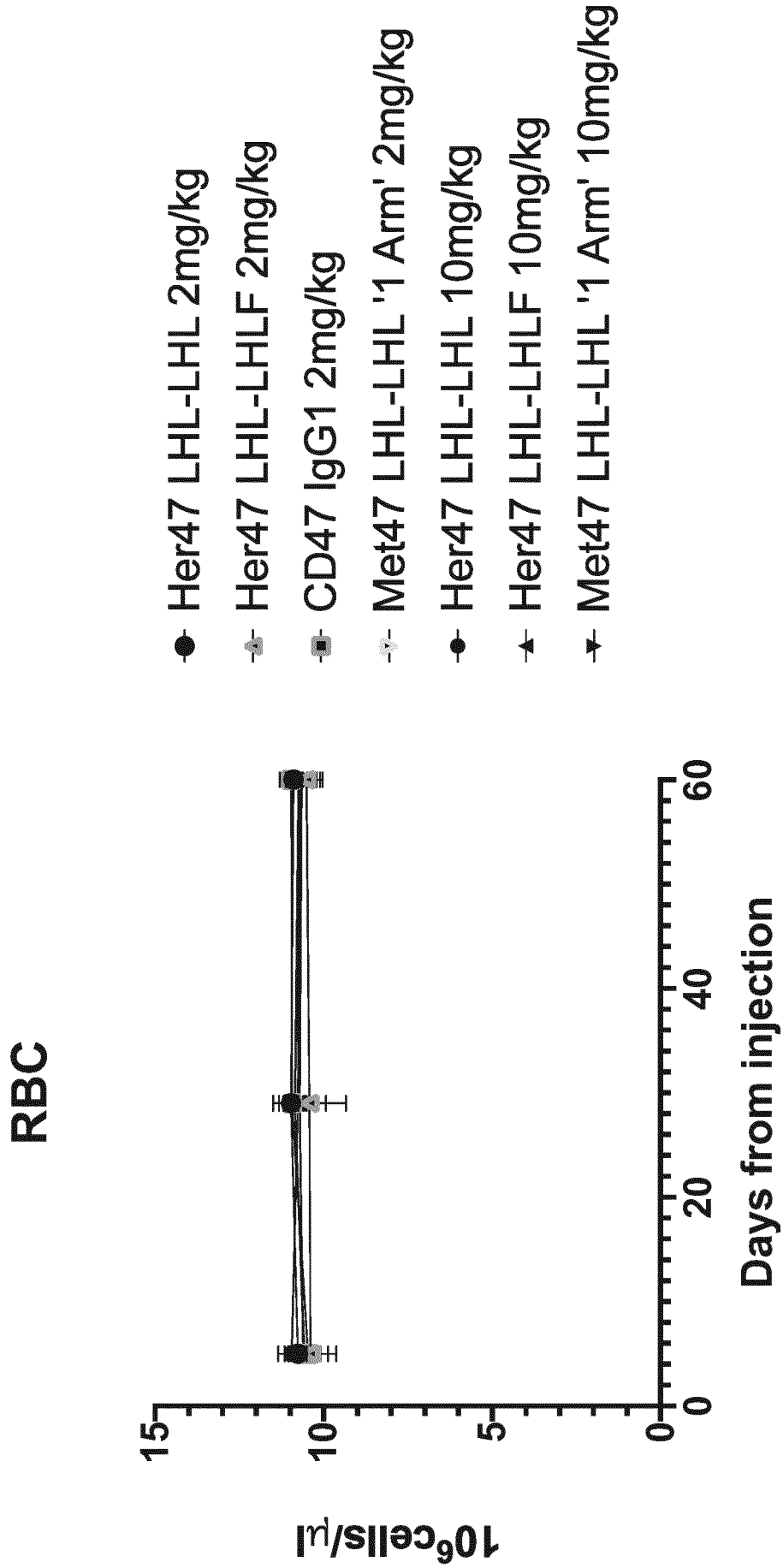

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
RBC
10⁶cells/µl
15
10
5
0
0
20
40
60
Days from injection

Figure 25C

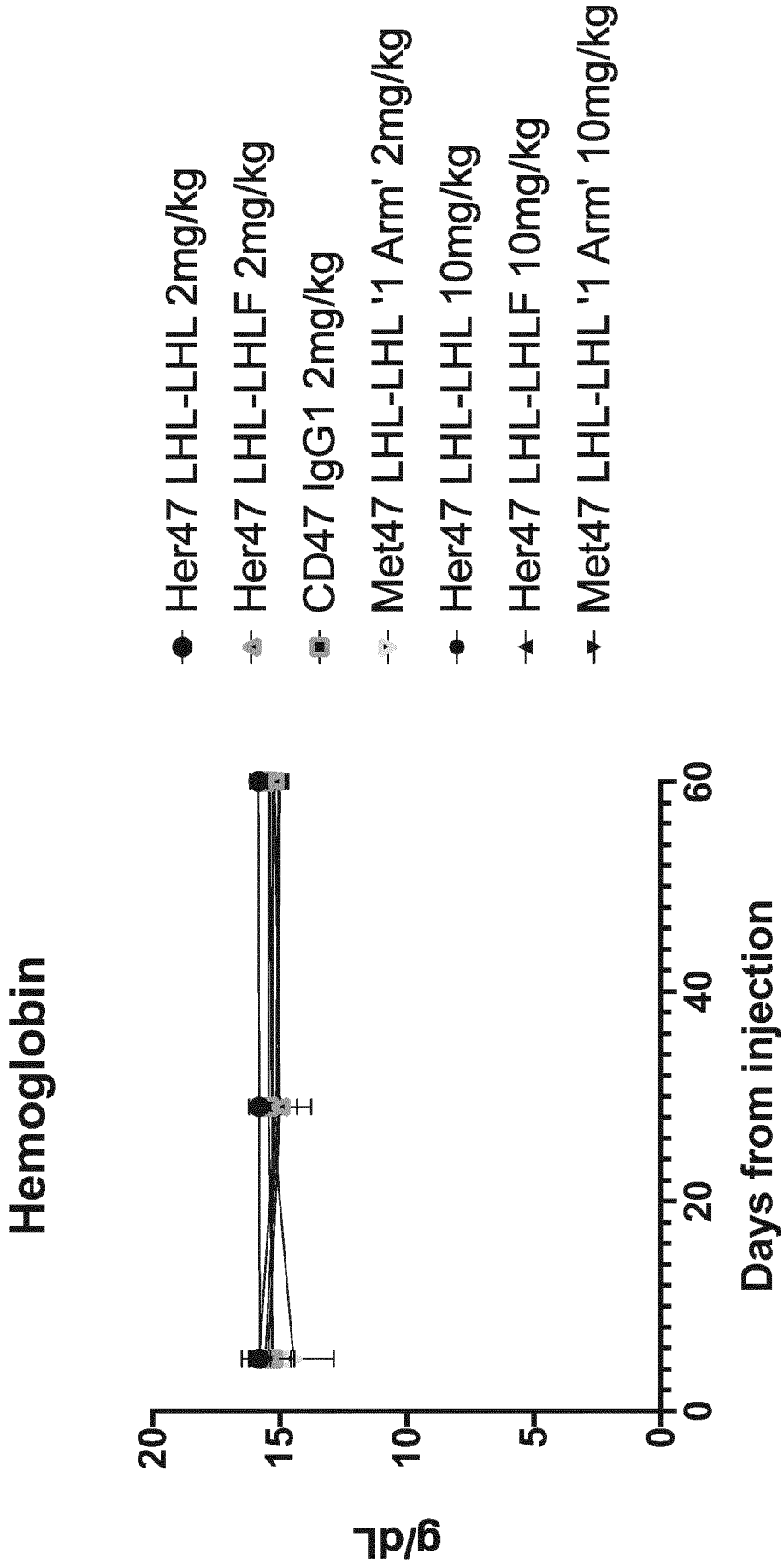

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Hemoglobin
g/dL
20
15
10
5
0
0
20
40
60
Days from injection

Figure 25D

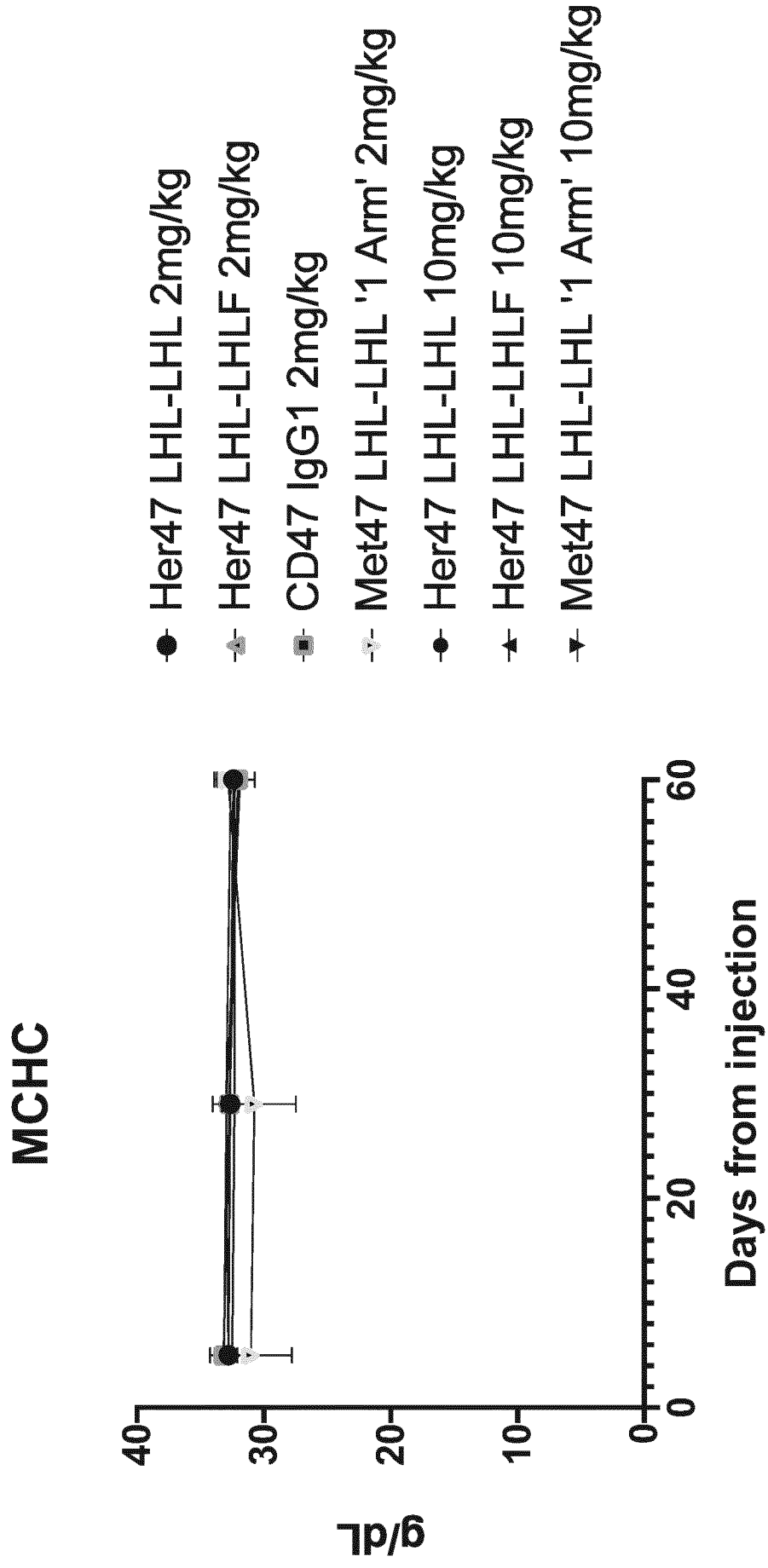

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
MCHC
g/dL
40
30
20
10
0
0
20
40
60
Days from injection

Figure 25E

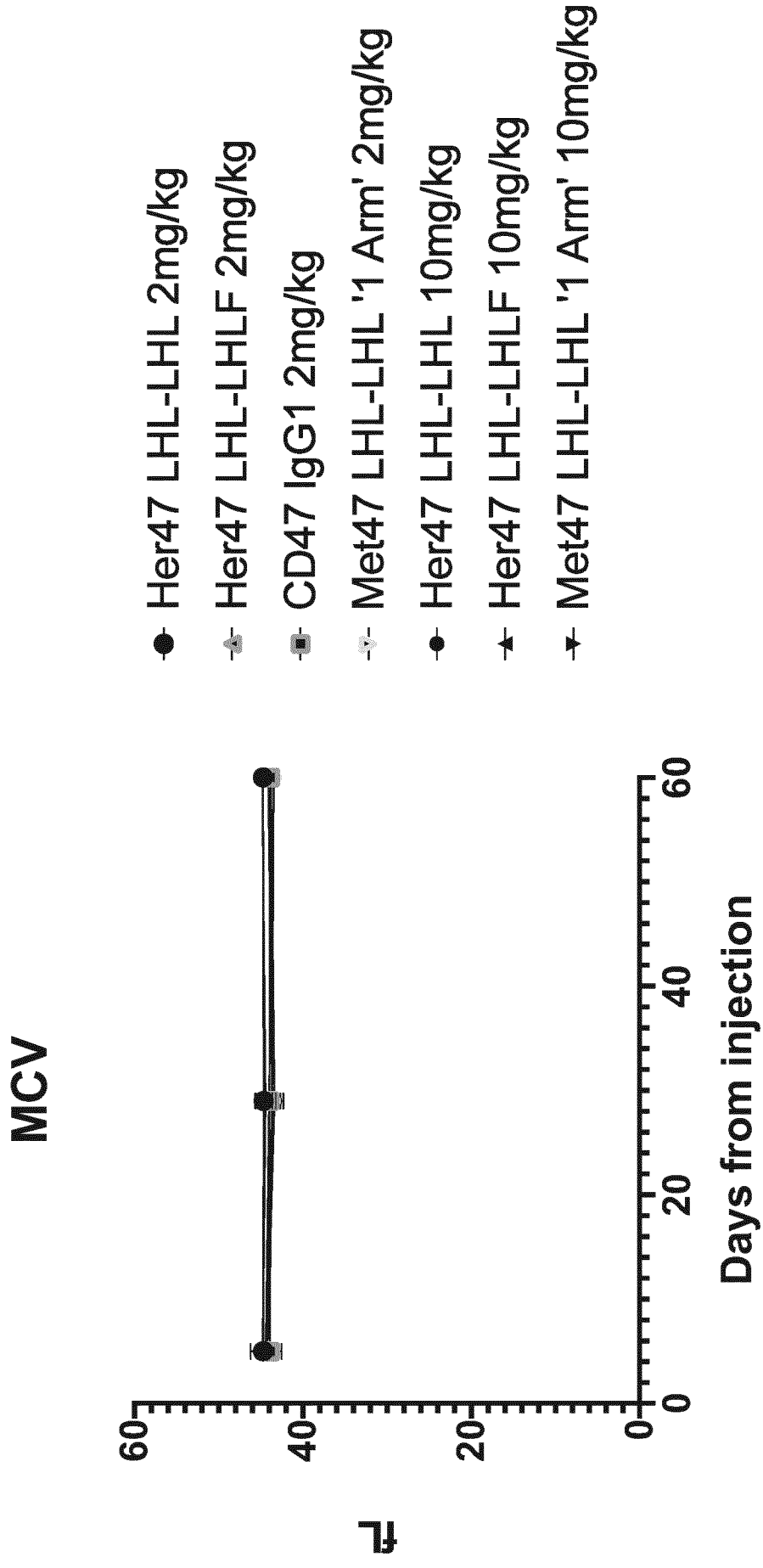

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
MCV
fL
60
40
20
0
0
20
40
60
Days from injection

Figure 25F

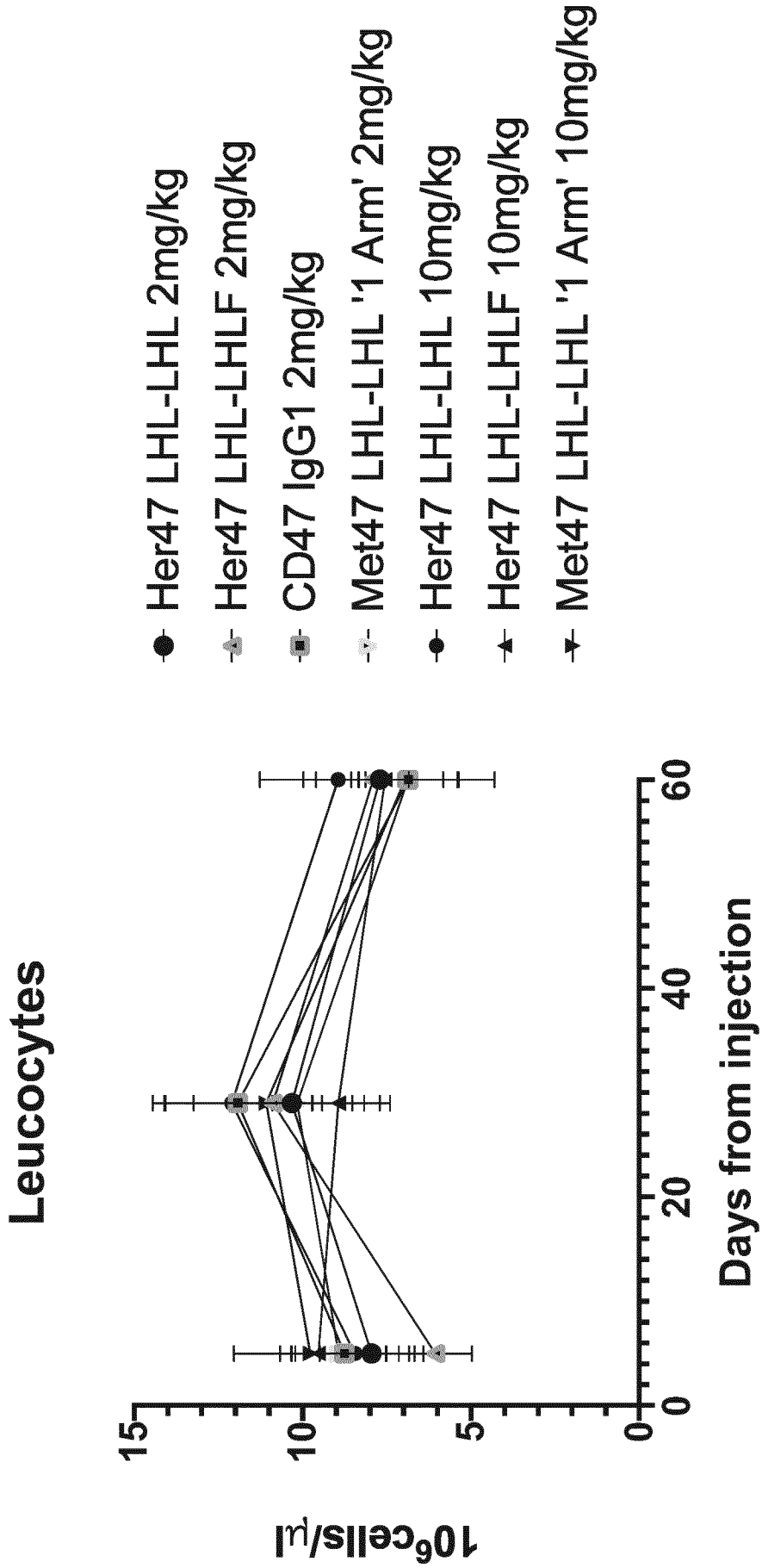

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Leucocytes
10⁶cells/µl
15
10
5
0
0
20
40
60
Days from injection

Figure 25G

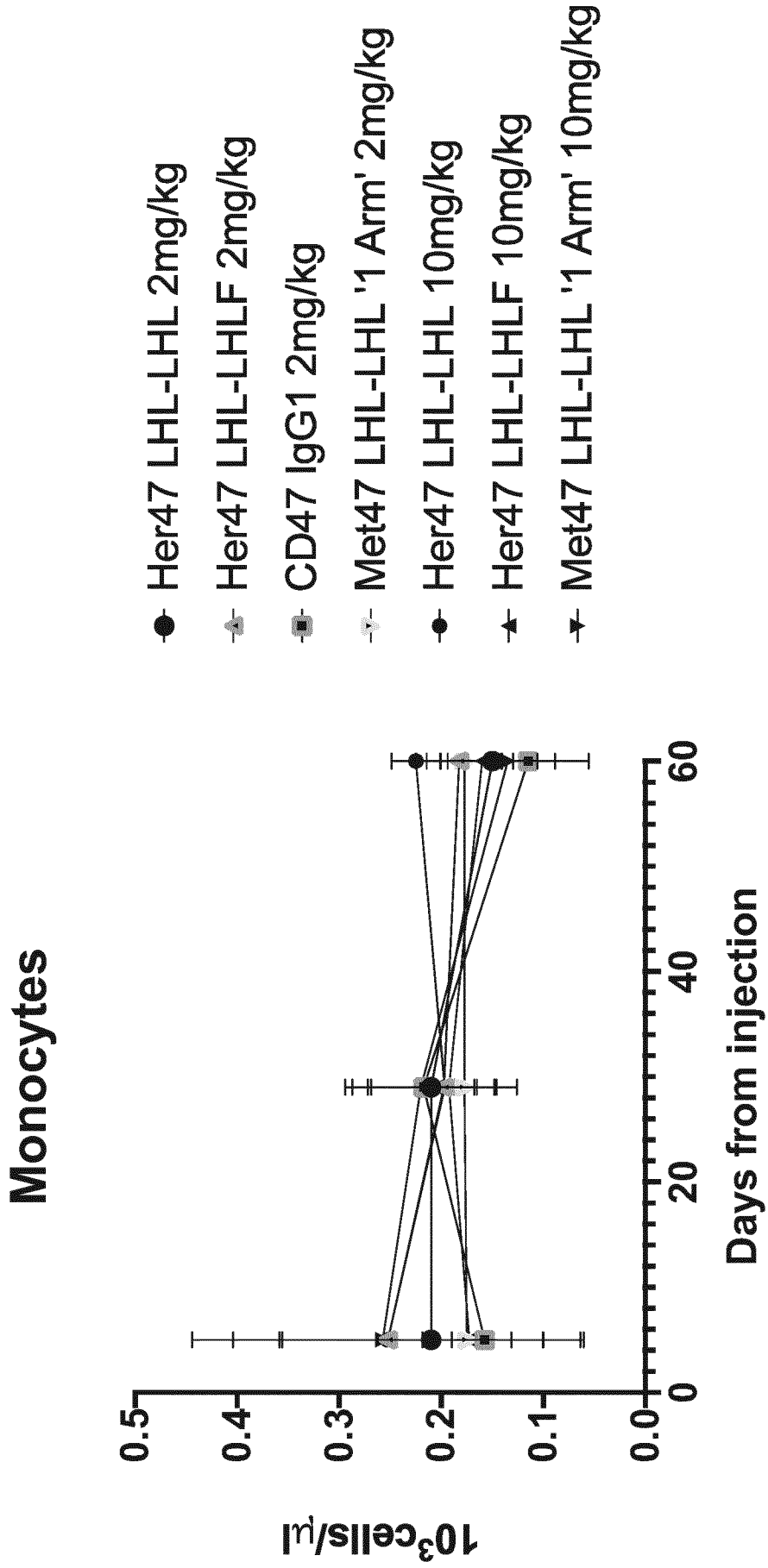

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Monocytes
10³cells/µl
0.0
0.1
0.2
0.3
0.4
0.5
0
20
40
60
Days from injection

Figure 25H

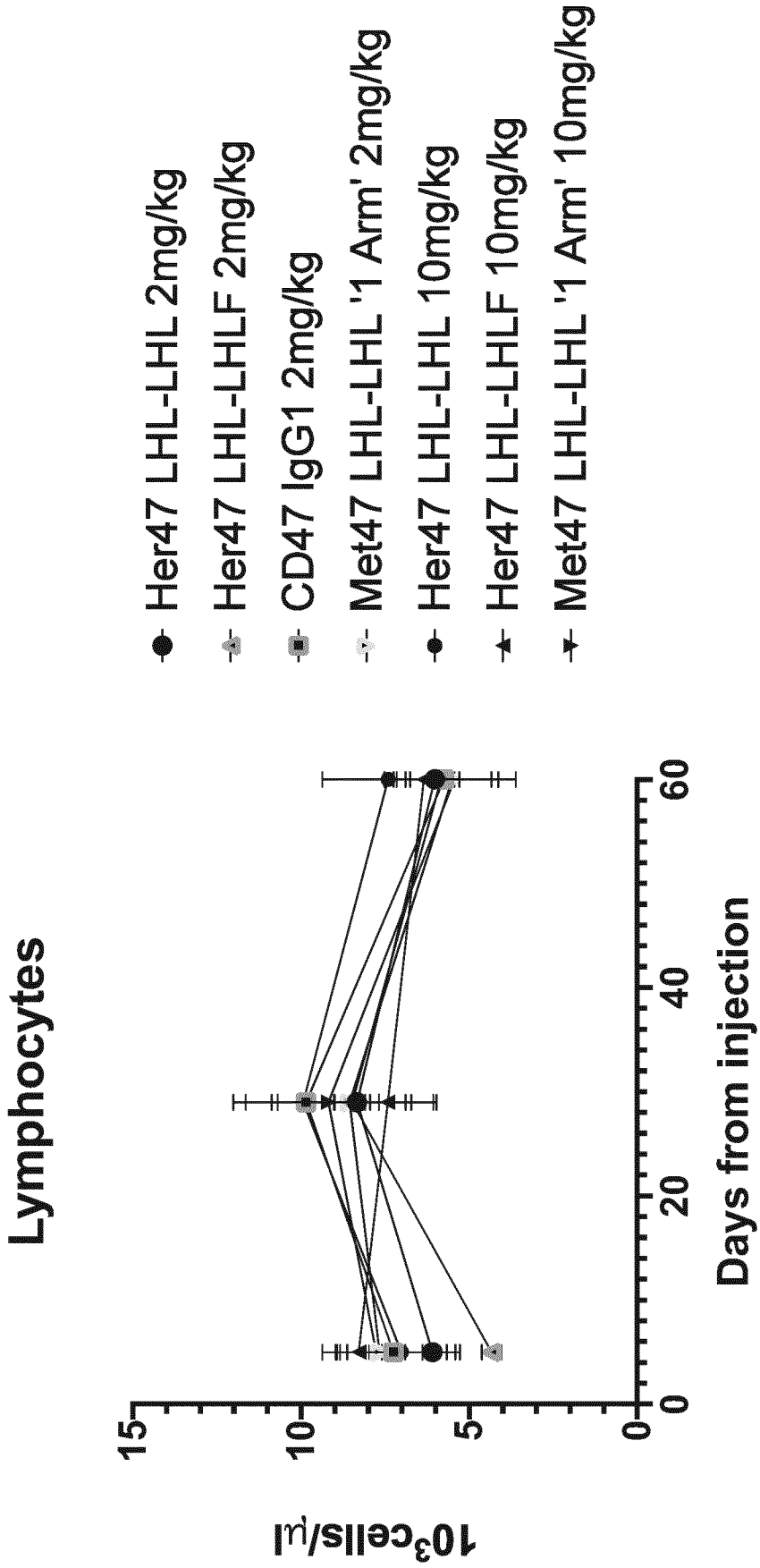

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Lymphocytes
10³cells/µl
15
10
5
0
0
20
40
60
Days from injection

Figure 25l

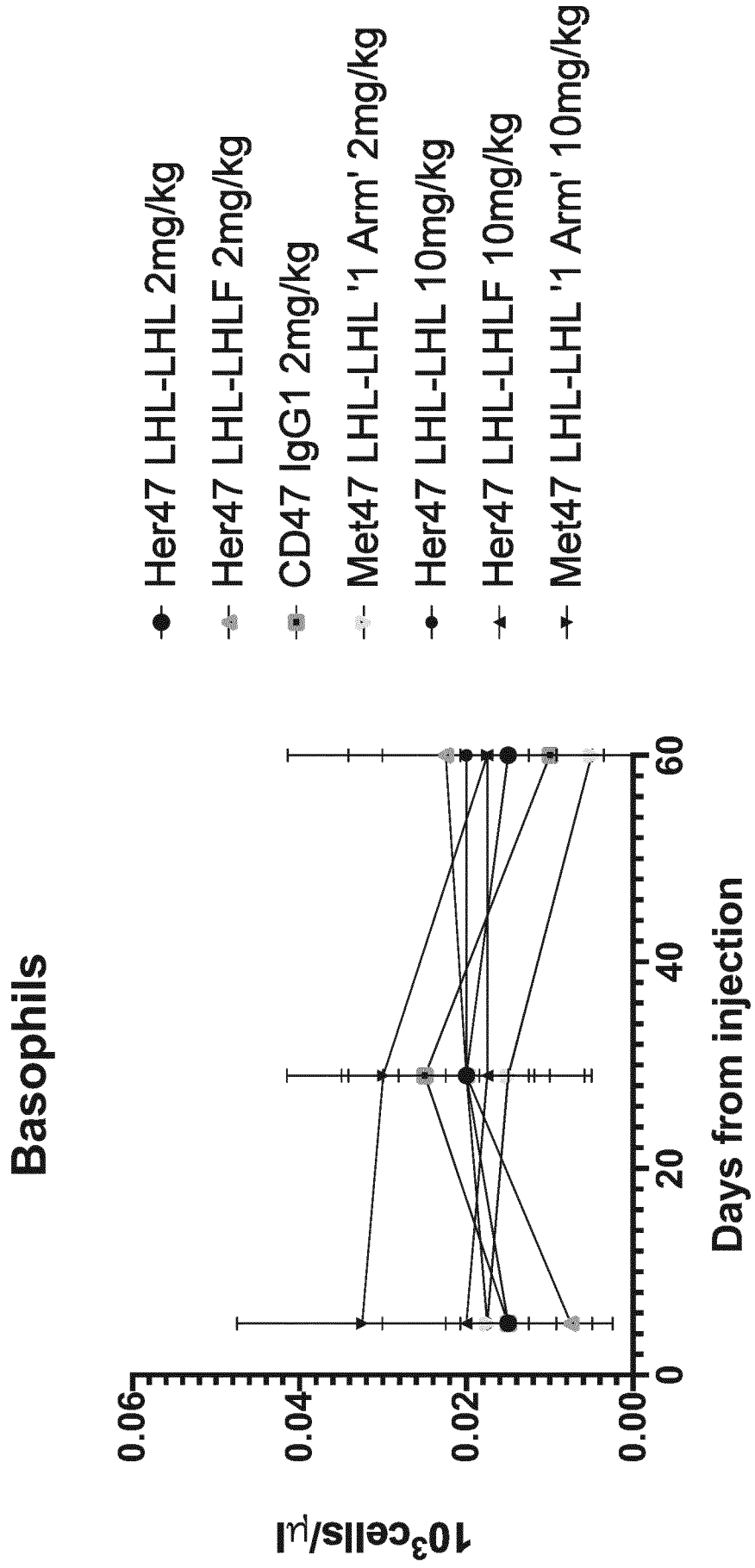

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Basophils
10³cells/µl
0.06
0.04
0.02
0.00
0
20
40
60
Days from injection

Figure 25J

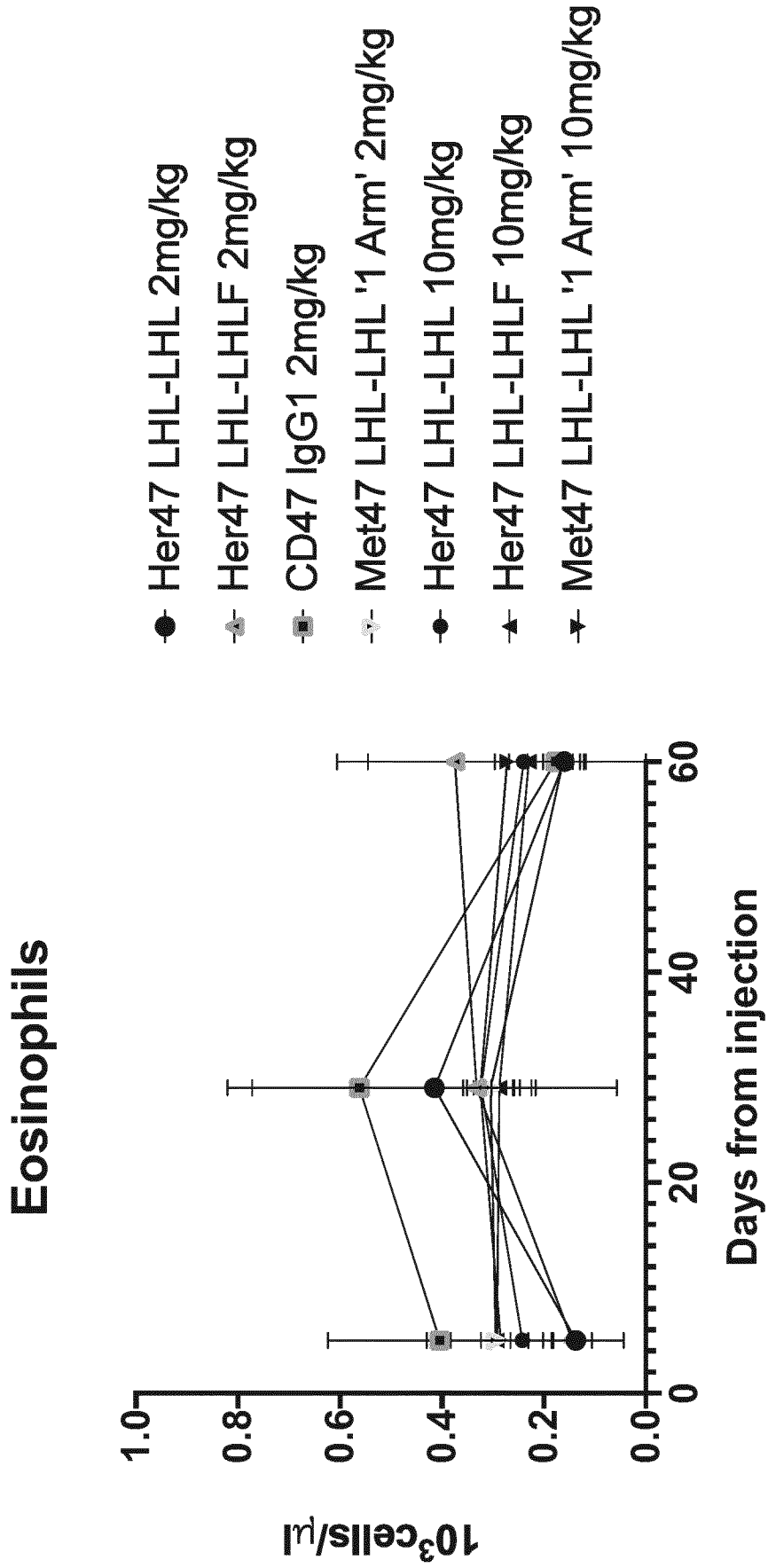

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Eosinophils
10³cells/µl
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
Days from injection

Figure 25K

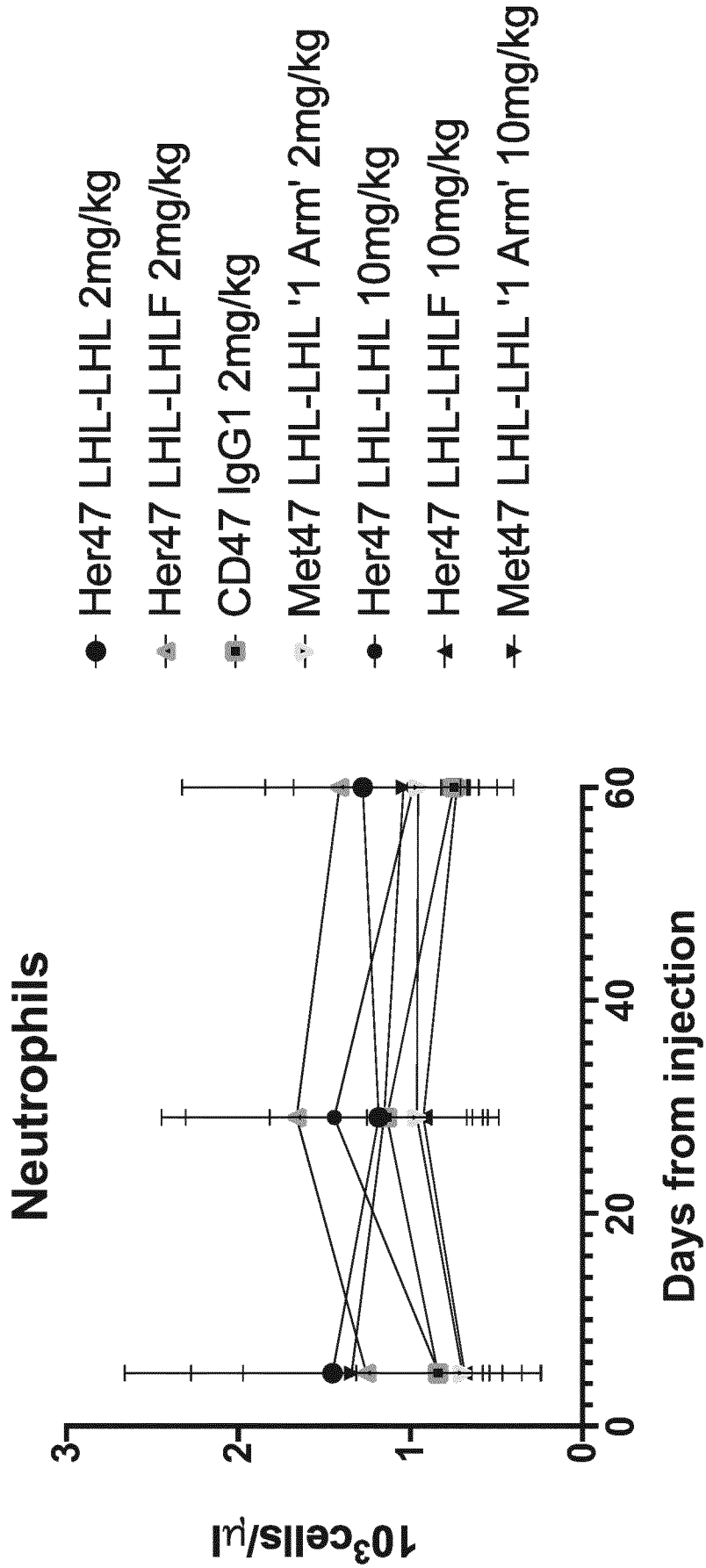

Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Neutrophils
10³cells/µl
0
1
2
3
0
20
40
60
Days from injection

Figure 26

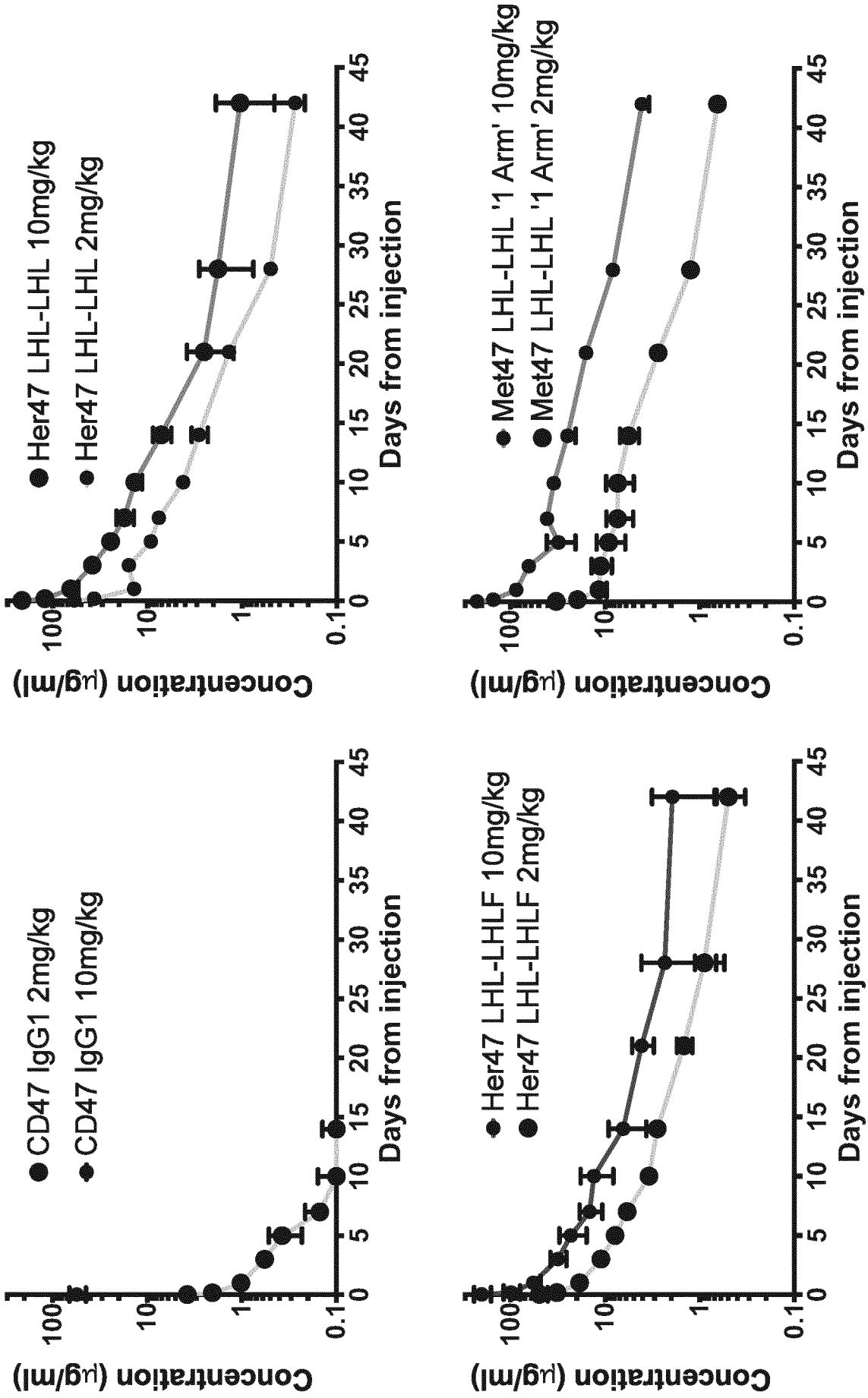

Her47 LHL-LHL 10mg/kg
Her47 LHL-LHL 2mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg
CD47 IgG1 2mg/kg
CD47 IgG1 10mg/kg
Her47 LHL-LHLF 10mg/kg
Her47 LHL-LHLF 2mg/kg
Concentration (µg/ml)
Days from injection
0.1
1
10
100
0
5
10
15
20
25
30
35
40
45

Figure 27A

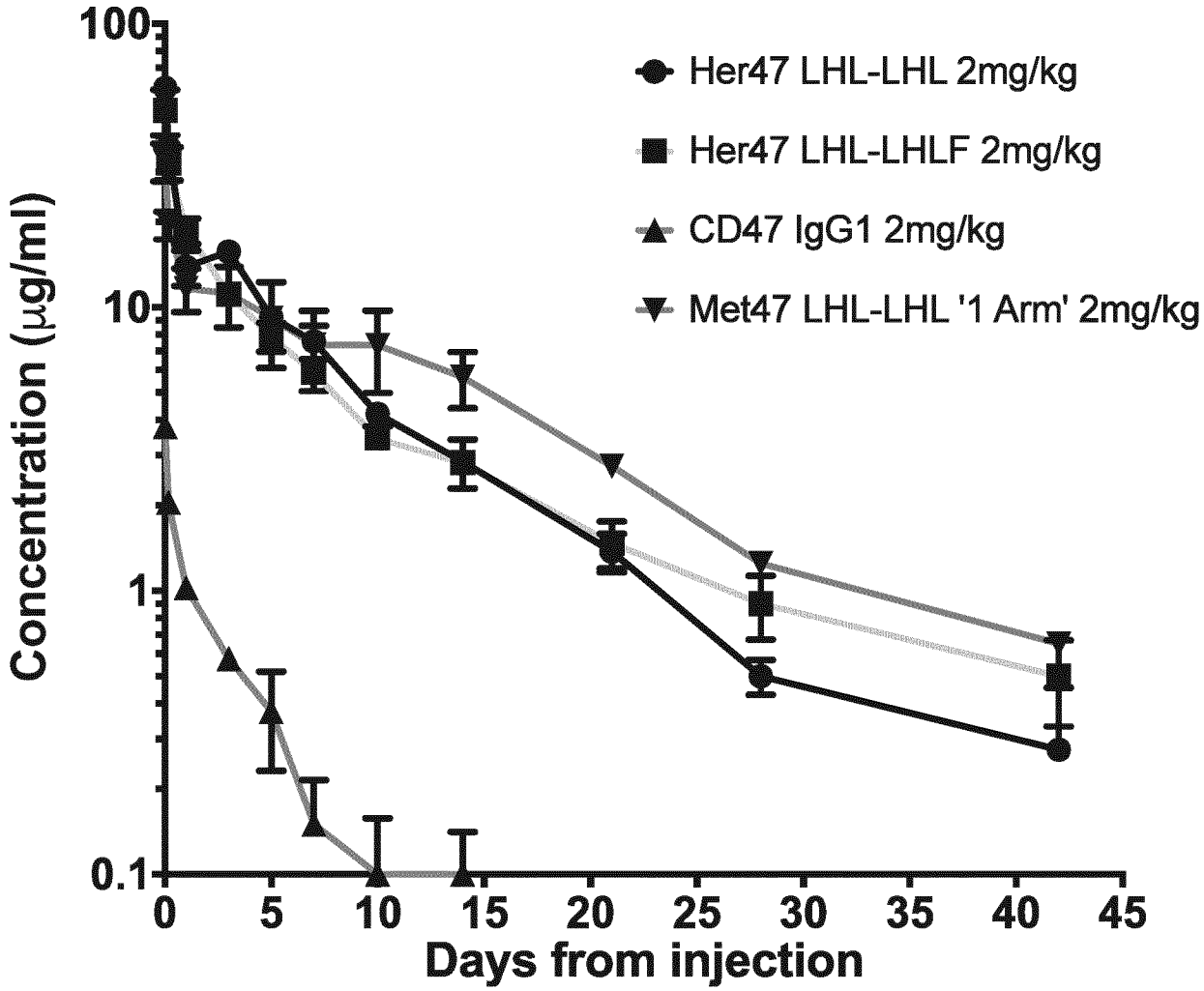

100
10
1
0.1
Concentration (µg/ml)
0
5
10
15
20
25
30
35
40
45
Days from injection
Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
CD47 IgG1 2mg/kg
Met47 LHL-LHL '1 Arm' 2mg/kg

Figure 27B

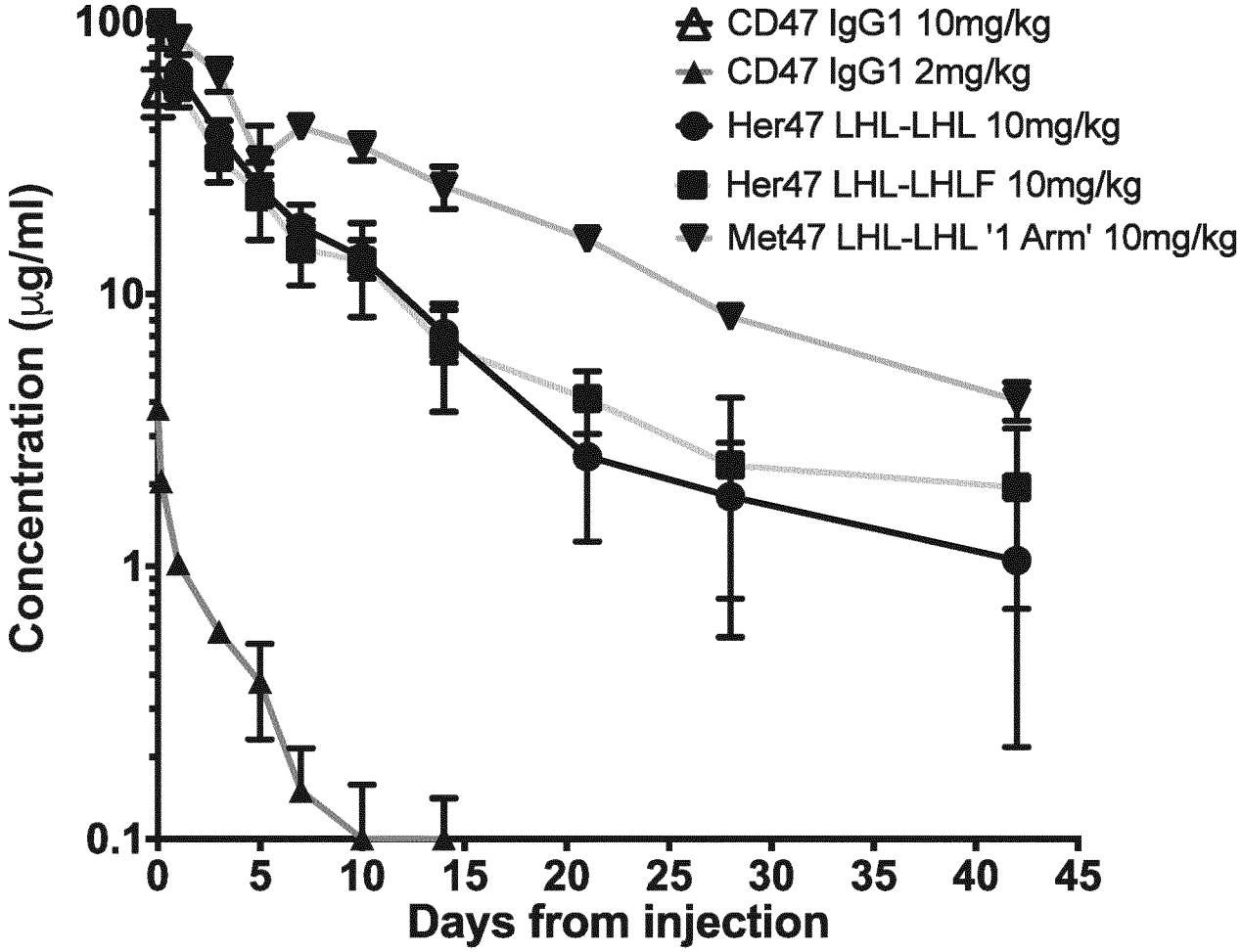

CD47 IgG1 10mg/kg
CD47 IgG1 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHLF 10mg/kg
Met47 LHL-LHL '1 Arm' 10mg/kg
Concentration (µg/ml)
100
10
1
0.1
0
5
10
15
20
25
30
35
40
45
Days from injection

Figure 28

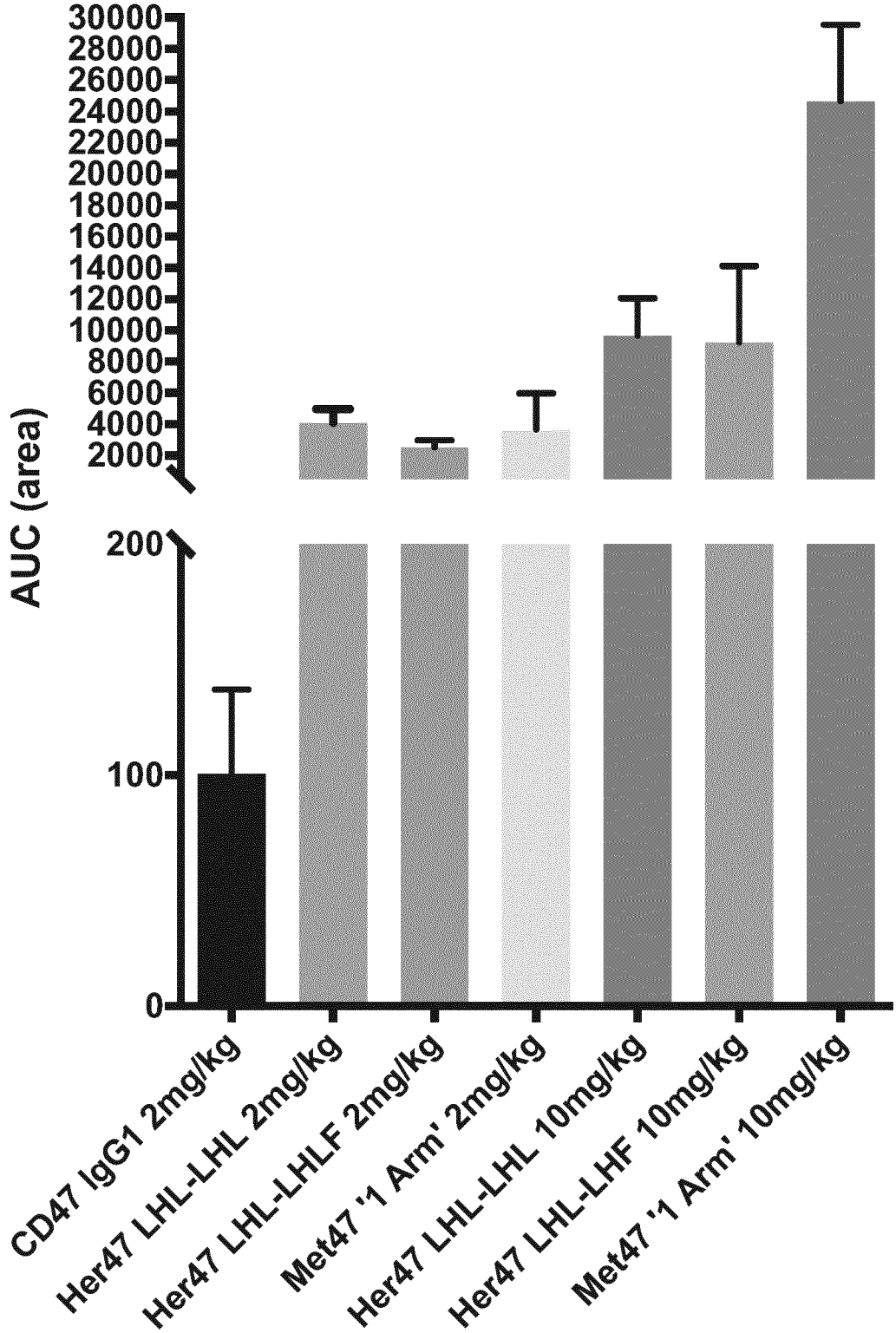

AUC (area)
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
200
100
0
CD47 IgG1 2mg/kg
Her47 LHL-LHL 2mg/kg
Her47 LHL-LHLF 2mg/kg
Met47 '1 Arm' 2mg/kg
Her47 LHL-LHL 10mg/kg
Her47 LHL-LHF 10mg/kg
Met47 '1 Arm' 10mg/kg

Figure 29A

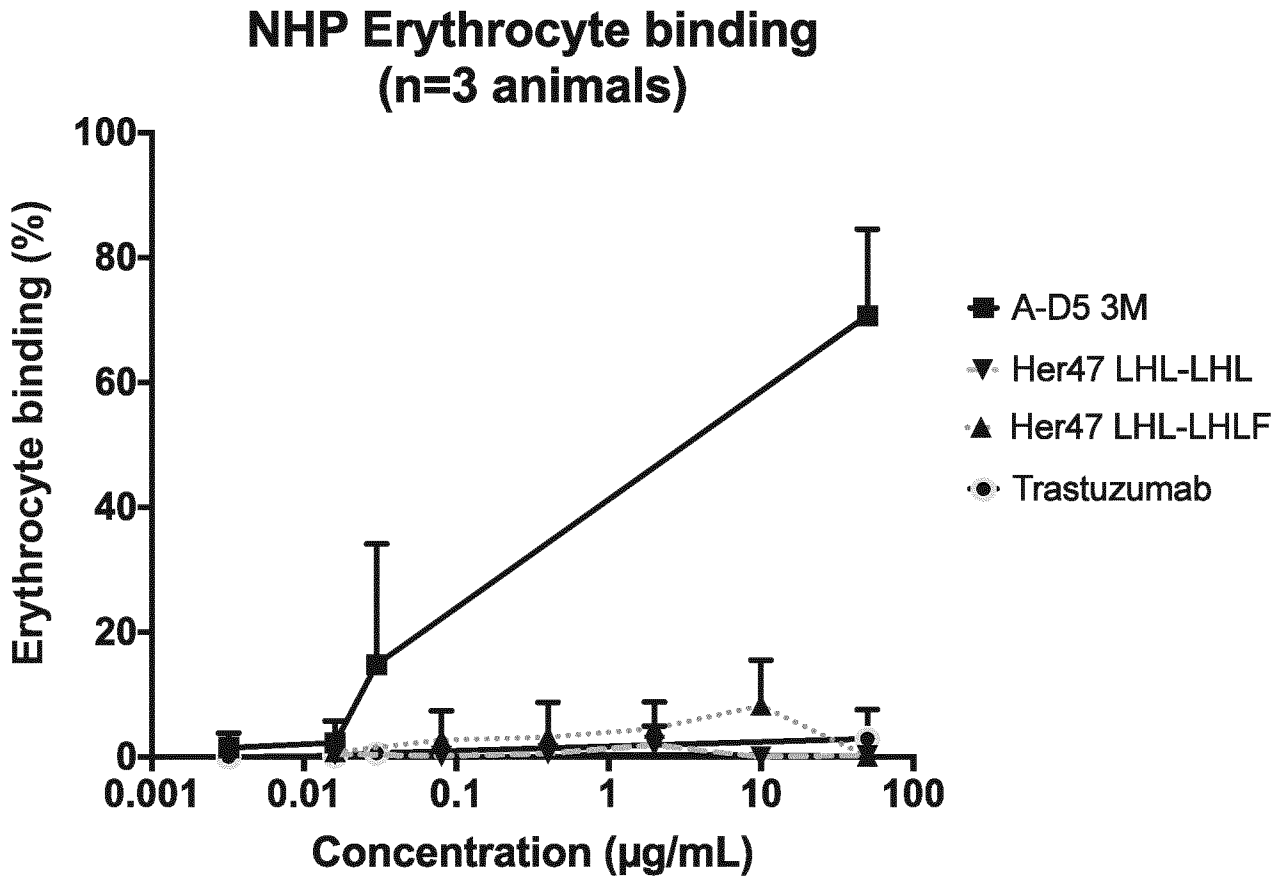

NHP Erythrocyte binding
(n=3 animals)
Erythrocyte binding (%)
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Concentration (µg/mL)
A-D5 3M
Her47 LHL-LHL
Her47 LHL-LHLF
Trastuzumab

Figure 29B

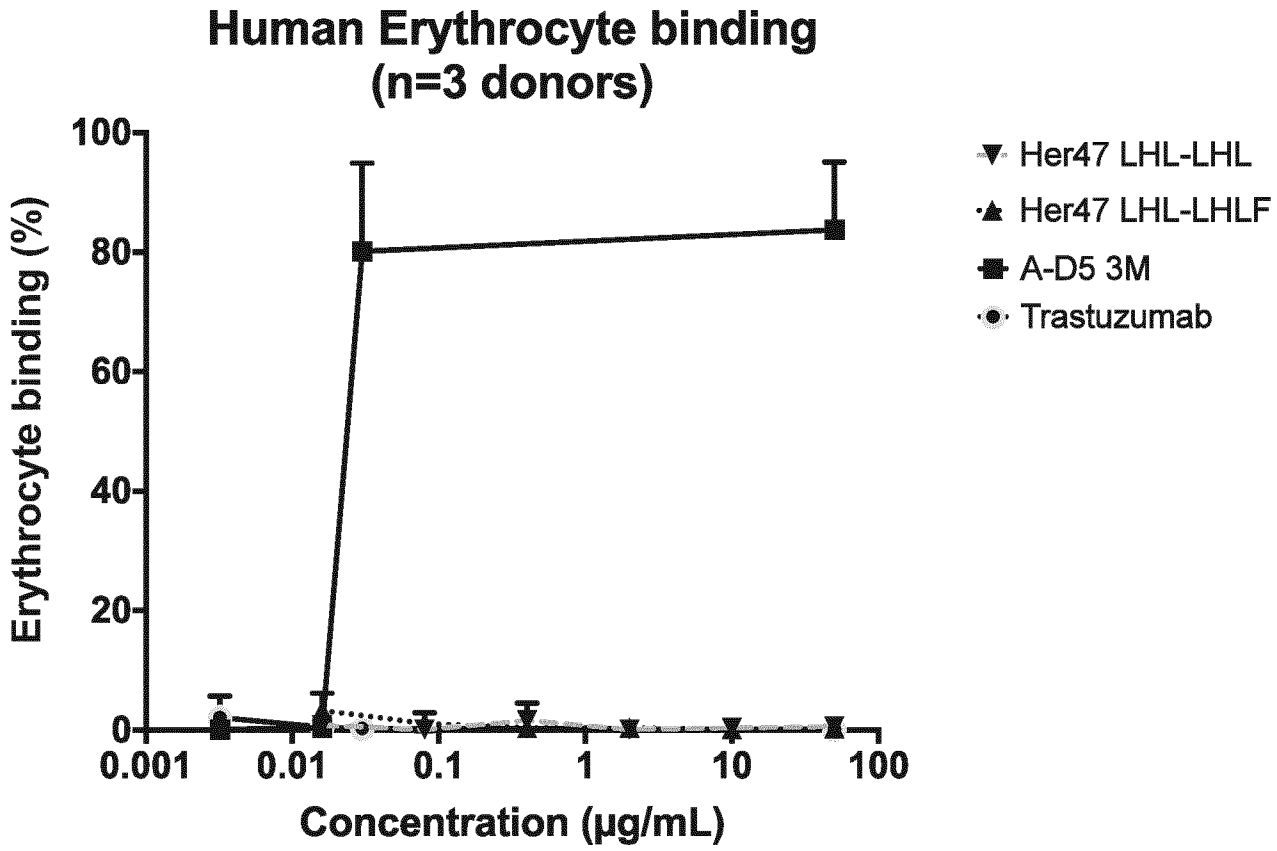

Human Erythrocyte binding
(n=3 donors)
Erythrocyte binding (%)
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
Concentration (µg/mL)
Her47 LHL-LHL
Her47 LHL-LHLF
A-D5 3M
Trastuzumab

Figure 30A

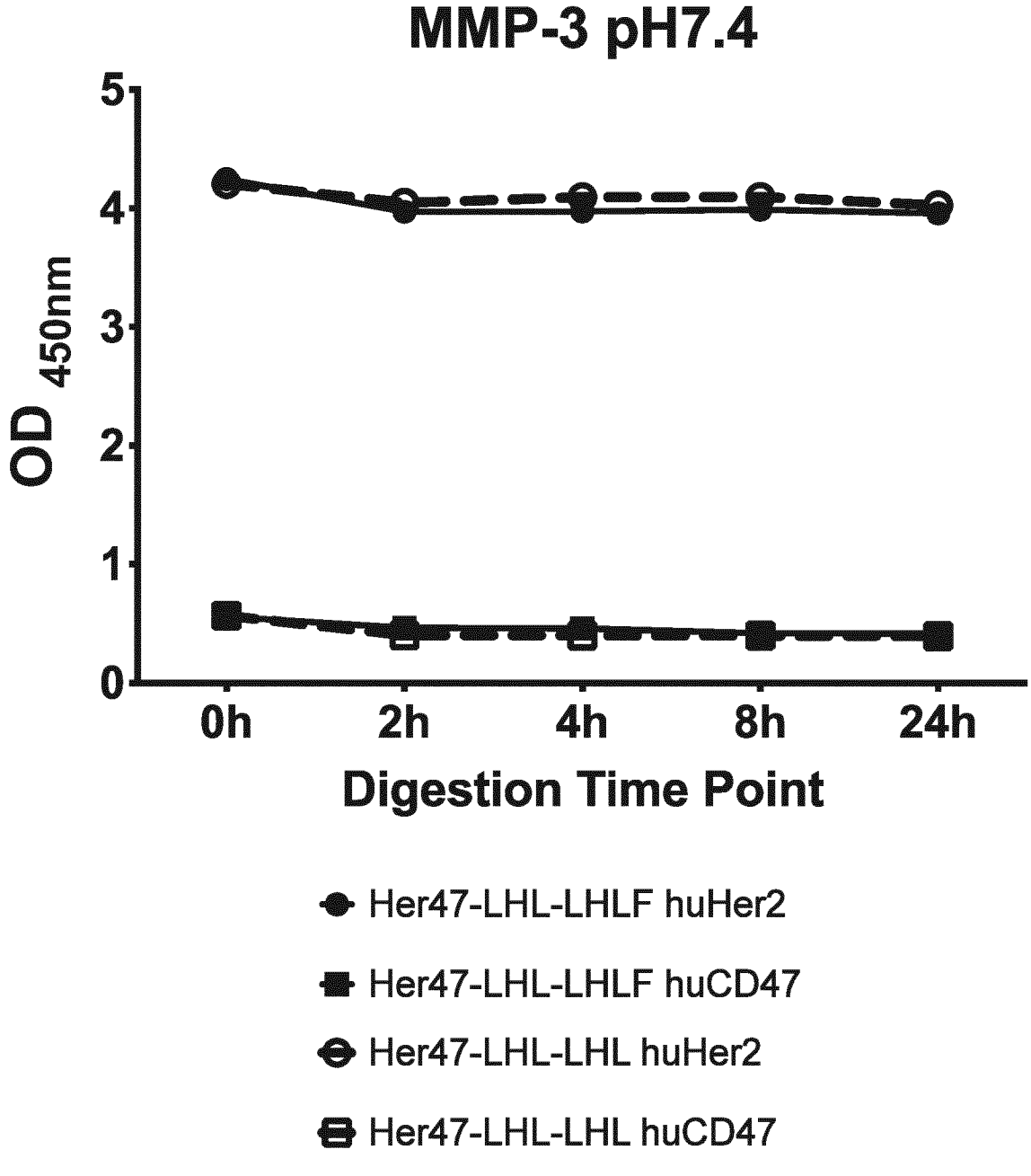

MMP-3 pH7.4
OD 450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30B

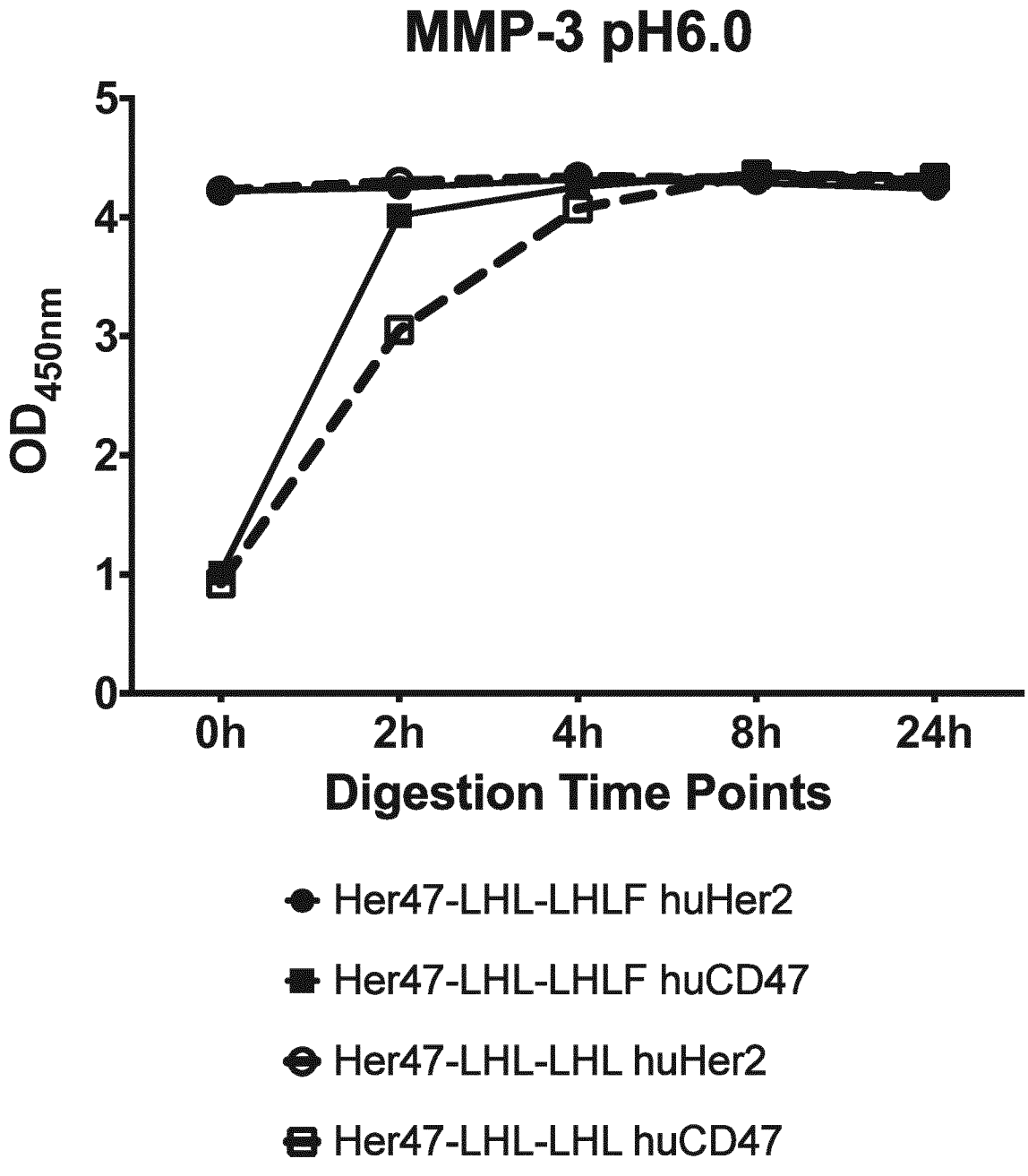

MMP-3 pH6.0
OD450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30C

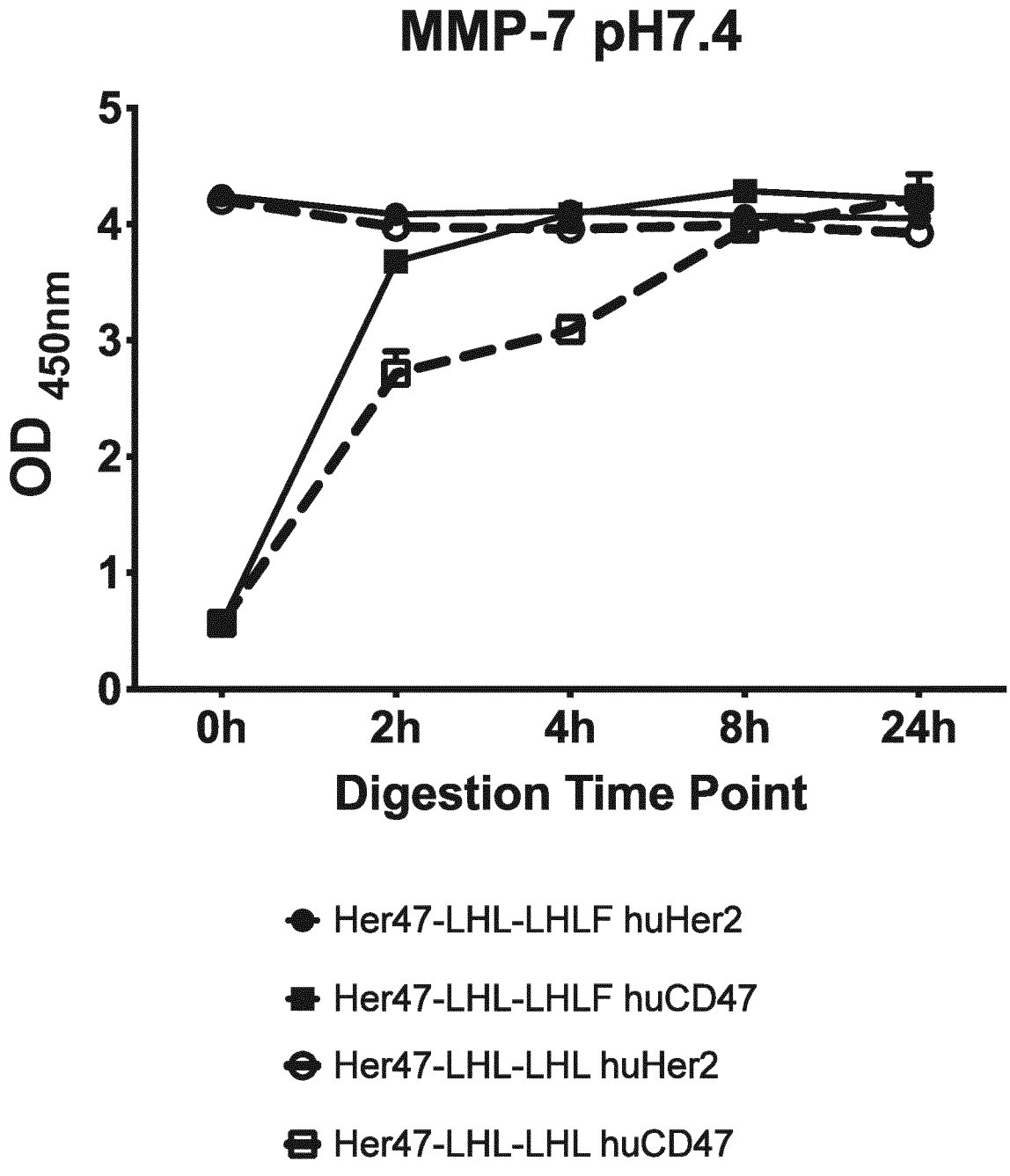

MMP-7 pH7.4
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30D

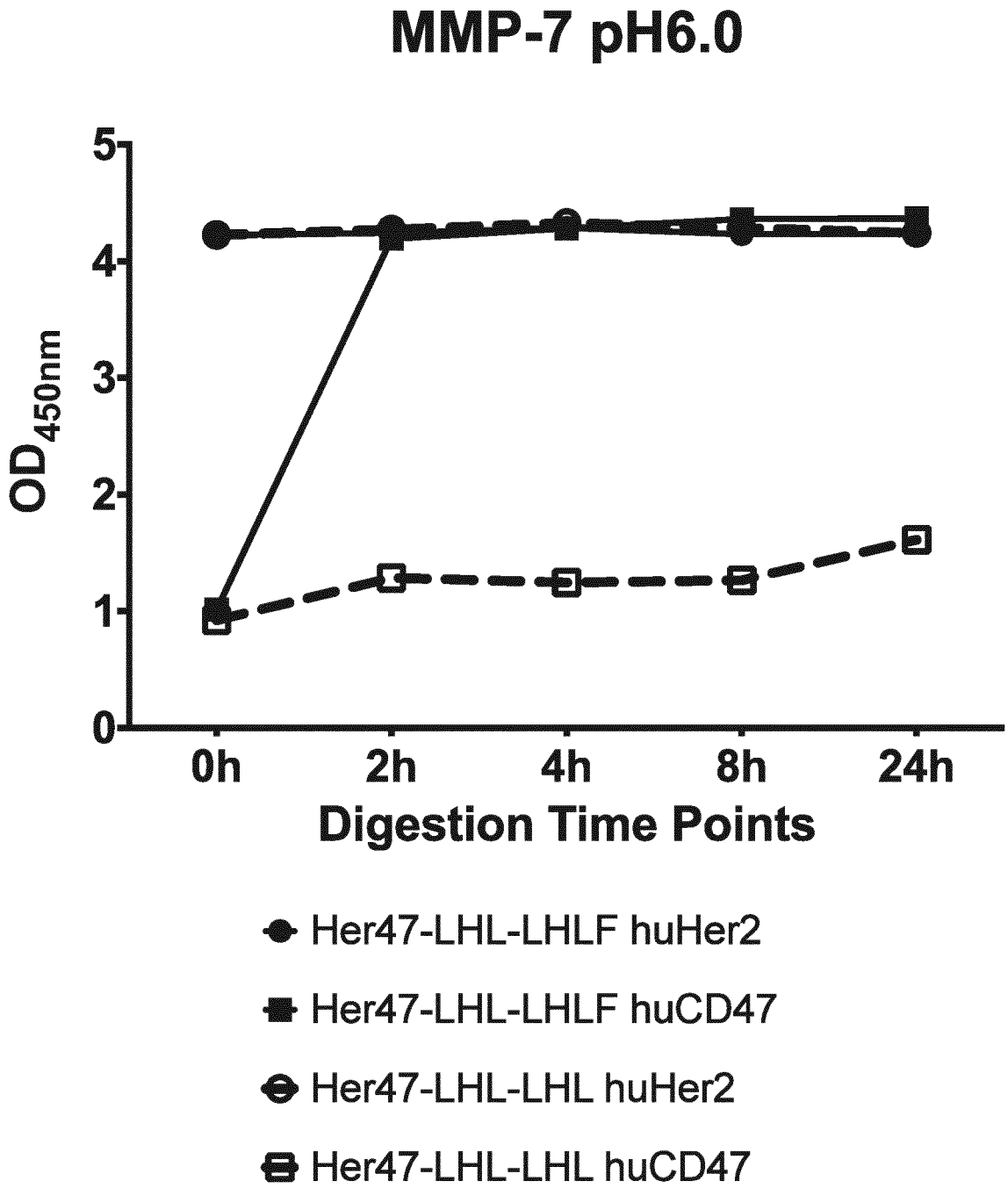

MMP-7 pH6.0
OD450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30E

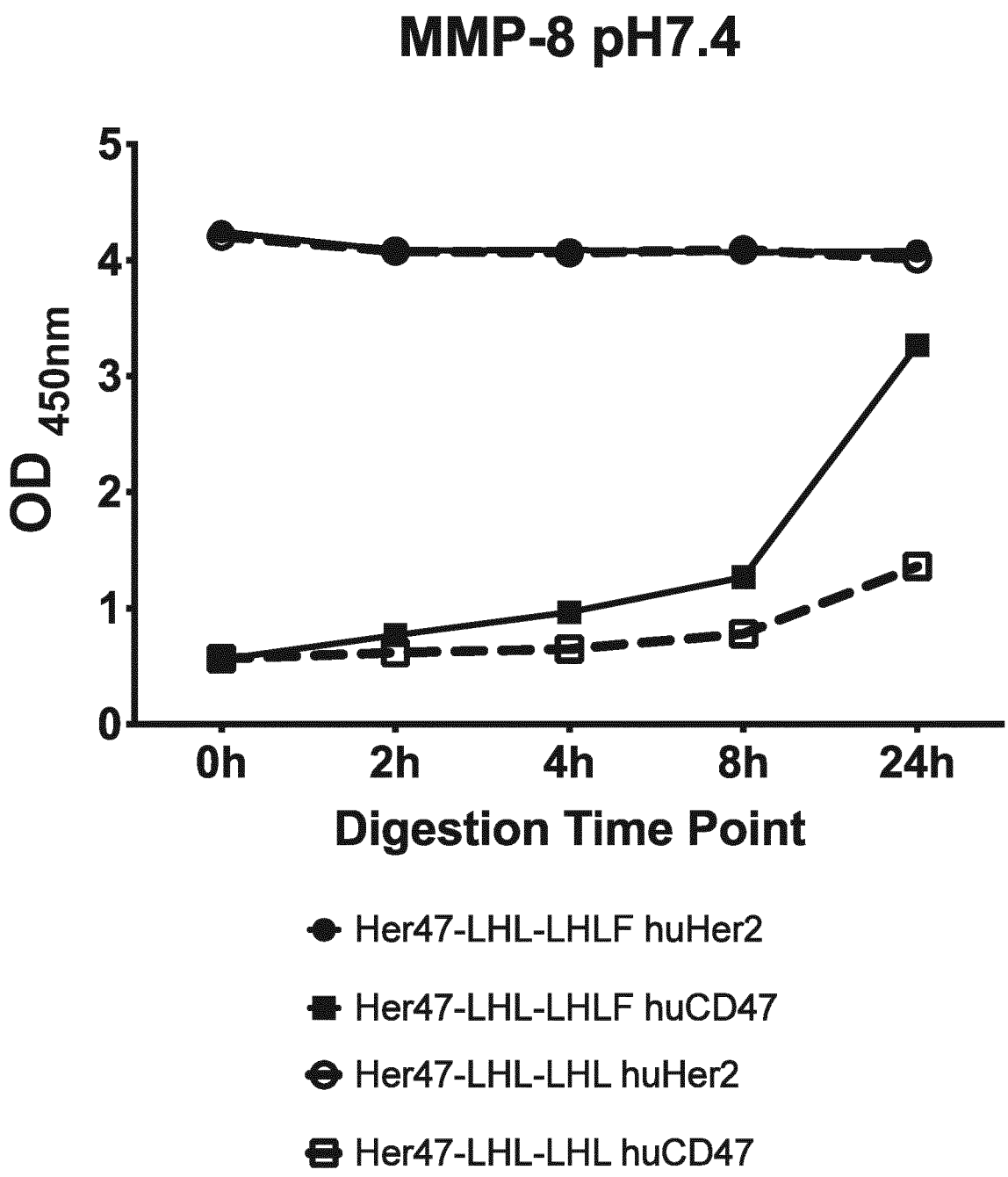

MMP-8 pH7.4
OD 450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30F

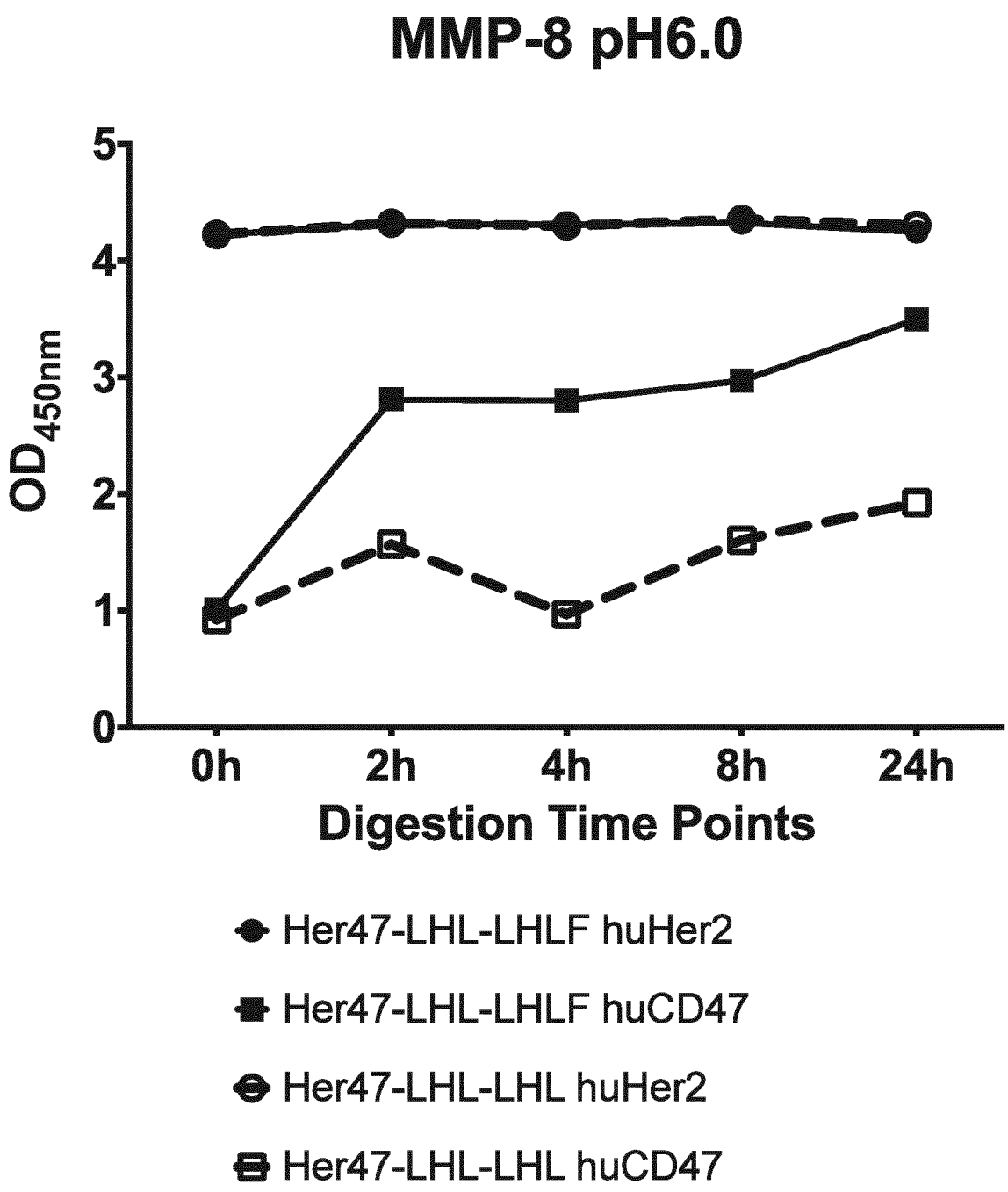

MMP-8 pH6.0
OD450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30G

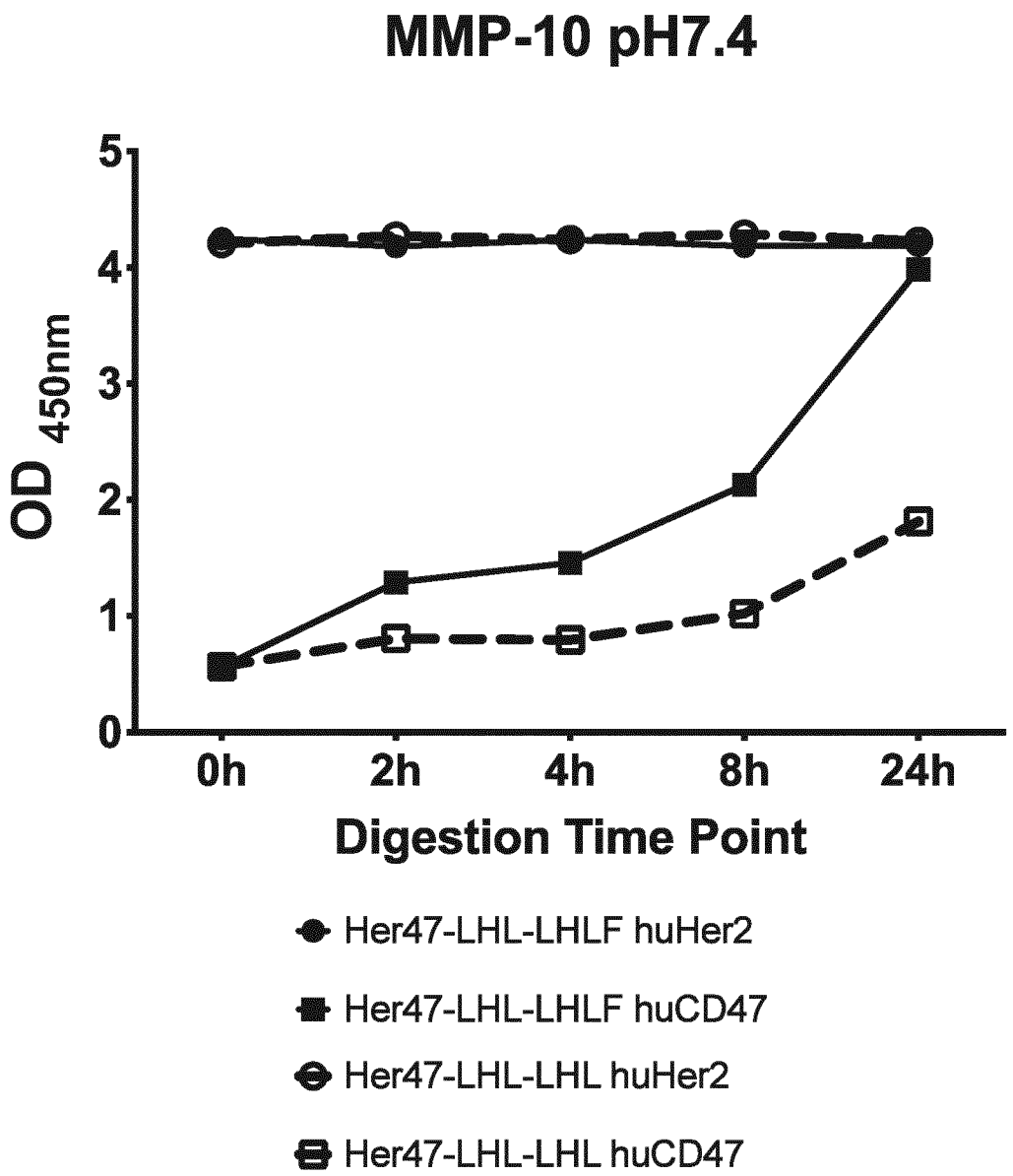

MMP-10 pH7.4
OD 450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30H

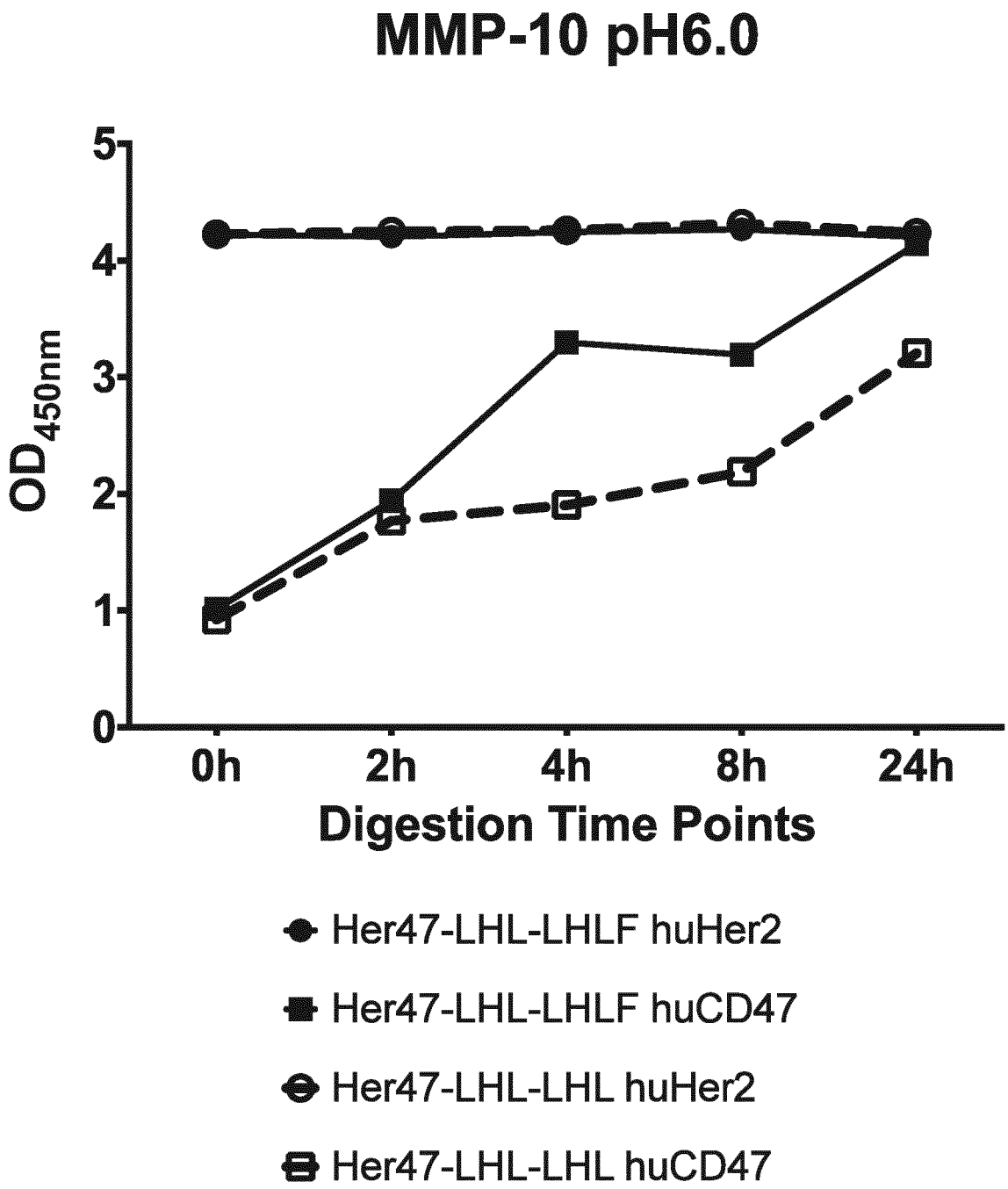

MMP-10 pH6.0
OD450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30I

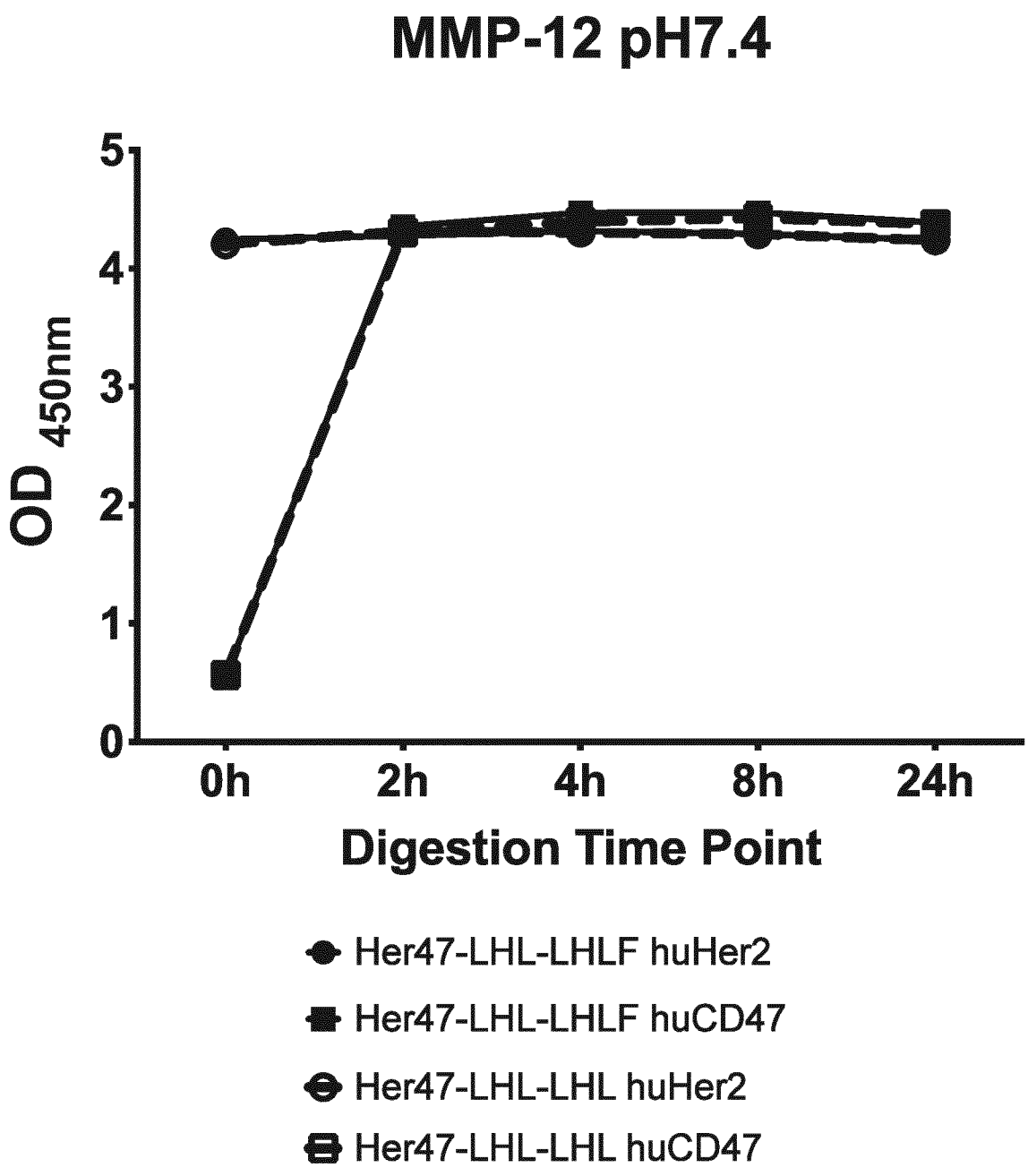

MMP-12 pH7.4
OD 450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30J

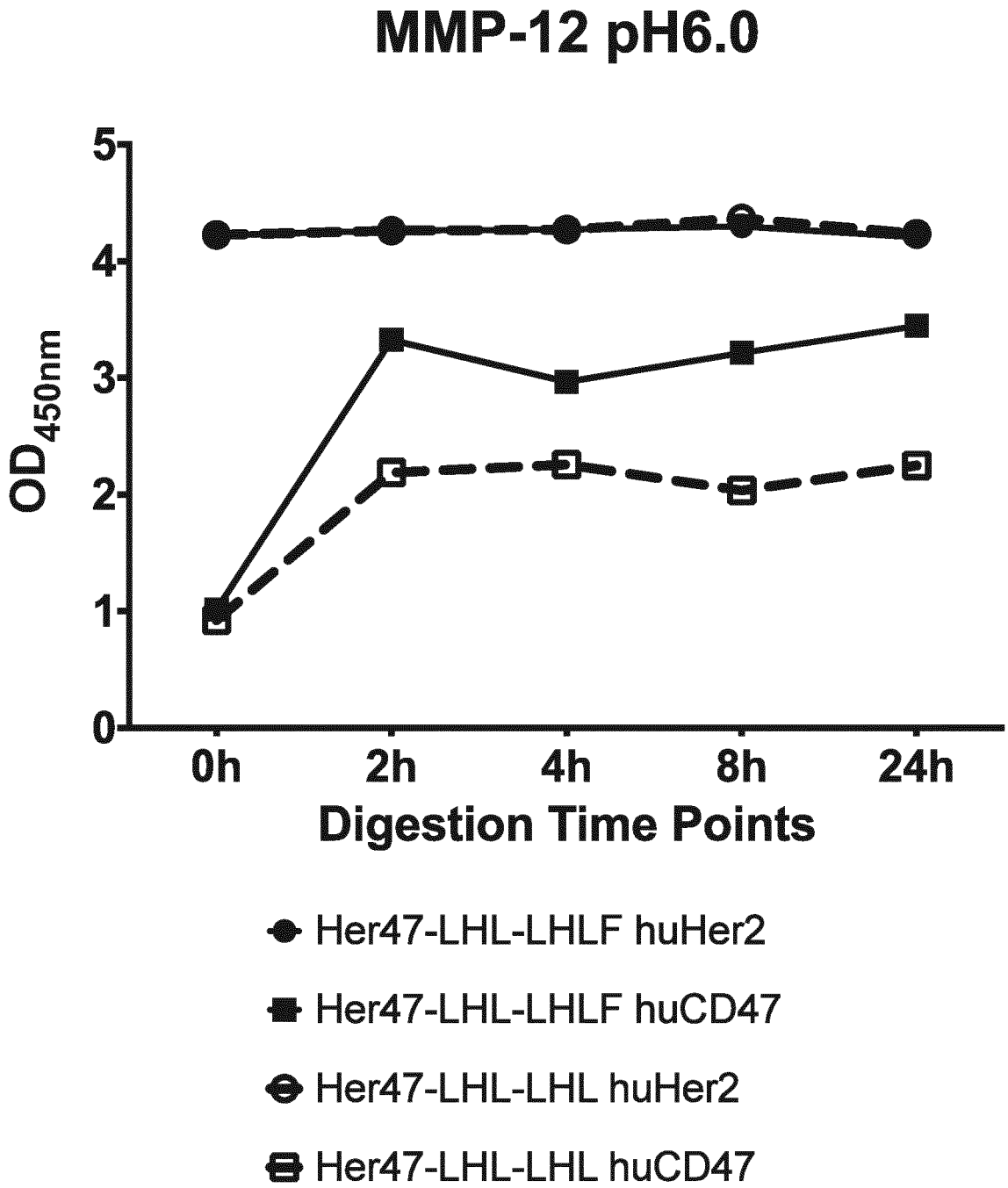

MMP-12 pH6.0
OD450nm
0
1
2
3
4
5
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30K

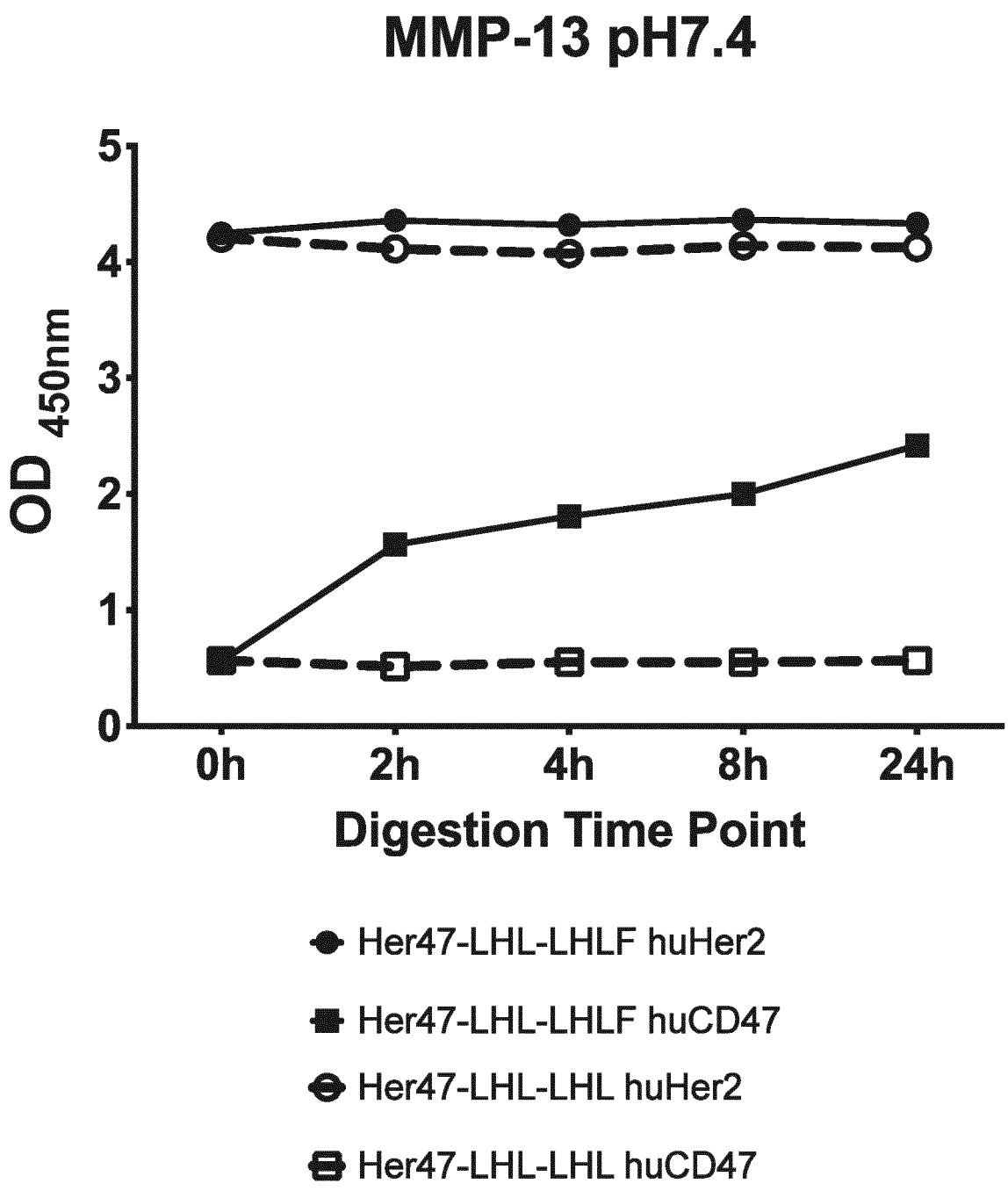

MMP-13 pH7.4
OD 450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30L

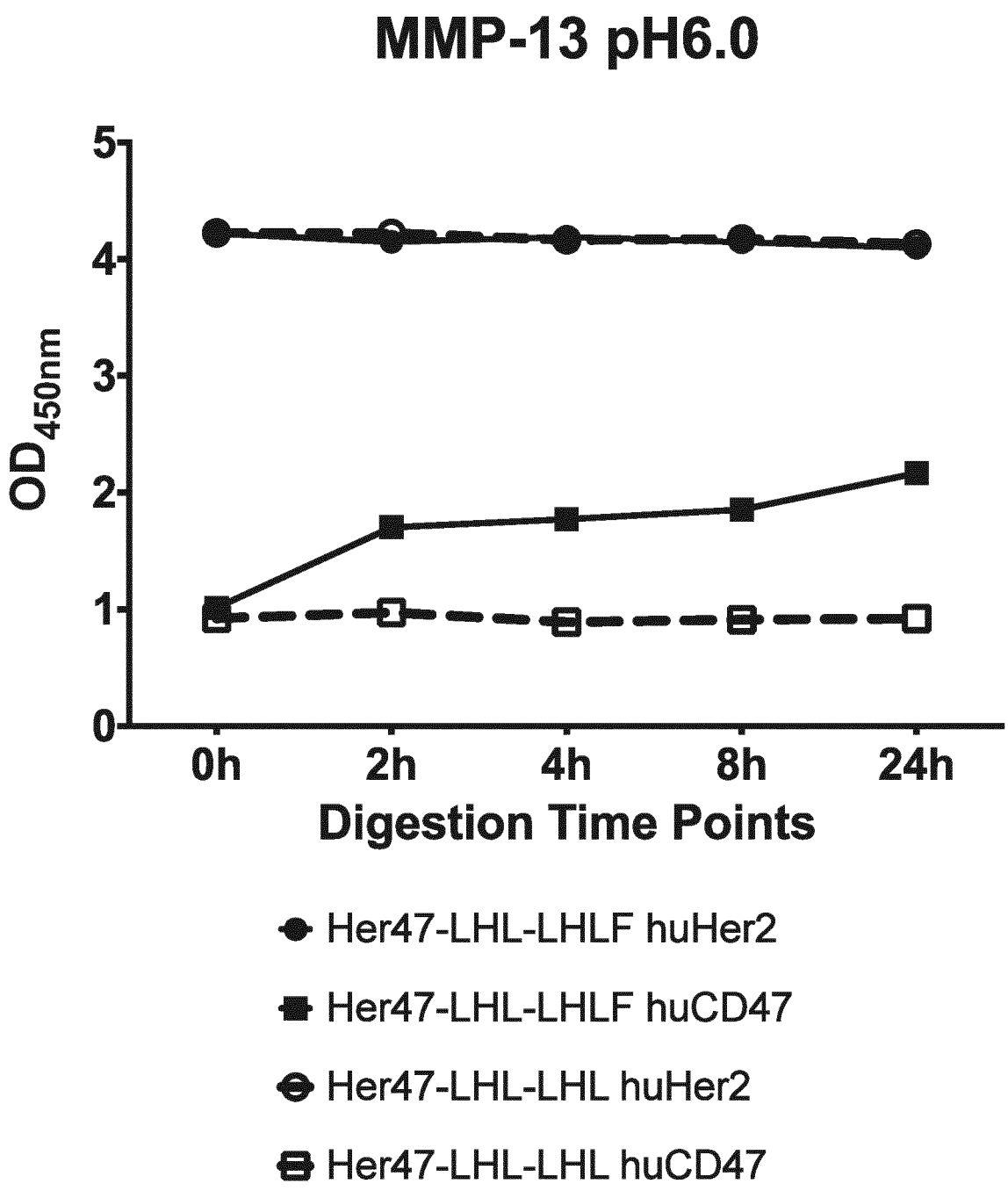

MMP-13 pH6.0
OD450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30M

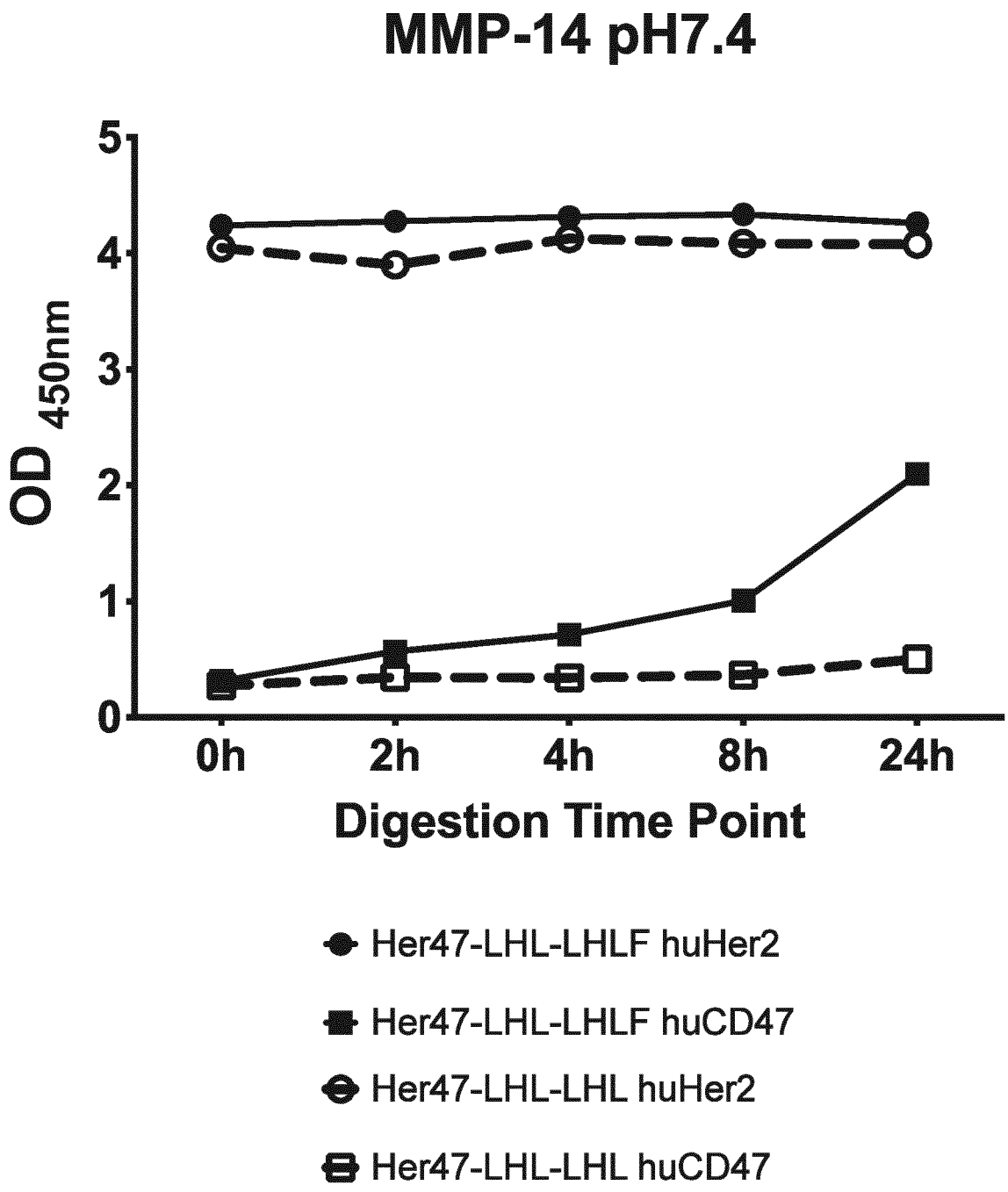

MMP-14 pH7.4
OD 450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Point
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 30N

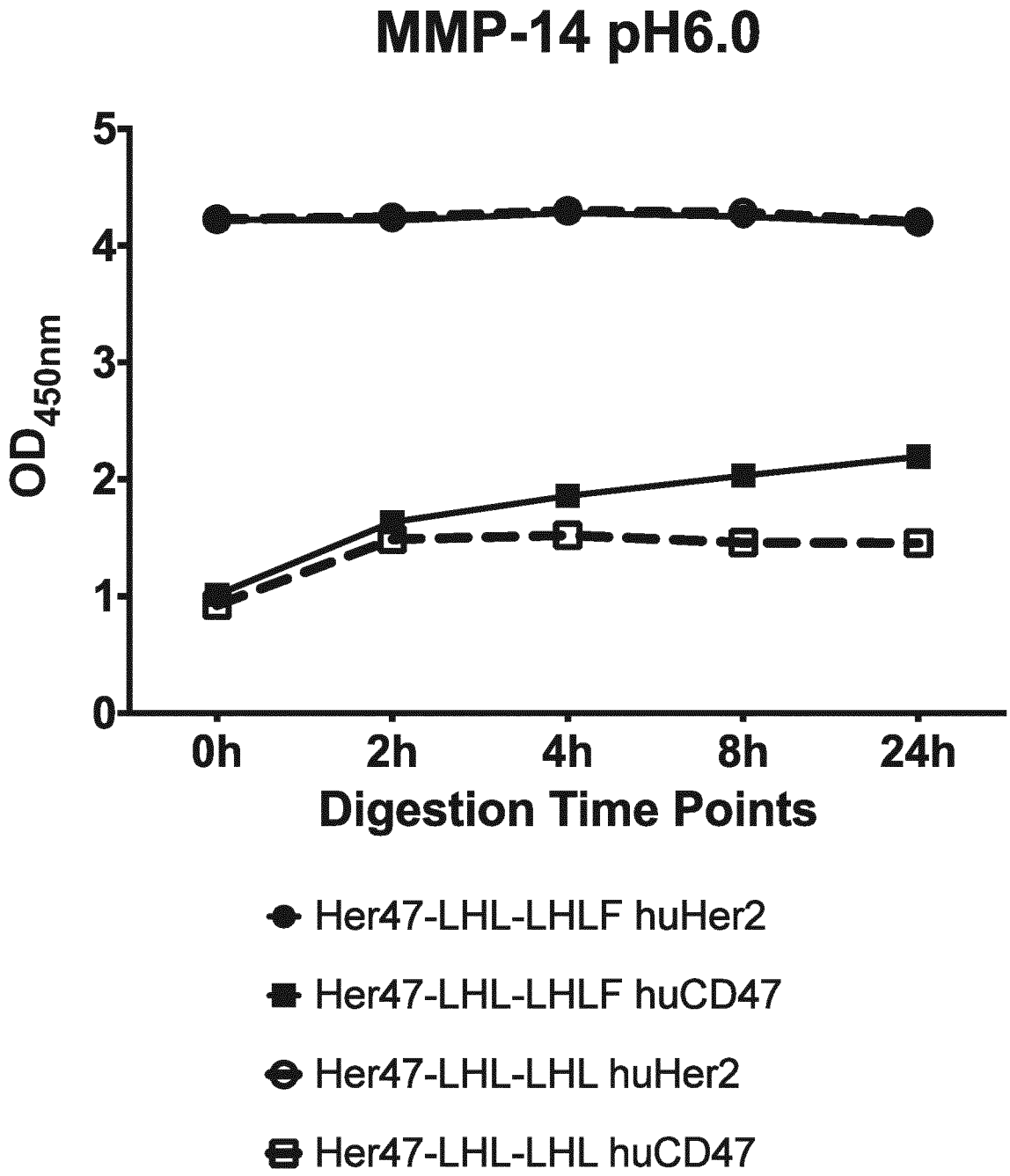

MMP-14 pH6.0
OD450nm
5
4
3
2
1
0
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF huHer2
Her47-LHL-LHLF huCD47
Her47-LHL-LHL huHer2
Her47-LHL-LHL huCD47

Figure 31A

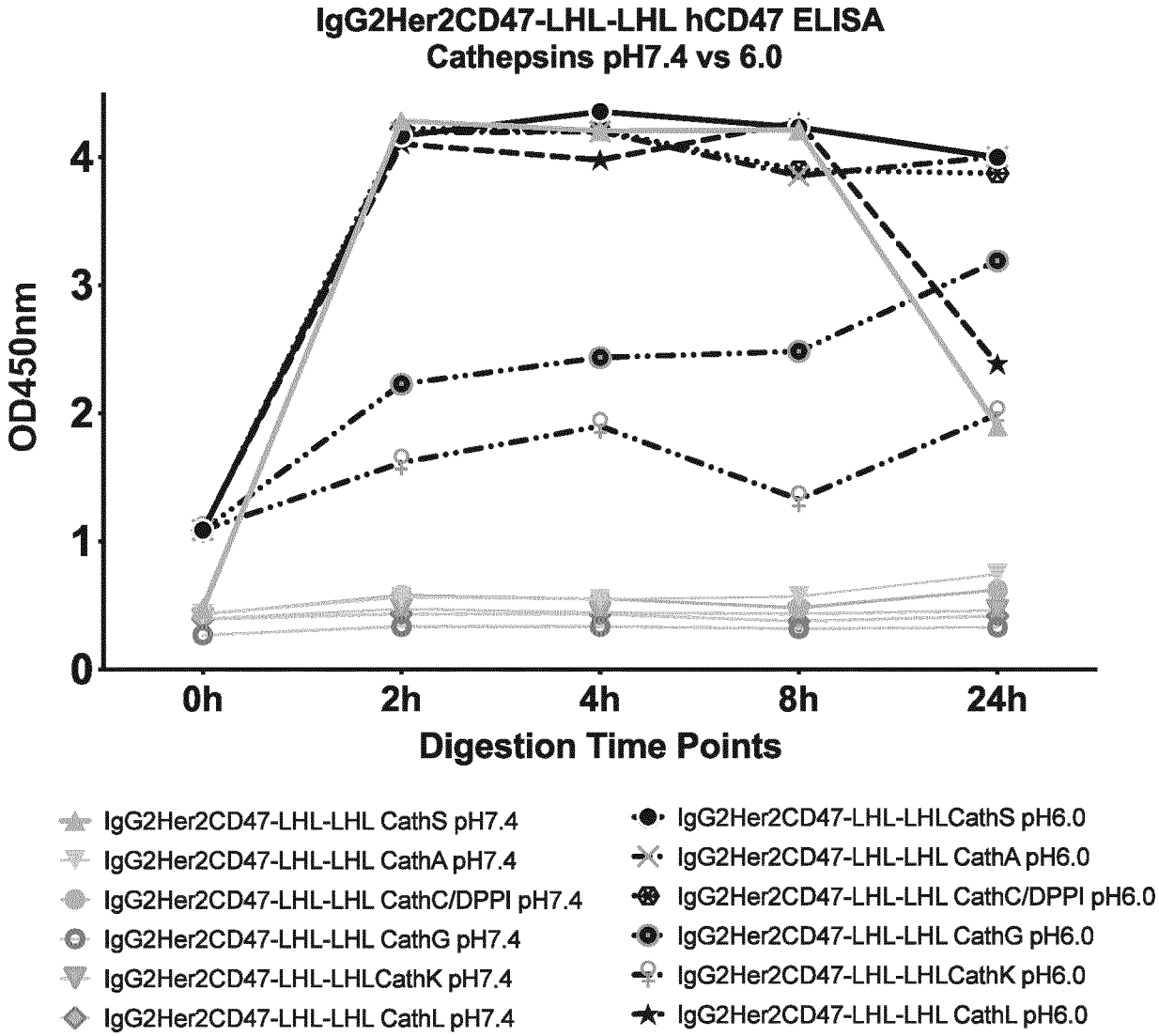

IgG2Her2CD47-LHL-LHL hCD47 ELISA
Cathepsins pH7.4 vs 6.0
OD450nm
0
1
2
3
4
0h
2h
4h
8h
24h
Digestion Time Points
IgG2Her2CD47-LHL-LHL CathS pH7.4
IgG2Her2CD47-LHL-LHL CathA pH7.4
IgG2Her2CD47-LHL-LHL CathC/DPPI pH7.4
IgG2Her2CD47-LHL-LHL CathG pH7.4
IgG2Her2CD47-LHL-LHLCathK pH7.4
IgG2Her2CD47-LHL-LHL CathL pH7.4
IgG2Her2CD47-LHL-LHLCathS pH6.0
IgG2Her2CD47-LHL-LHL CathA pH6.0
IgG2Her2CD47-LHL-LHL CathC/DPPI pH6.0
IgG2Her2CD47-LHL-LHL CathG pH6.0
IgG2Her2CD47-LHL-LHLCathK pH6.0
IgG2Her2CD47-LHL-LHL CathL pH6.0

Figure 31B

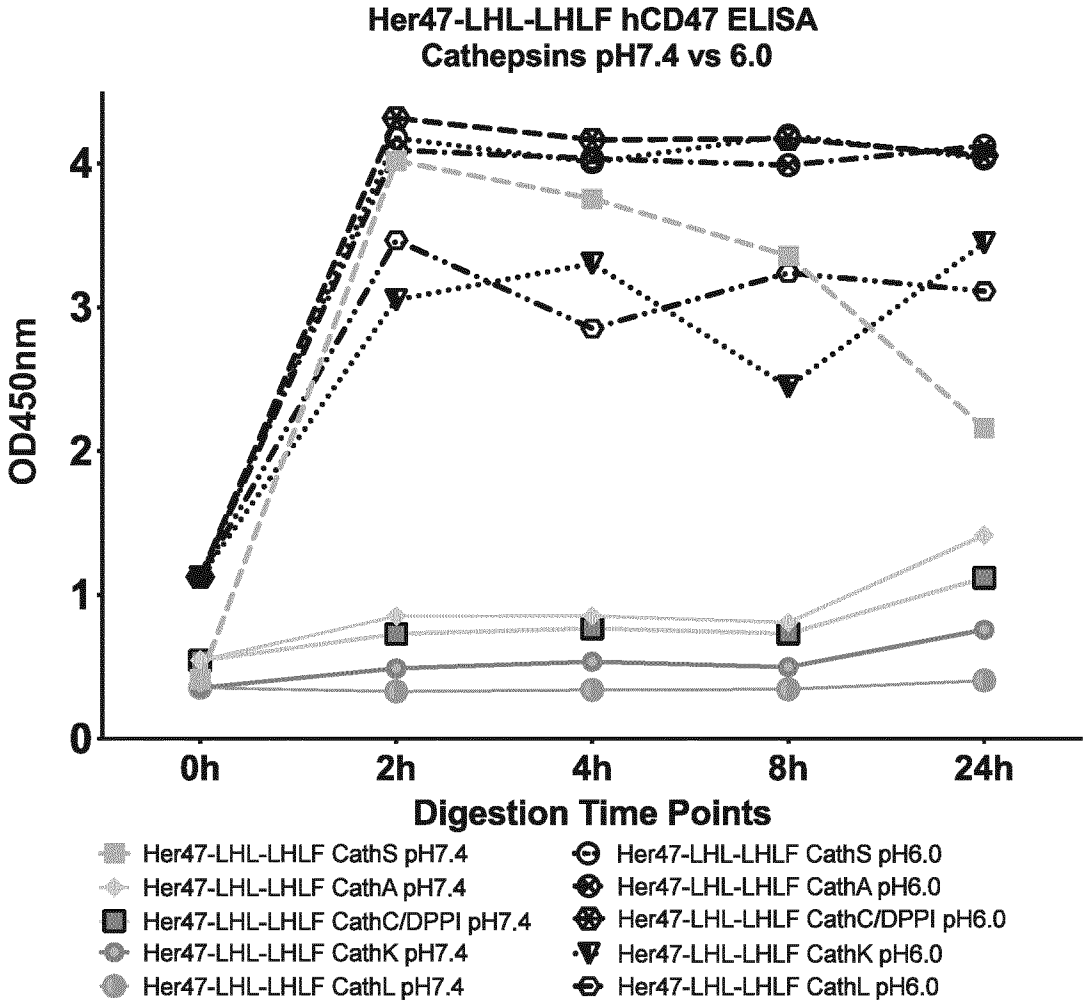

Her47-LHL-LHLF hCD47 ELISA
Cathepsins pH7.4 vs 6.0
OD450nm
0
1
2
3
4
0h
2h
4h
8h
24h
Digestion Time Points
Her47-LHL-LHLF CathS pH7.4
Her47-LHL-LHLF CathA pH7.4
Her47-LHL-LHLF CathC/DPPI pH7.4
Her47-LHL-LHLF CathK pH7.4
Her47-LHL-LHLF CathL pH7.4
Her47-LHL-LHLF CathS pH6.0
Her47-LHL-LHLF CathA pH6.0
Her47-LHL-LHLF CathC/DPPI pH6.0
Her47-LHL-LHLF CathK pH6.0
Her47-LHL-LHLF CathL pH6.0

Figure 32A

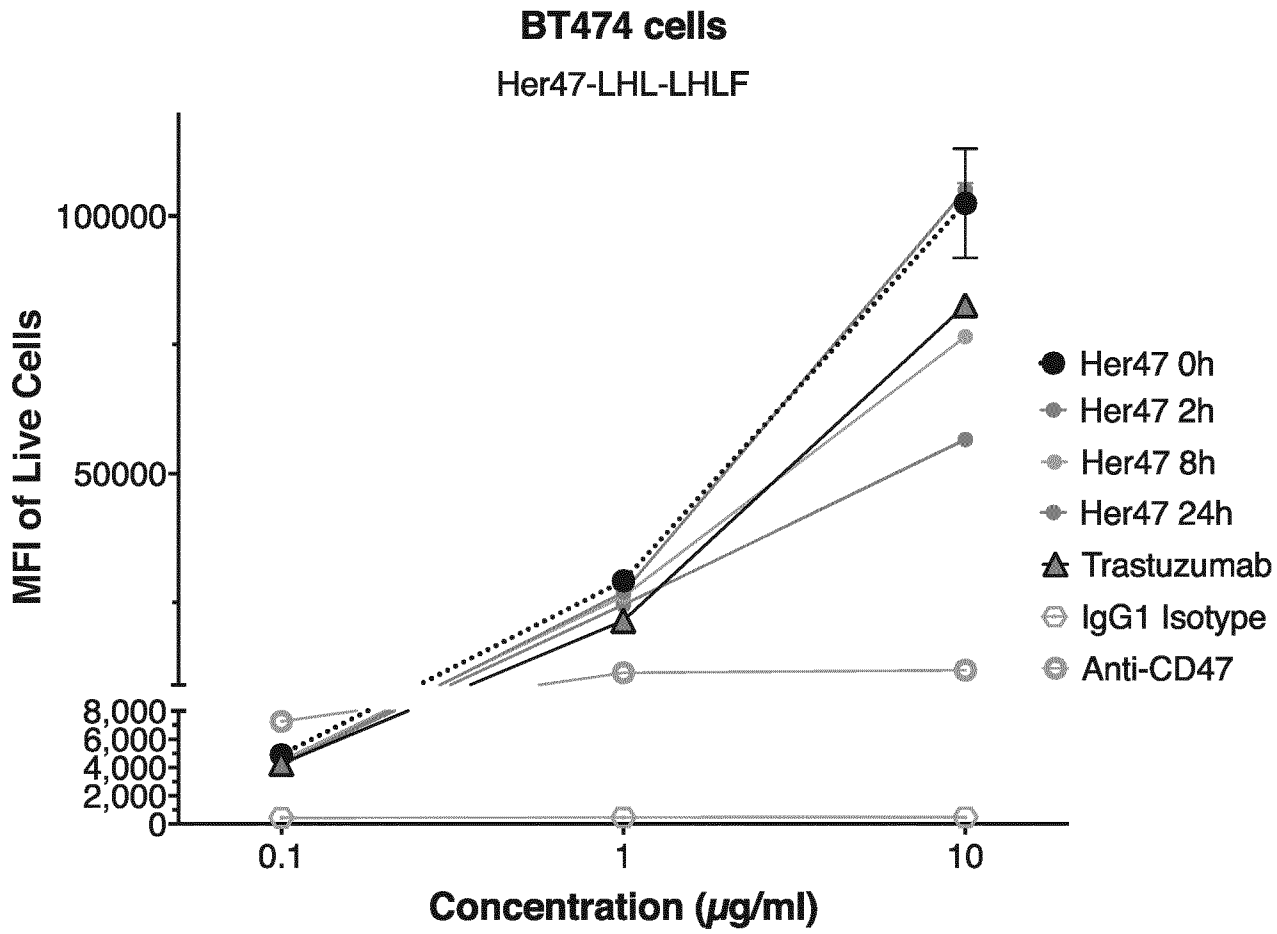

BT474 cells
Her47-LHL-LHLF
MFI of Live Cells
100000
50000
8,000
6,000
4,000
2,000
0
0.1
1
10
Concentration (μg/ml)
Her47 0h
Her47 2h
Her47 8h
Her47 24h
Trastuzumab
IgG1 Isotype
Anti-CD47

Figure 32B

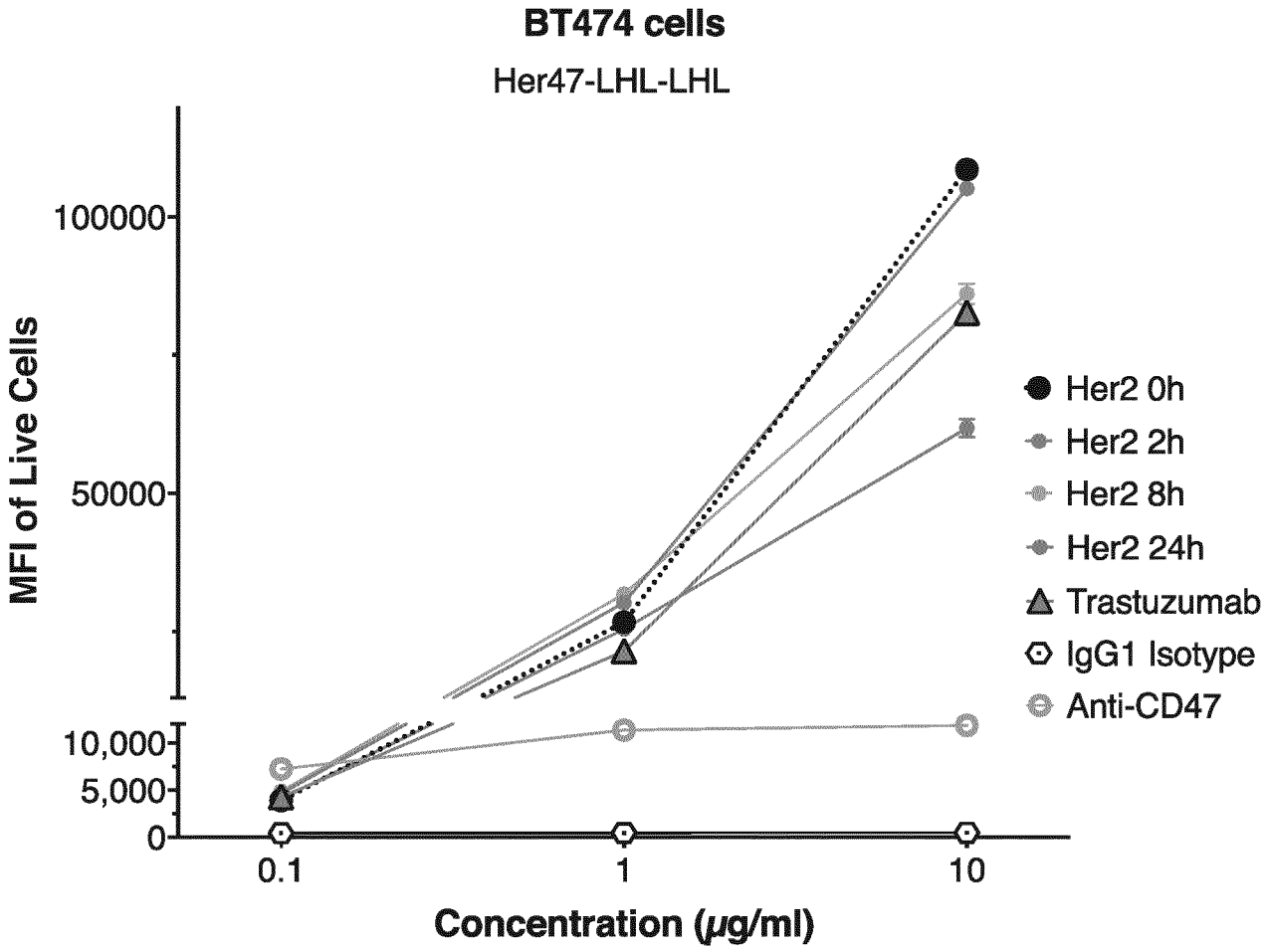

BT474 cells
Her47-LHL-LHL
MFI of Live Cells
100000
50000
10,000
5,000
0
0.1
1
10
Concentration (μg/ml)
Her2 0h
Her2 2h
Her2 8h
Her2 24h
Trastuzumab
IgG1 Isotype
Anti-CD47

Figure 32C

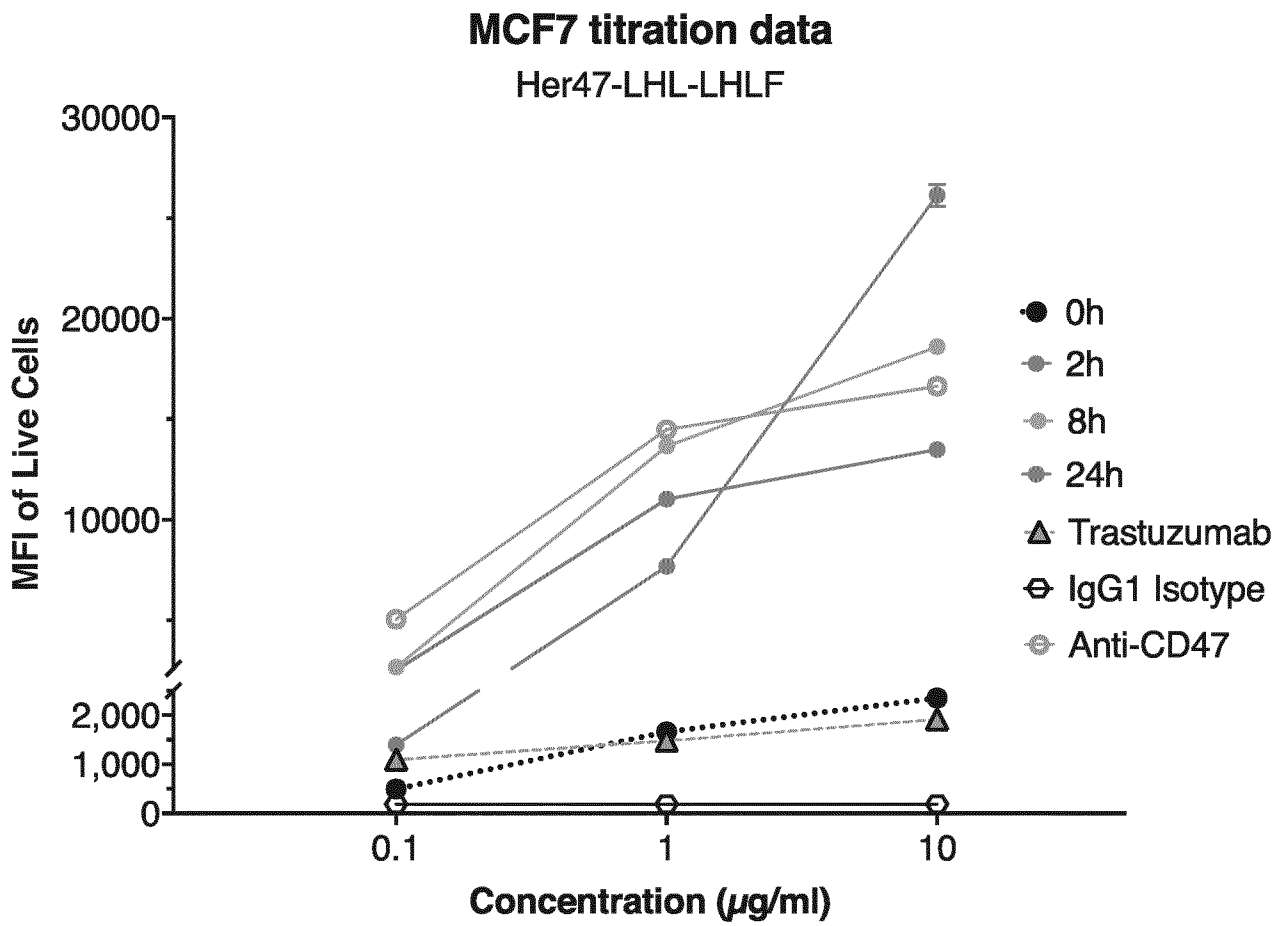

MCF7 titration data
Her47-LHL-LHLF
MFI of Live Cells
30000
20000
10000
2,000
1,000
0
0.1
1
10
Concentration (µg/ml)
0h
2h
8h
24h
Trastuzumab
IgG1 Isotype
Anti-CD47

Figure 32D

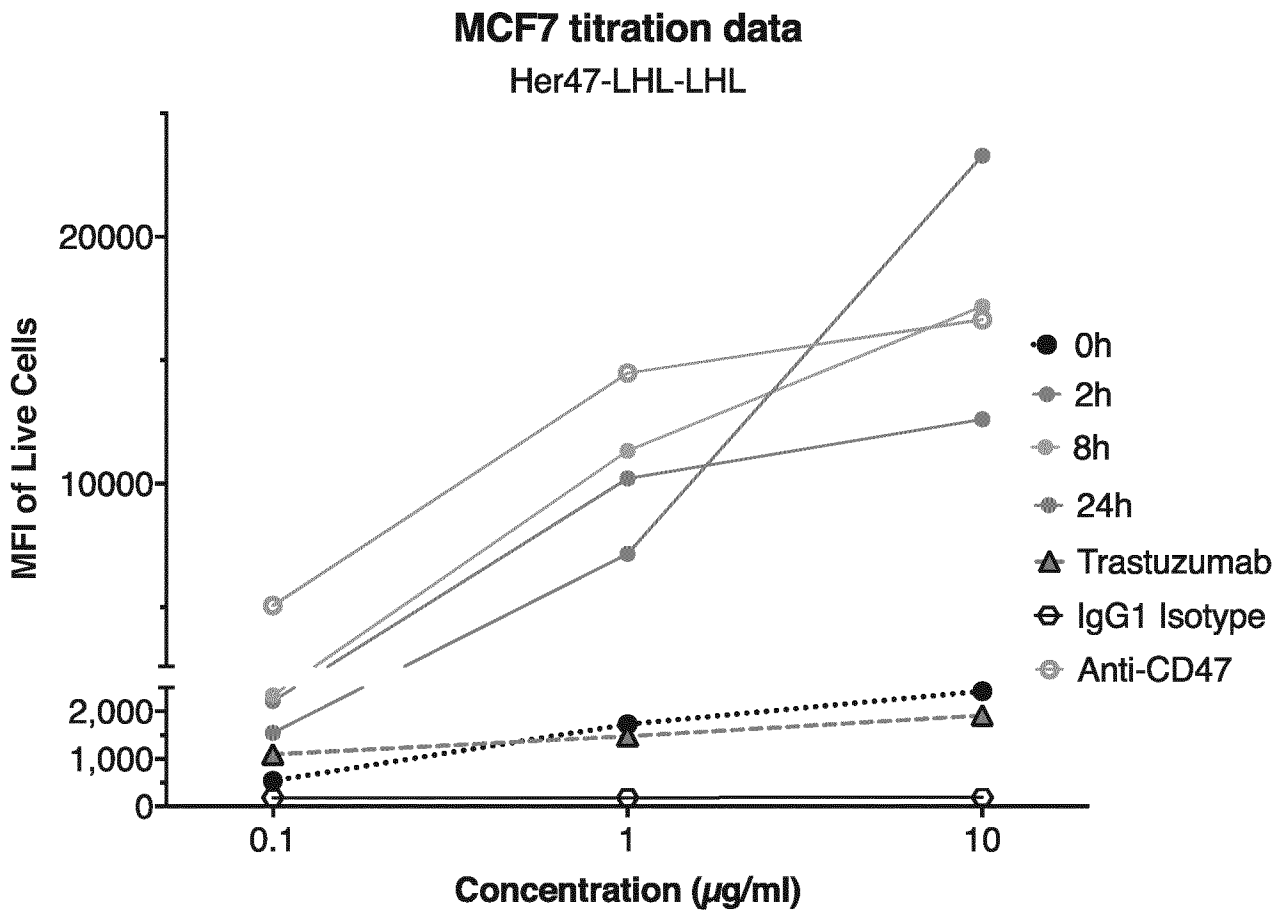

MCF7 titration data
Her47-LHL-LHL
MFI of Live Cells
20000
10000
2,000
1,000
0
0.1
1
10
Concentration (μg/ml)
0h
2h
8h
24h
Trastuzumab
IgG1 Isotype
Anti-CD47

Figure 33

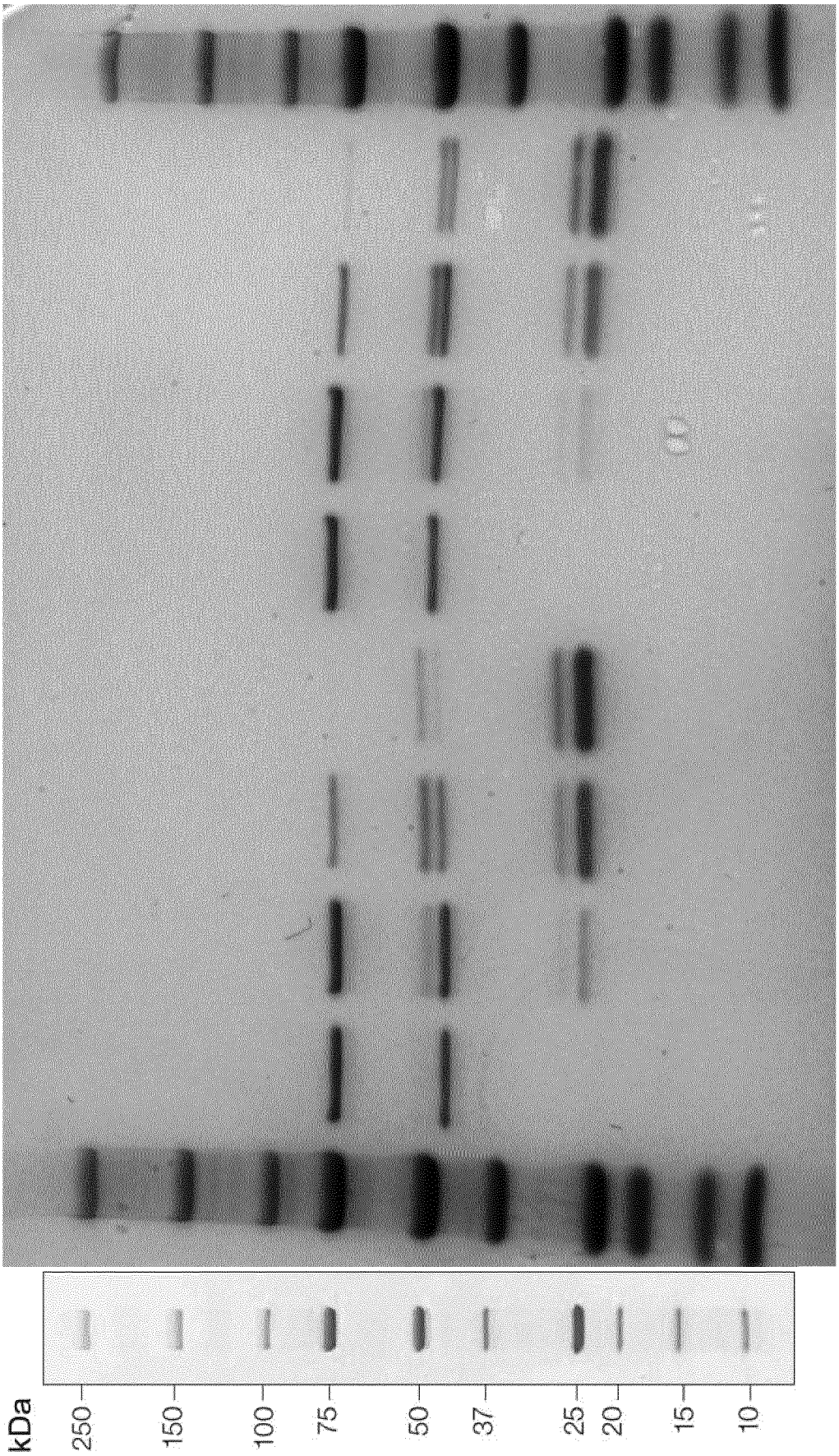

M
Her47-LHL-LHLF
0h
2h
8h
24h
IgG2Her2CD47-LHL-LHL
0h
2h
8h
24h
M
kDa
250
150
100
75
50
37
25
20
15
10

Figure 34A

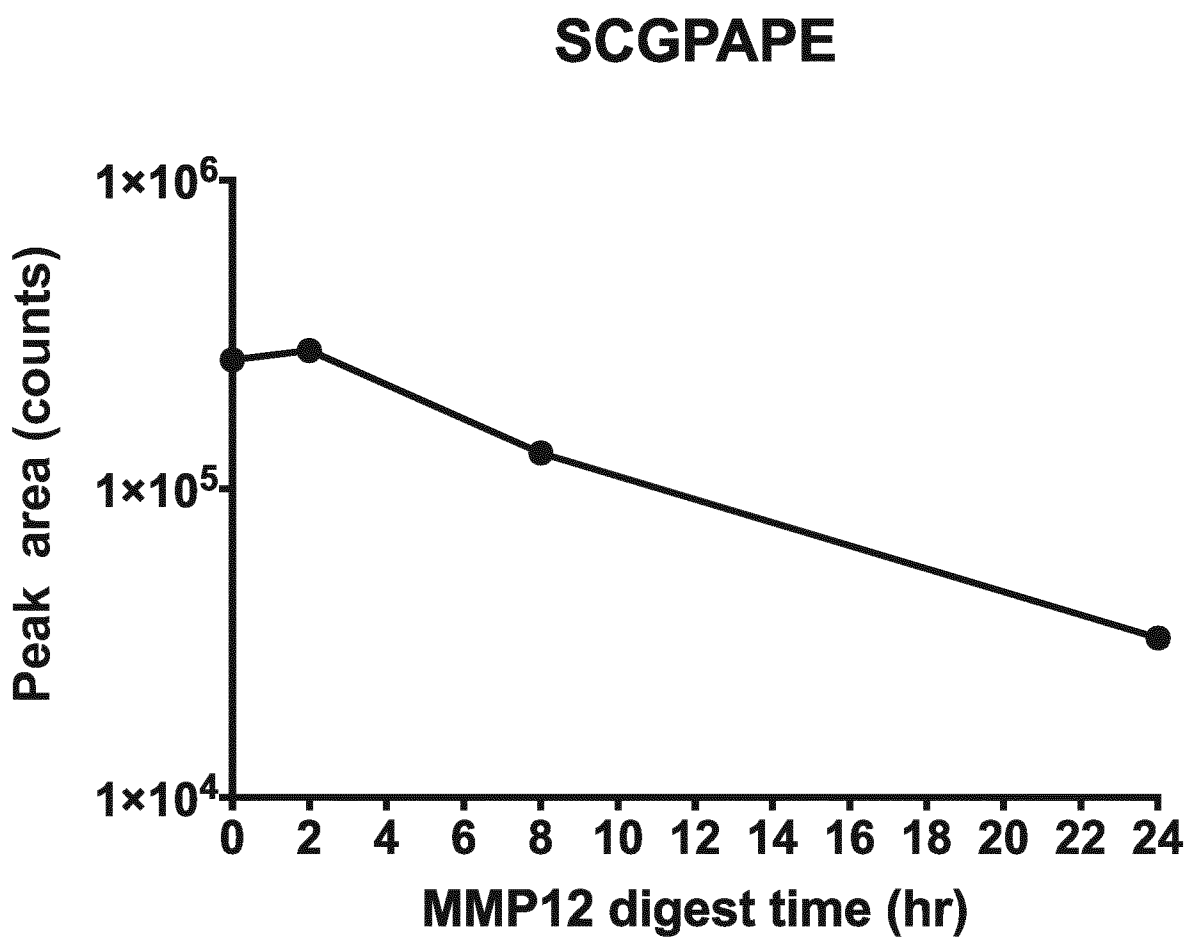

SCGPAPE
Peak area (counts)
1×10^6
1×10^5
1×10^4
0 2 4 6 8 10 12 14 16 18 20 22 24
MMP12 digest time (hr)

Figure 34B

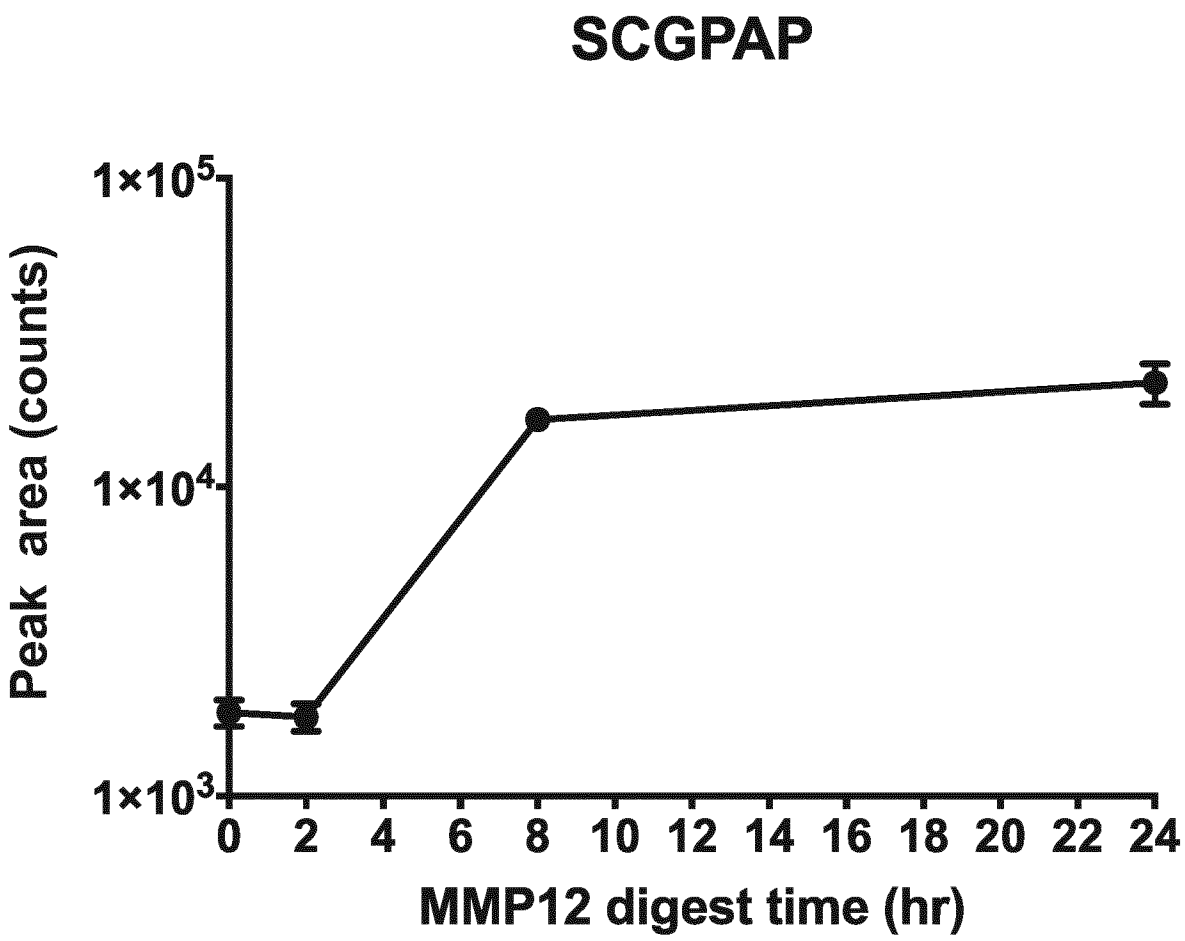

SCGPAP
Peak area (counts)
1×10^5
1×10^4
1×10^3
0 2 4 6 8 10 12 14 16 18 20 22 24
MMP12 digest time (hr)

Figure 35

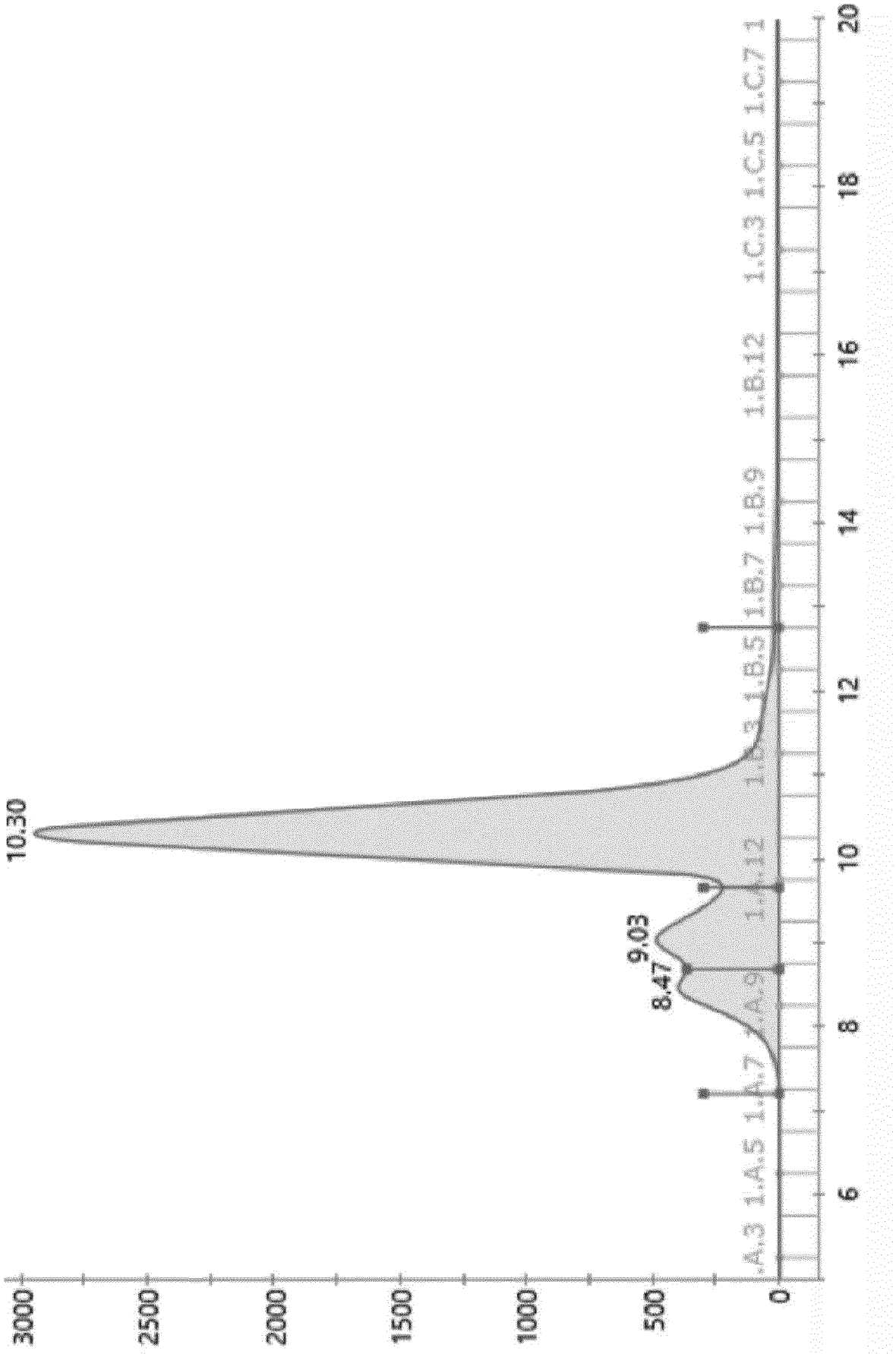


Figure 36

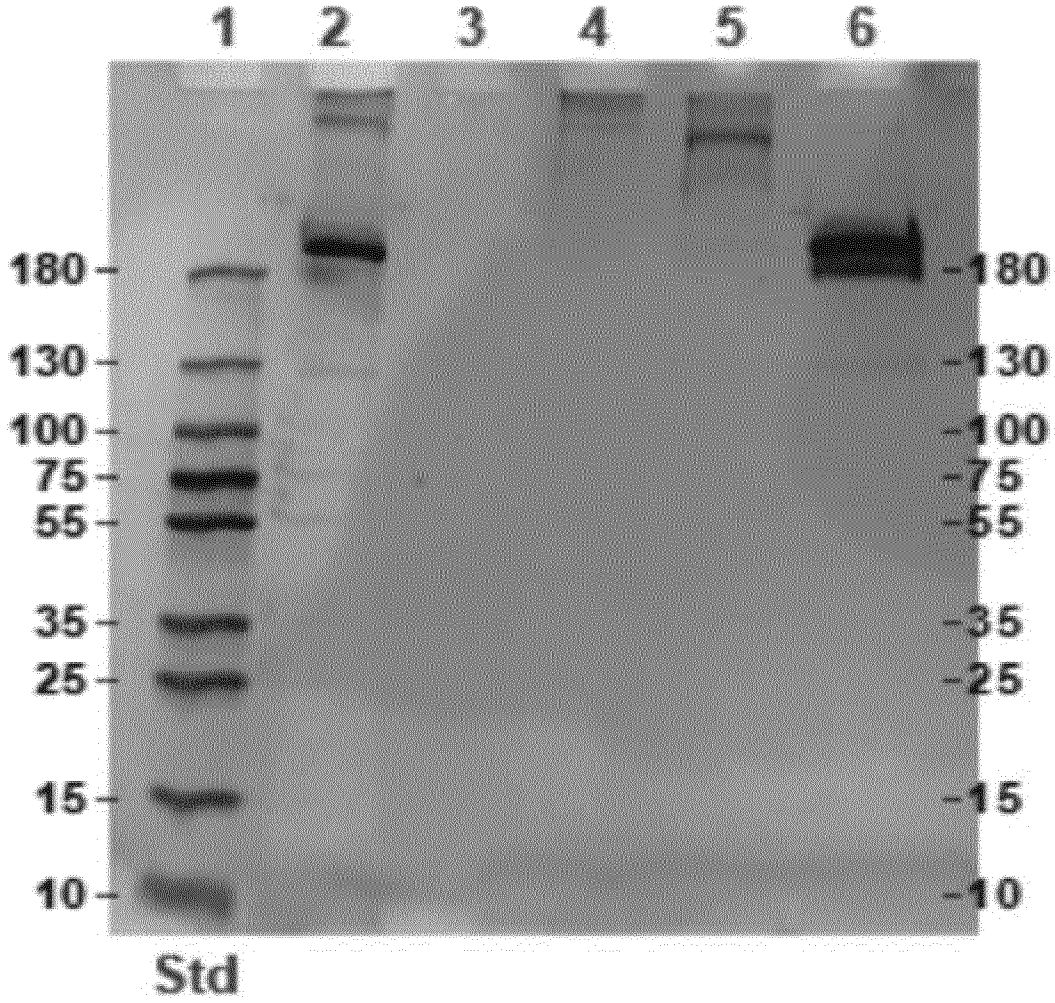

1
2
3
4
5
6
180
130
100
75
55
35
25
15
10
Std
180
130
100
75
55
35
25
15
10

Figure 37

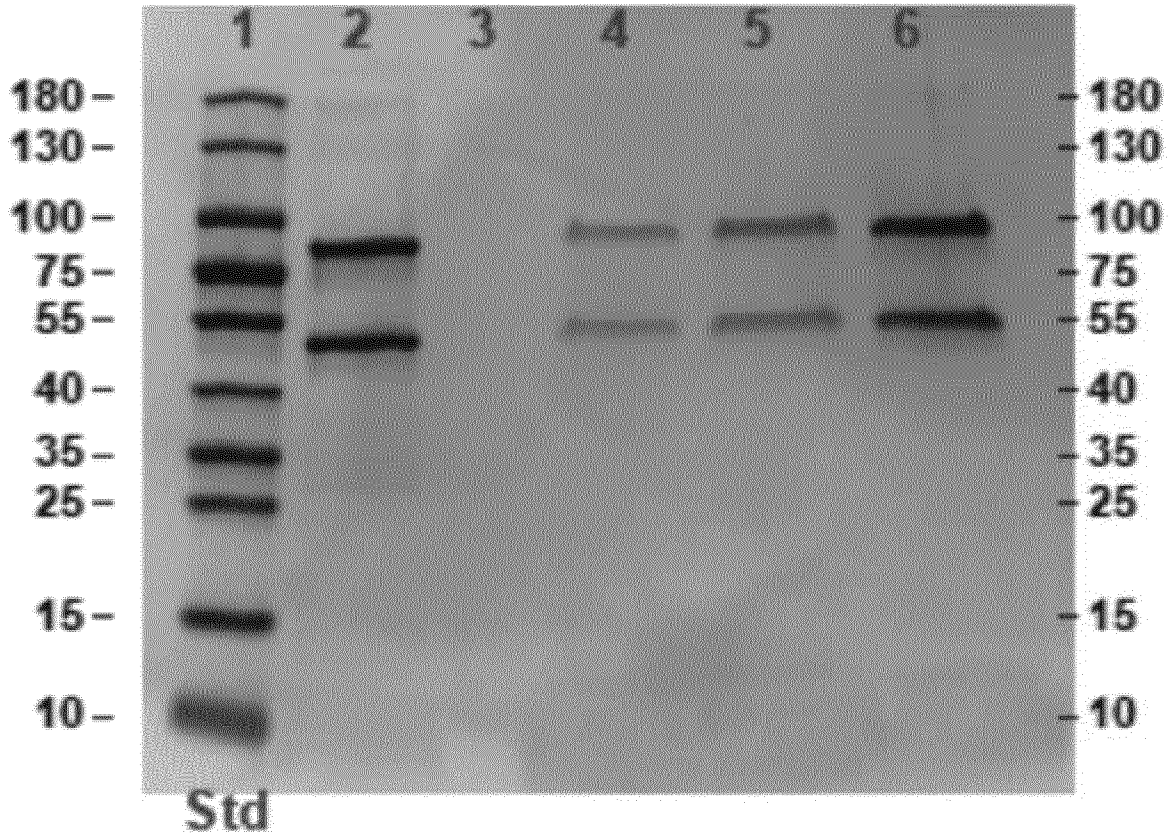


Figure 38A

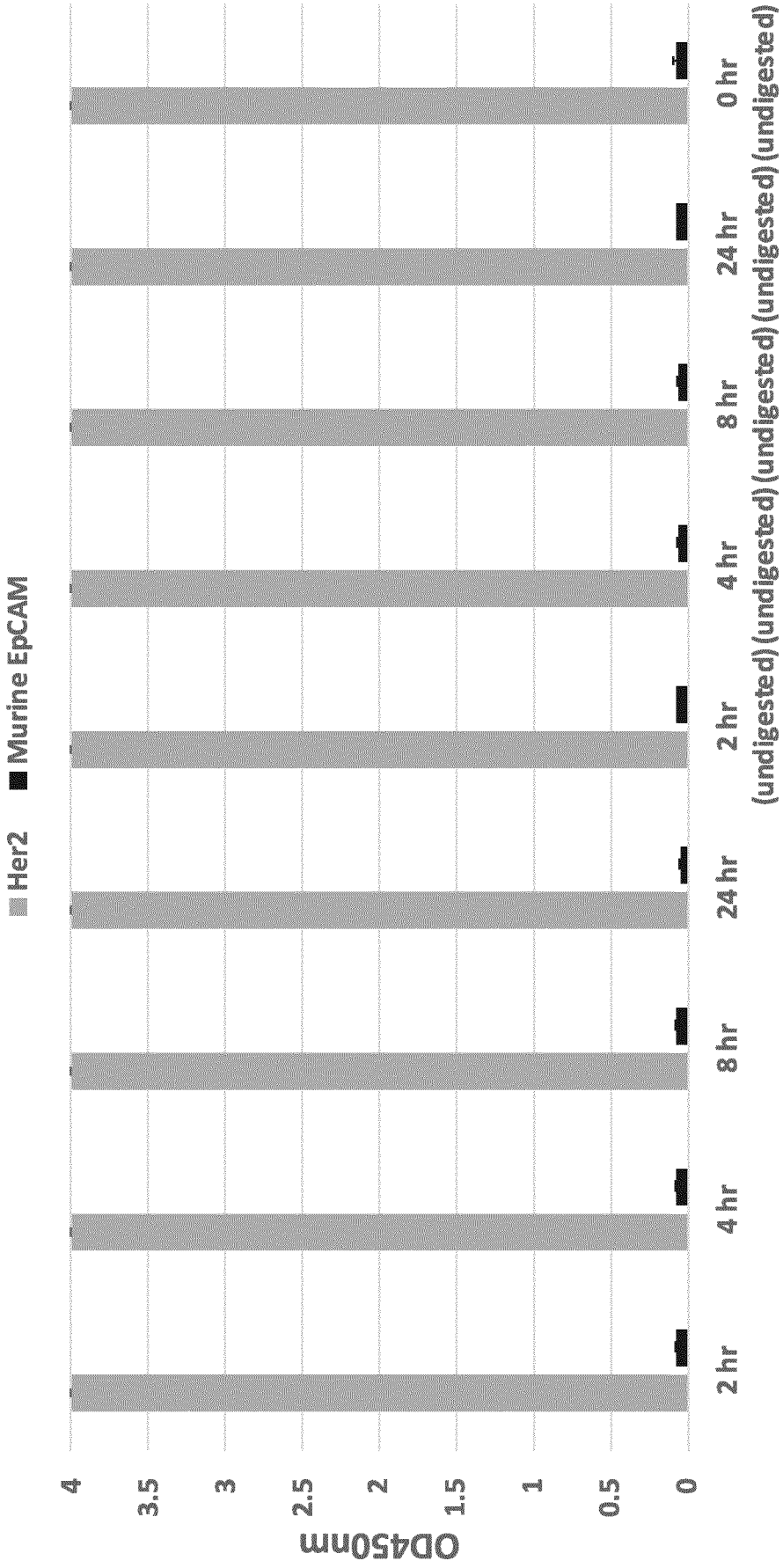

Her2
Murine EpCAM
OD450nm
4
3.5
3
2.5
2
1.5
1
0.5
0
2 hr
4 hr
8 hr
24 hr
2 hr
4 hr
8 hr
24 hr
0 hr
(undigested)
(undigested)
(undigested)
(undigested)
(undigested)

Figure 38B

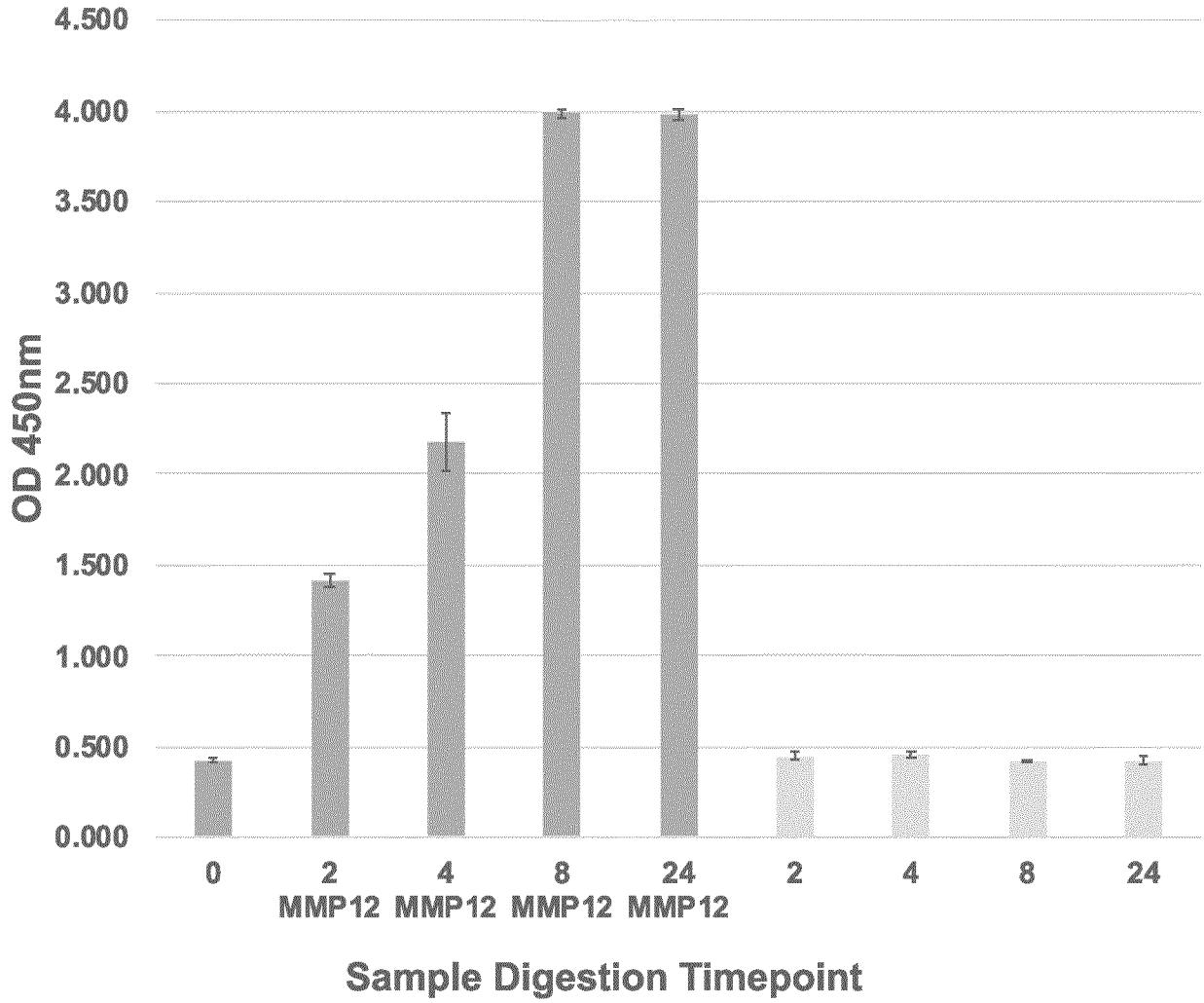

4.500
4.000
3.500
3.000
2.500
2.000
1.500
1.000
0.500
0.000
OD 450nm
0
2
4
8
24
2
4
8
24
MMP12
MMP12
MMP12
MMP12
Sample Digestion Timepoint

Figure 38C

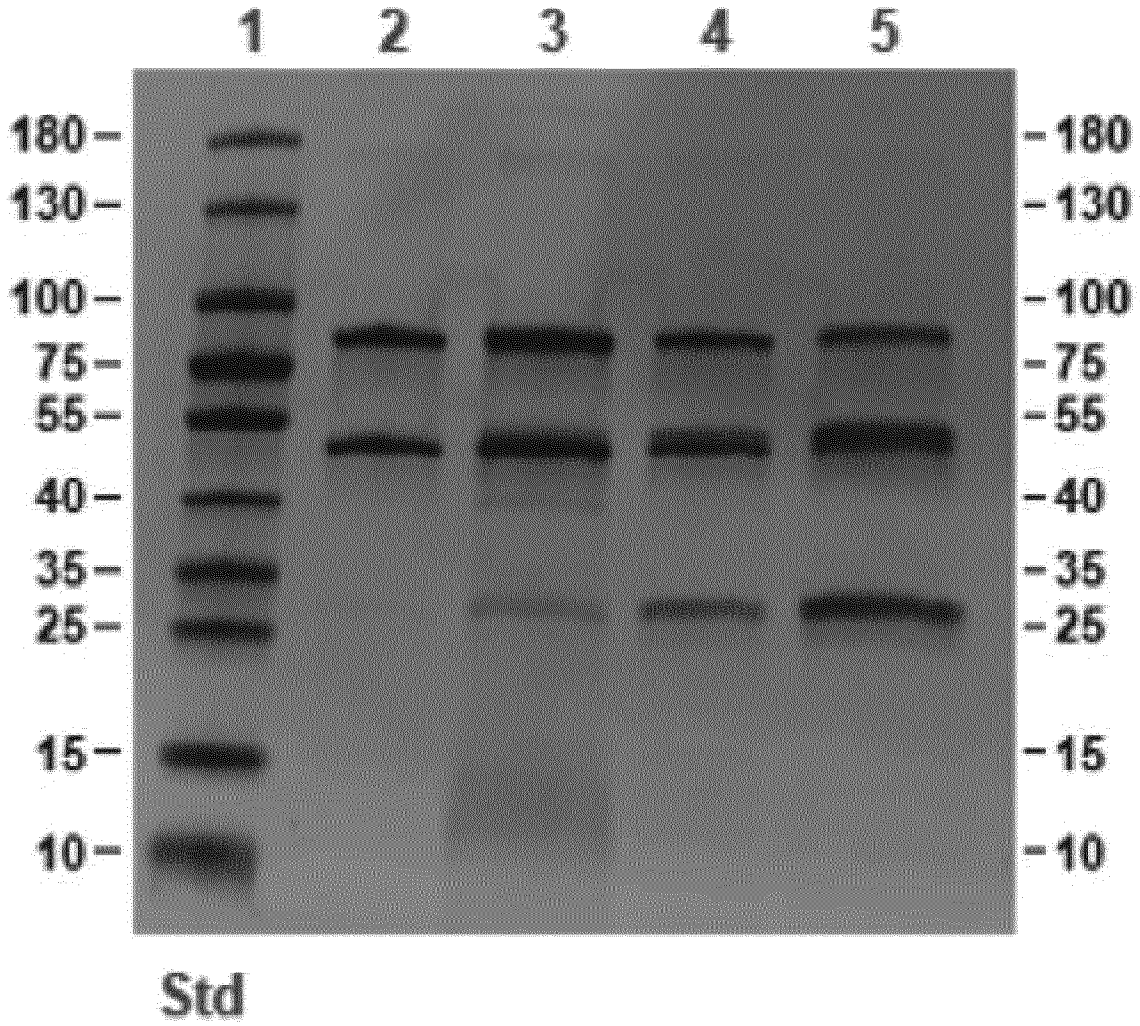


Figure 39A

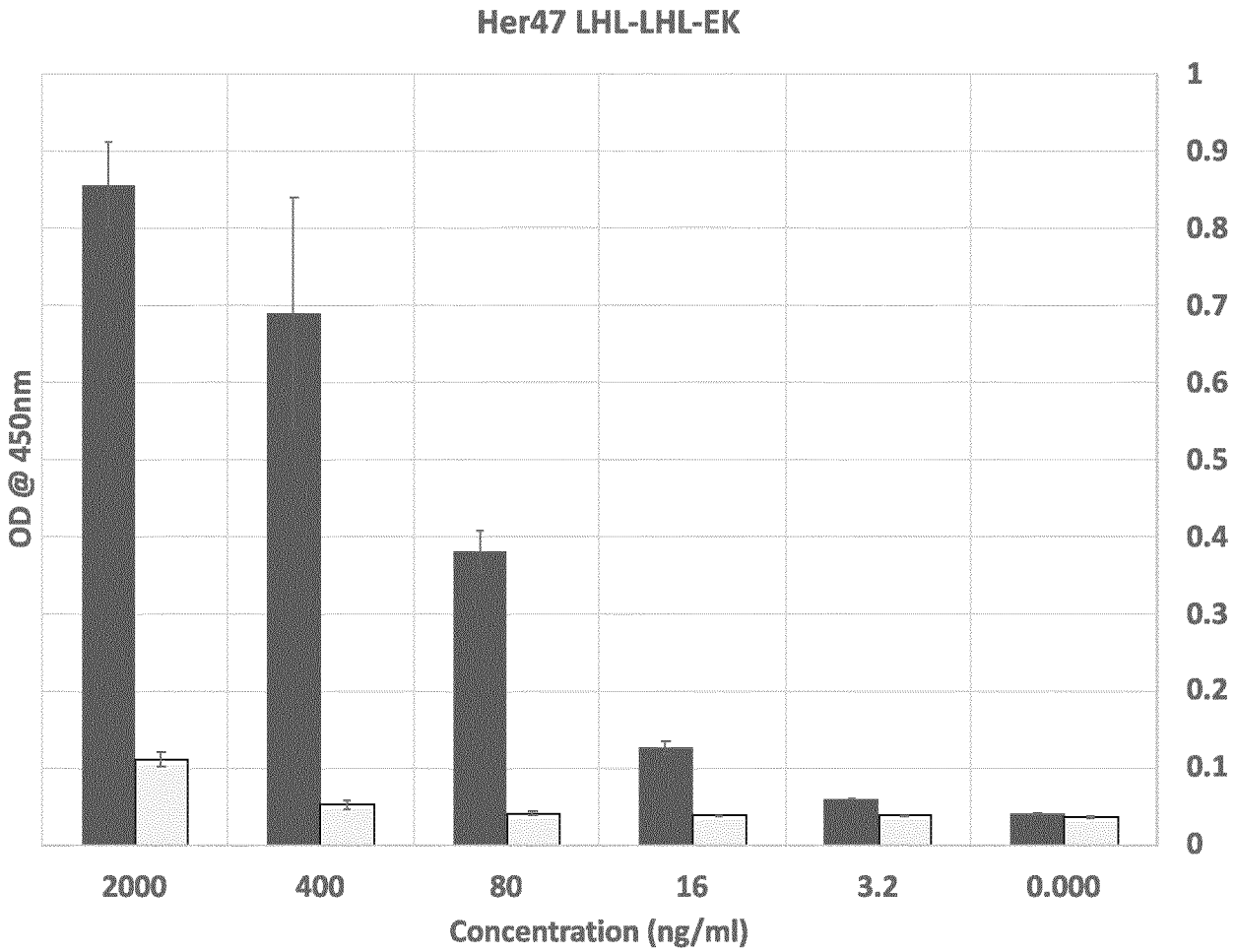

Her47 LHL-LHL-EK
OD @ 450nm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2000
400
80
16
3.2
0.000
Concentration (ng/ml)

Figure 39B

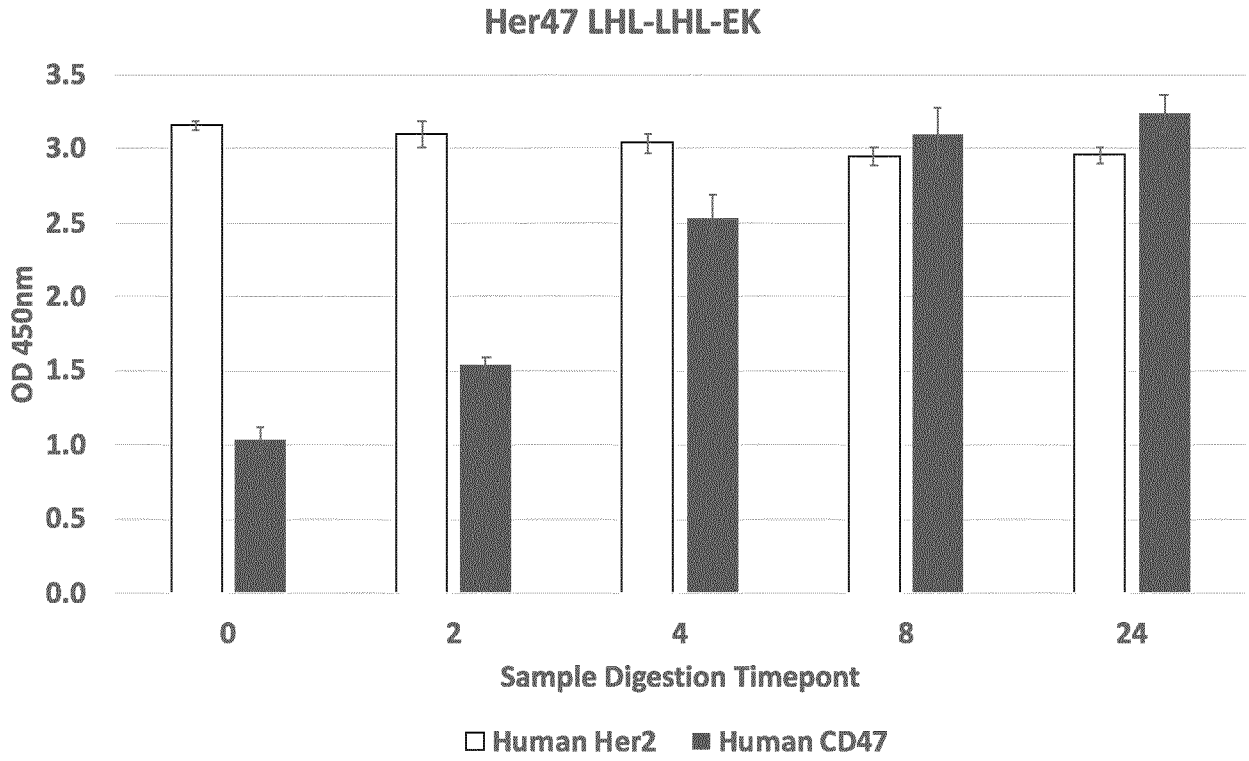

Her47 LHL-LHL-EK
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD 450nm
0
2
4
8
24
Sample Digestion Timepont
Human Her2
Human CD47

Figure 39C

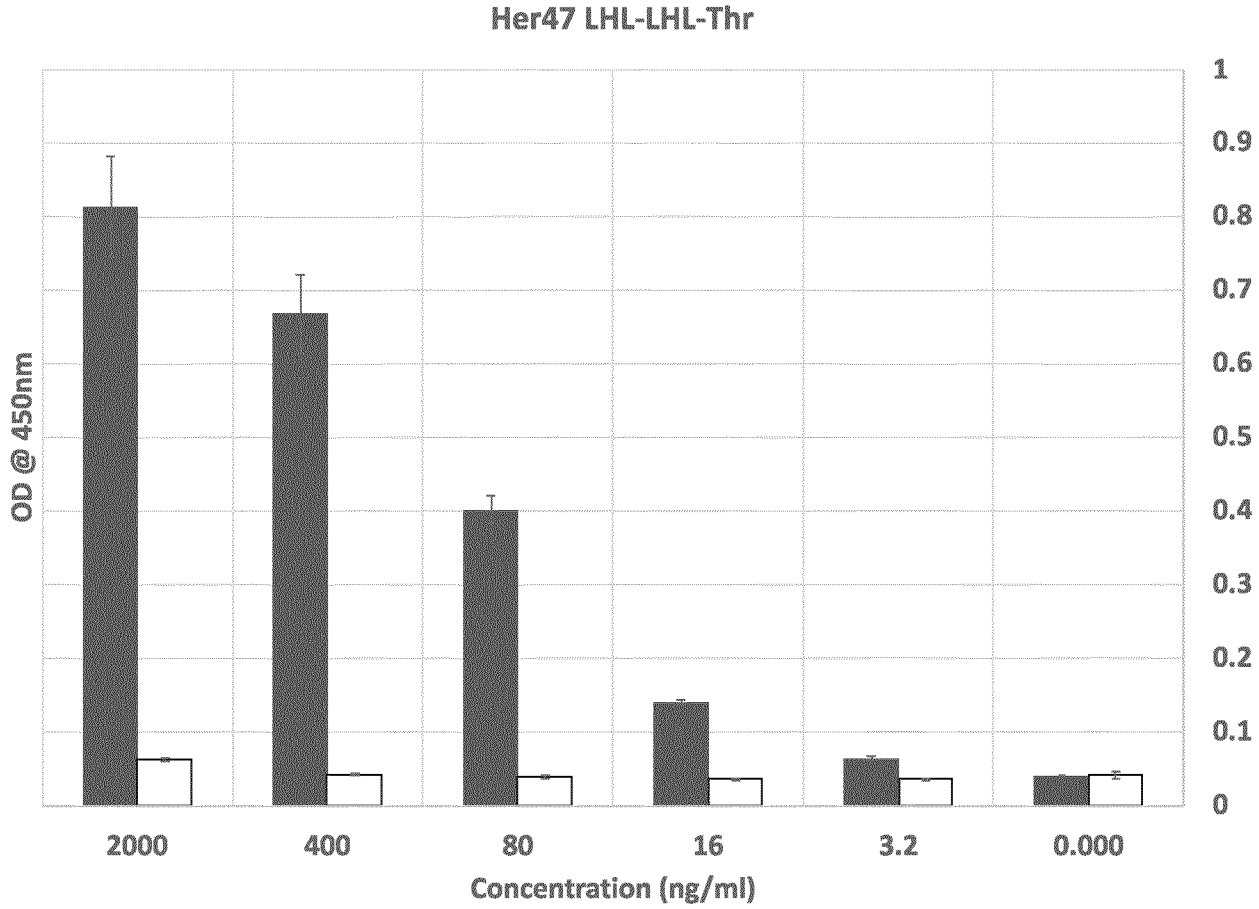

Her47 LHL-LHL-Thr
OD @ 450nm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2000
400
80
16
3.2
0.000
Concentration (ng/ml)

Figure 39D

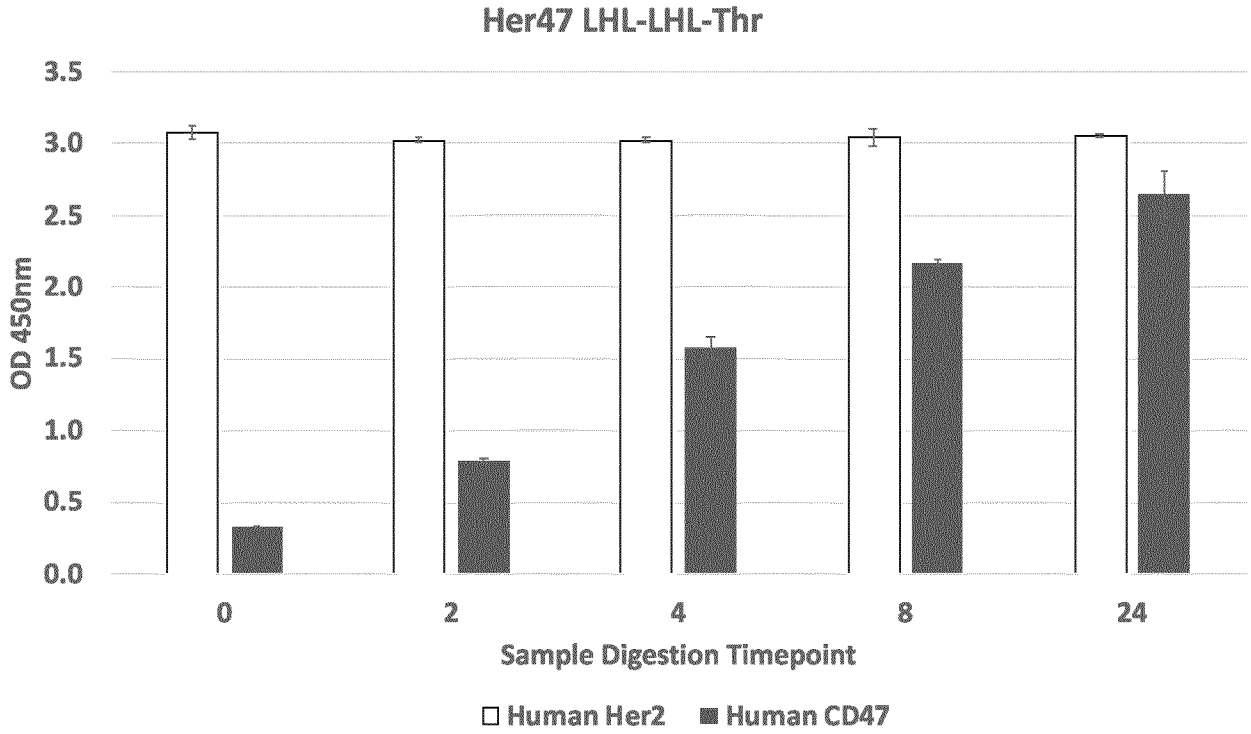

Her47 LHL-LHL-Thr
OD 450nm
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
2
4
8
24
Sample Digestion Timepoint
Human Her2
Human CD47

Figure 39E

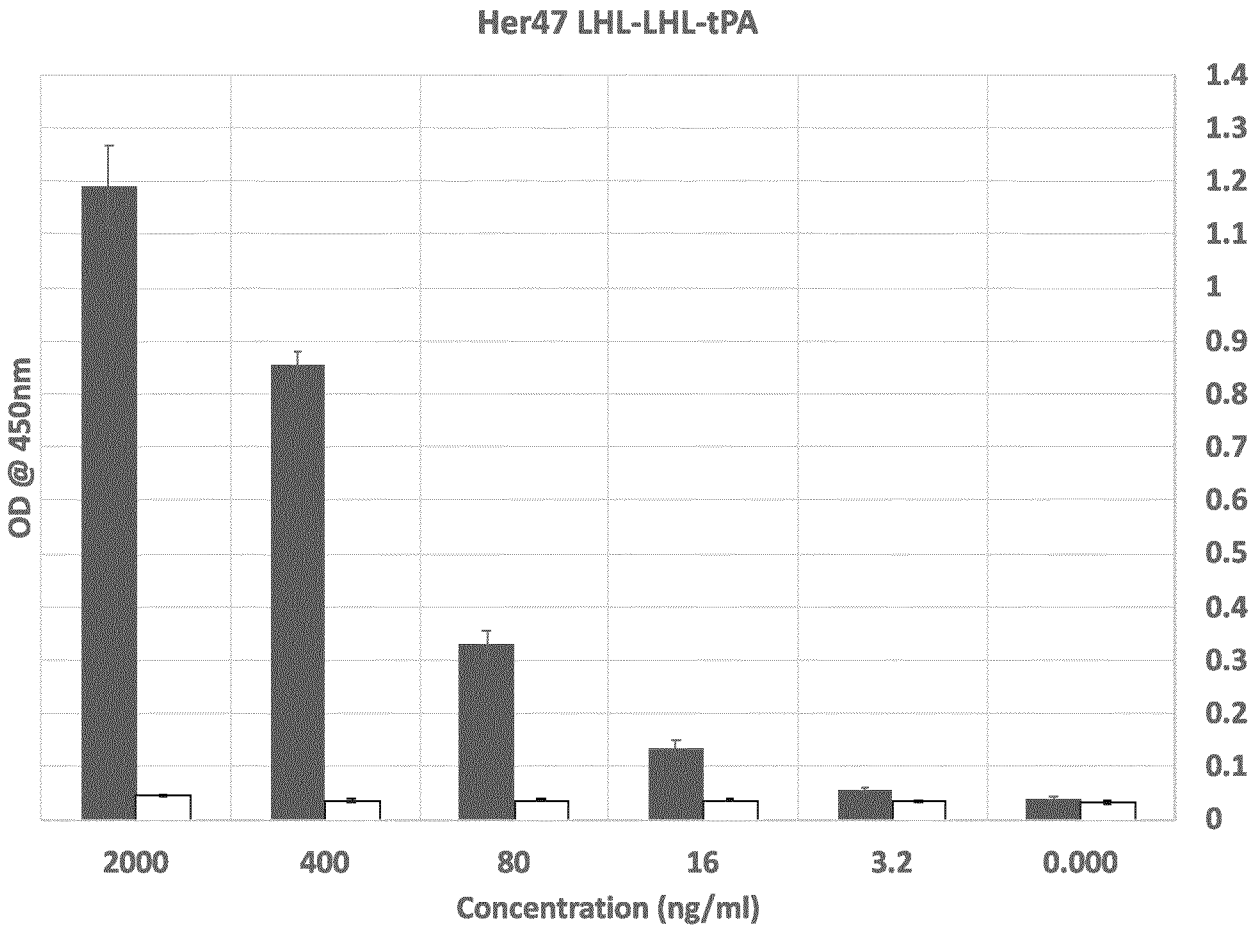

Her47 LHL-LHL-tPA
OD @ 450nm
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2000
400
80
16
3.2
0.000
Concentration (ng/ml)

Figure 39F

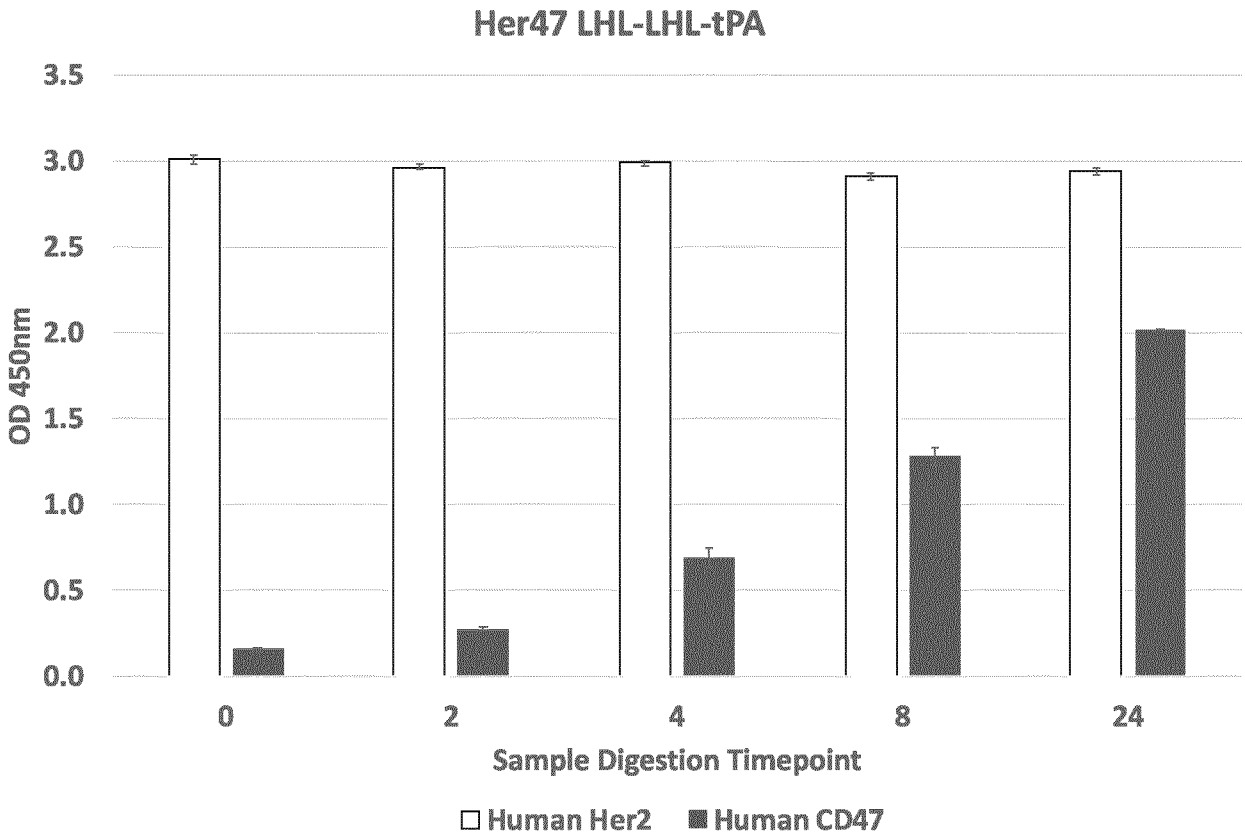

Her47 LHL-LHL-tPA
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD 450nm
0
2
4
8
24
Sample Digestion Timepoint
Human Her2
Human CD47

Figure 39G

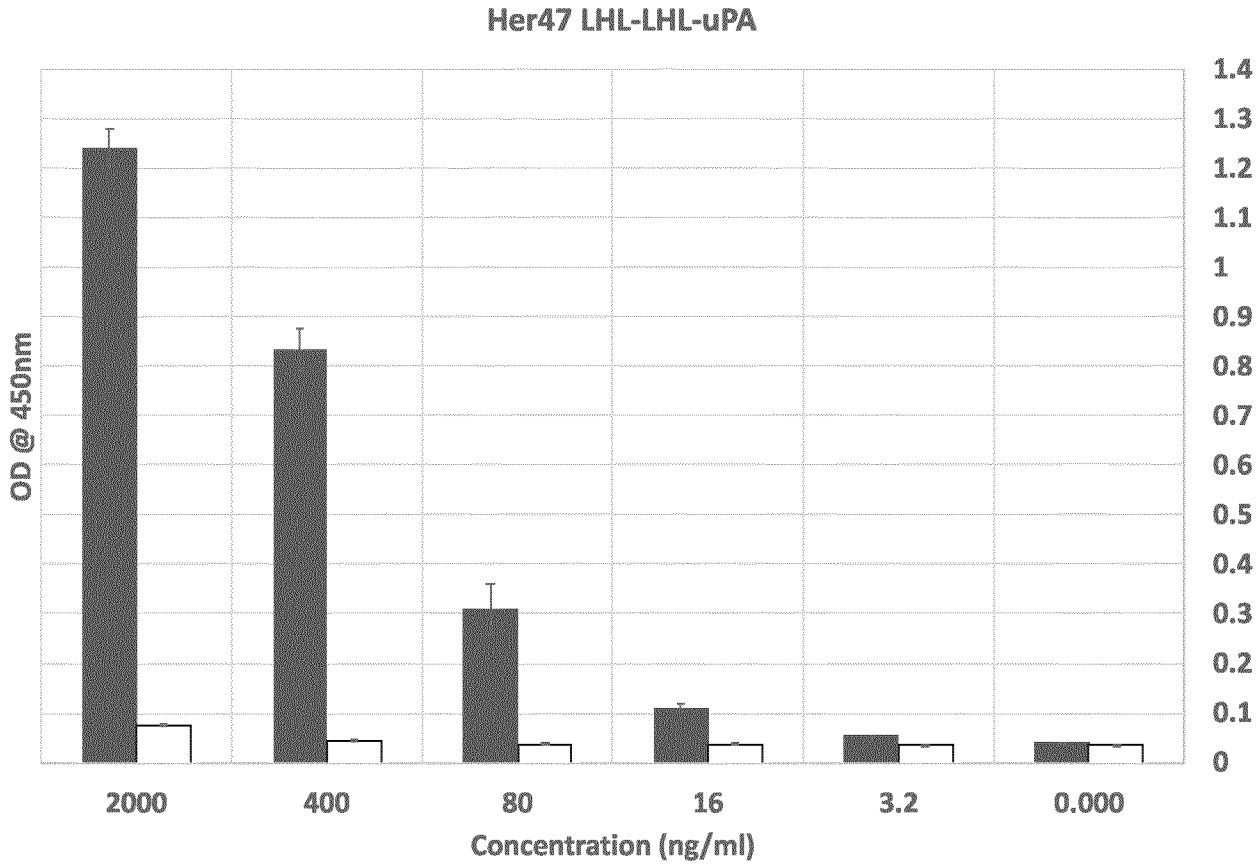

Her47 LHL-LHL-uPA
OD @ 450nm
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2000
400
80
16
3.2
0.000
Concentration (ng/ml)

Figure 39H

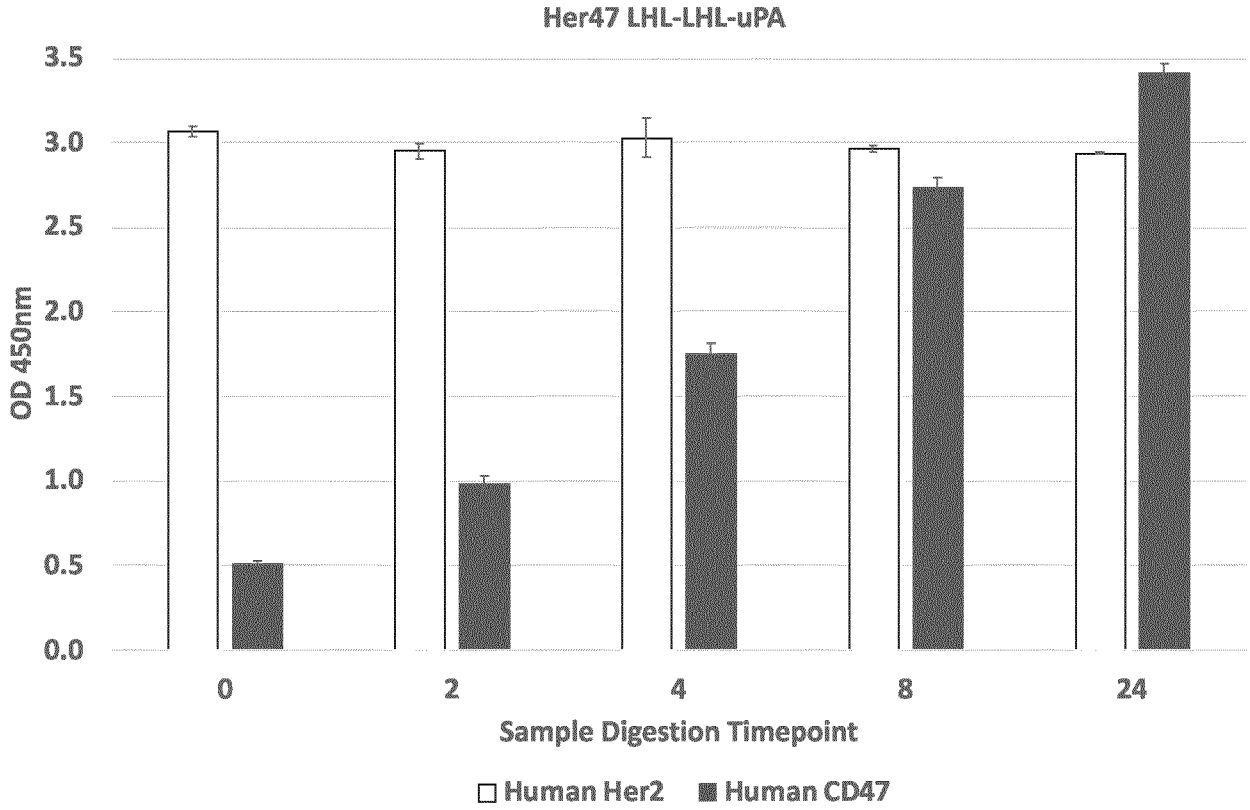

Her47 LHL-LHL-uPA
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD 450nm
0
2
4
8
24
Sample Digestion Timepoint
Human Her2
Human CD47

Figure 39I

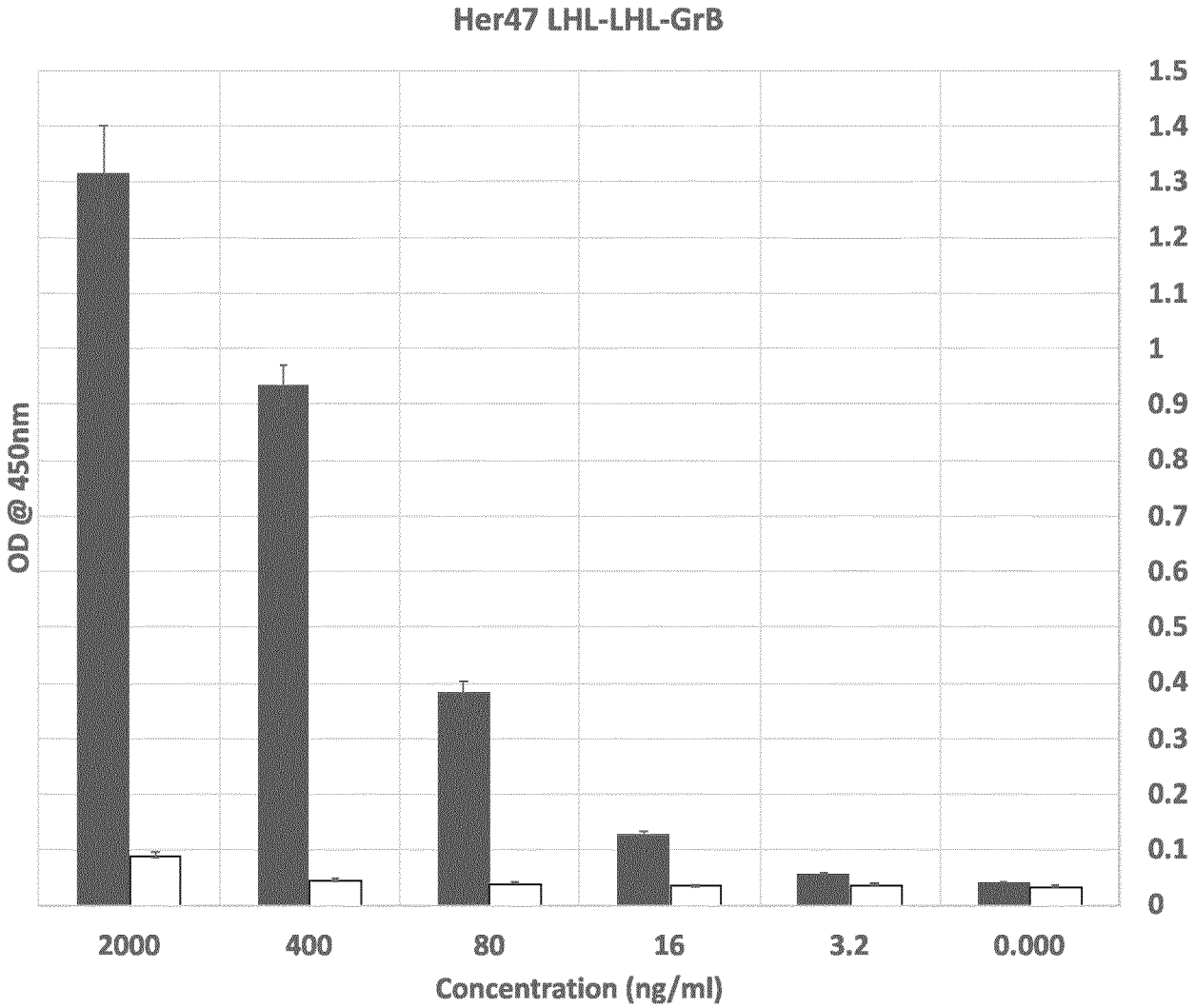

Her47 LHL-LHL-GrB
OD @ 450nm
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2000
400
80
16
3.2
0.000
Concentration (ng/ml)

Figure 39J

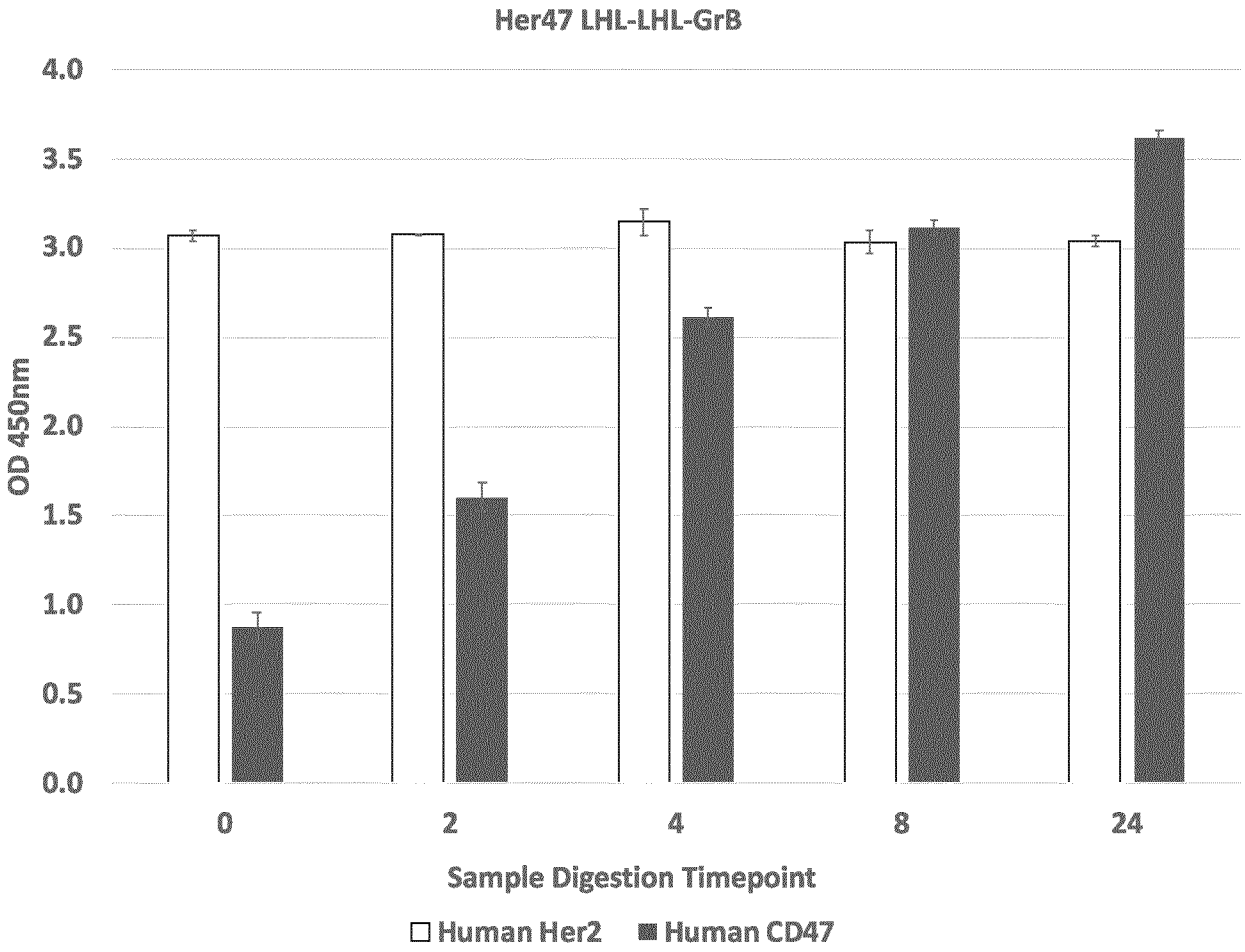

Her47 LHL-LHL-GrB
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD 450nm
0
2
4
8
24
Sample Digestion Timepoint
Human Her2
Human CD47

Figure 39K

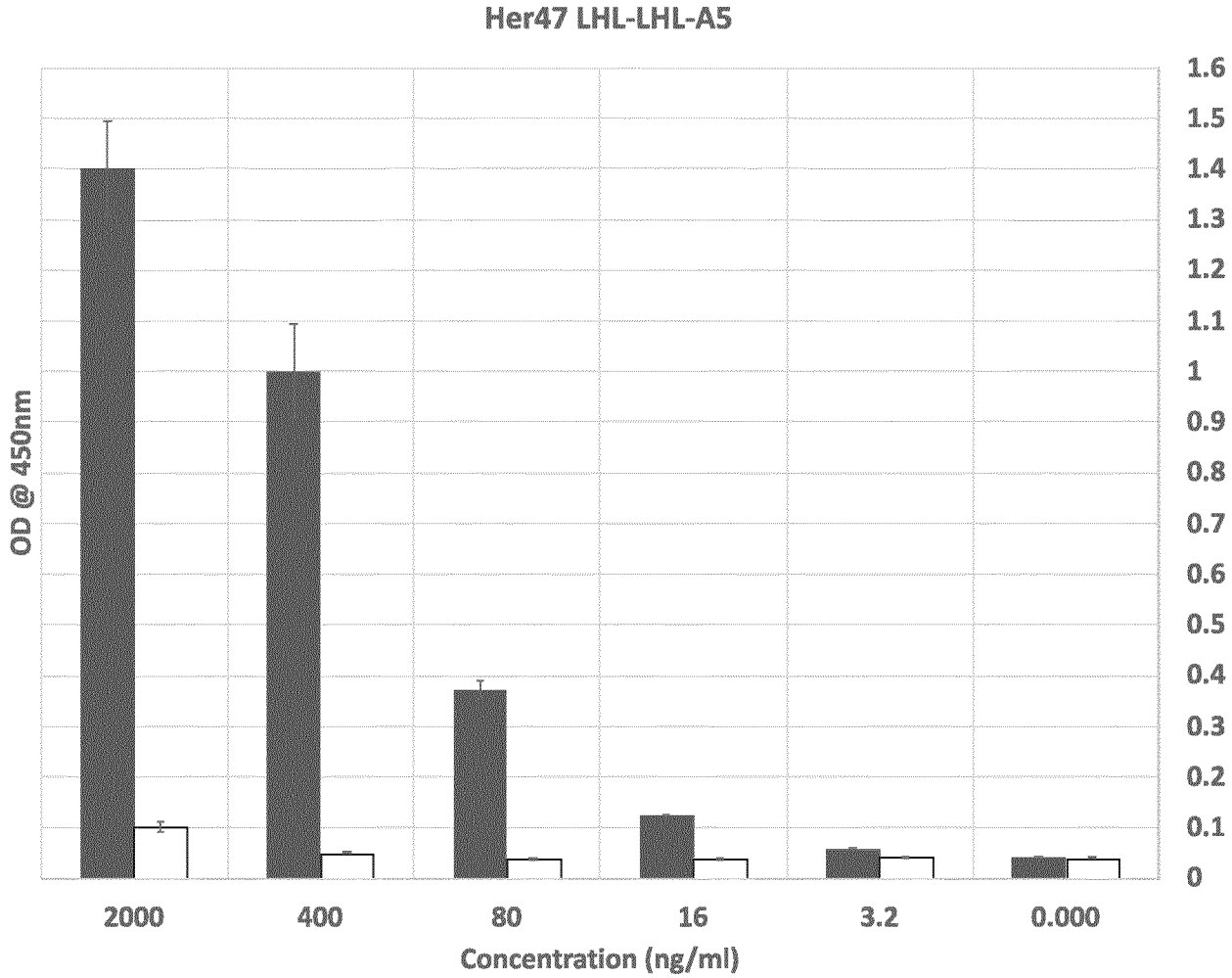

Her47 LHL-LHL-A5
OD @ 450nm
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2000
400
80
16
3.2
0.000
Concentration (ng/ml)

Figure 39L

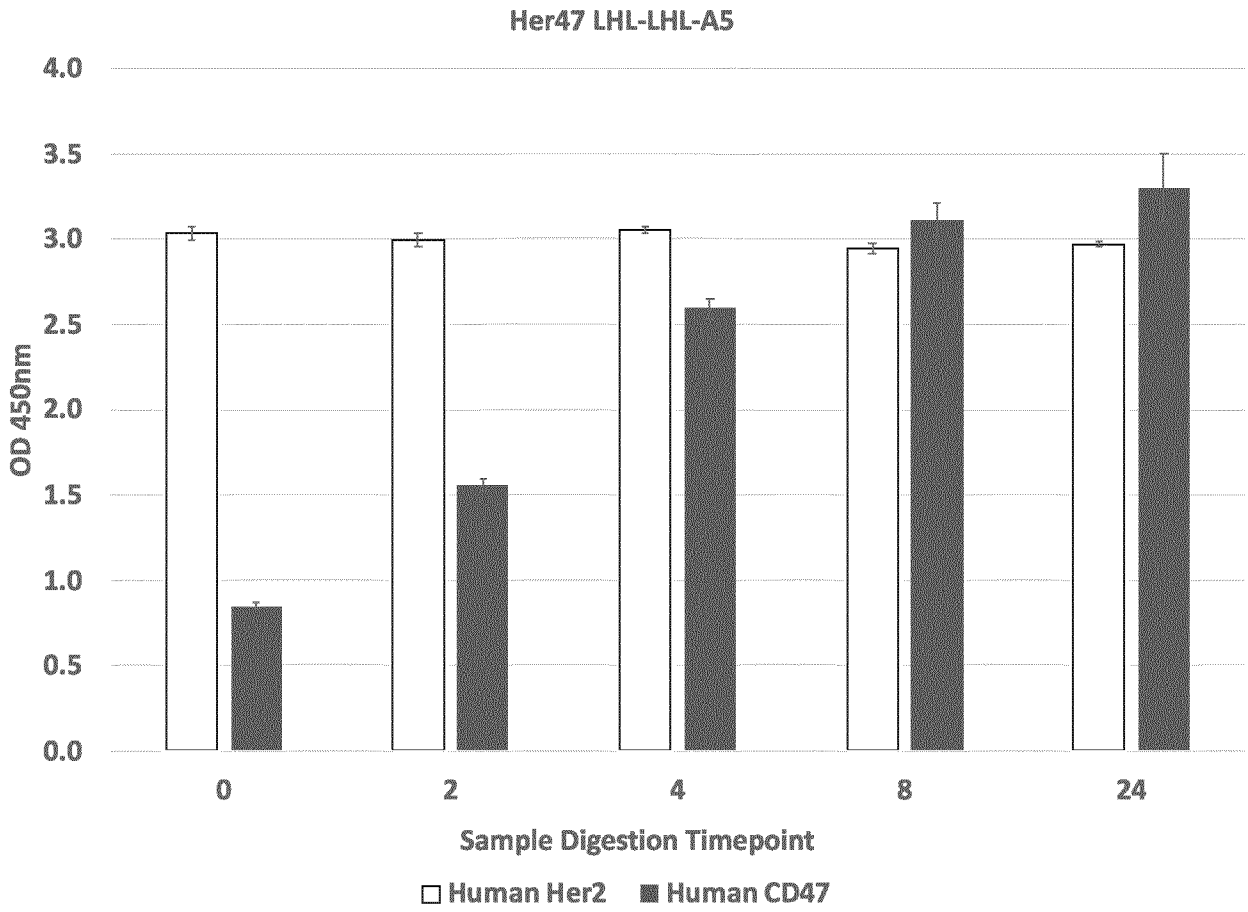

Her47 LHL-LHL-A5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
OD 450nm
0
2
4
8
24
Sample Digestion Timepoint
Human Her2
Human CD47

Figure 40

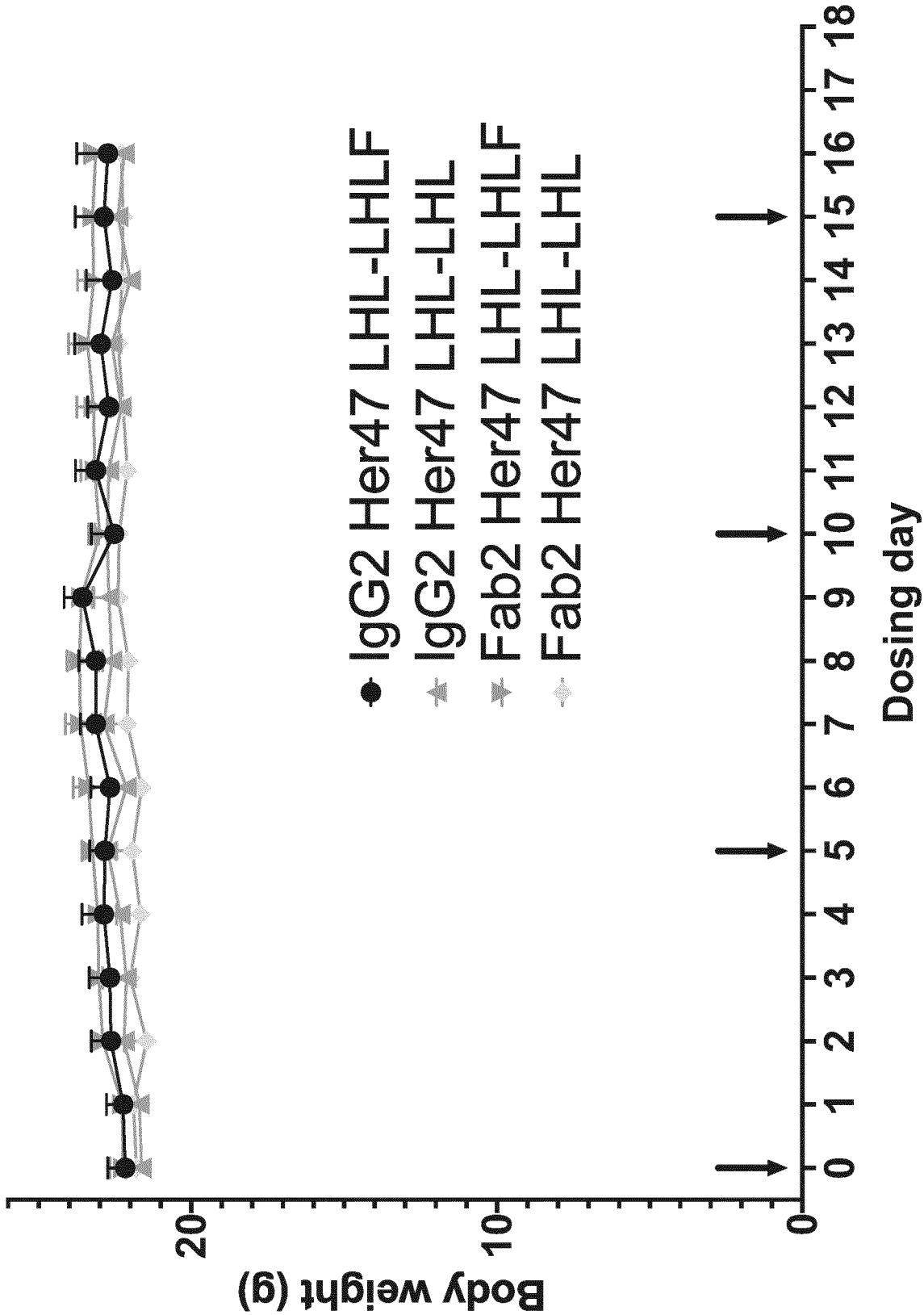

IgG2 Her47 LHL-LHLF
IgG2 Her47 LHL-LHL
Fab2 Her47 LHL-LHLF
Fab2 Her47 LHL-LHL
Body weight (g)
Dosing day
0
10
20
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Figure 41A

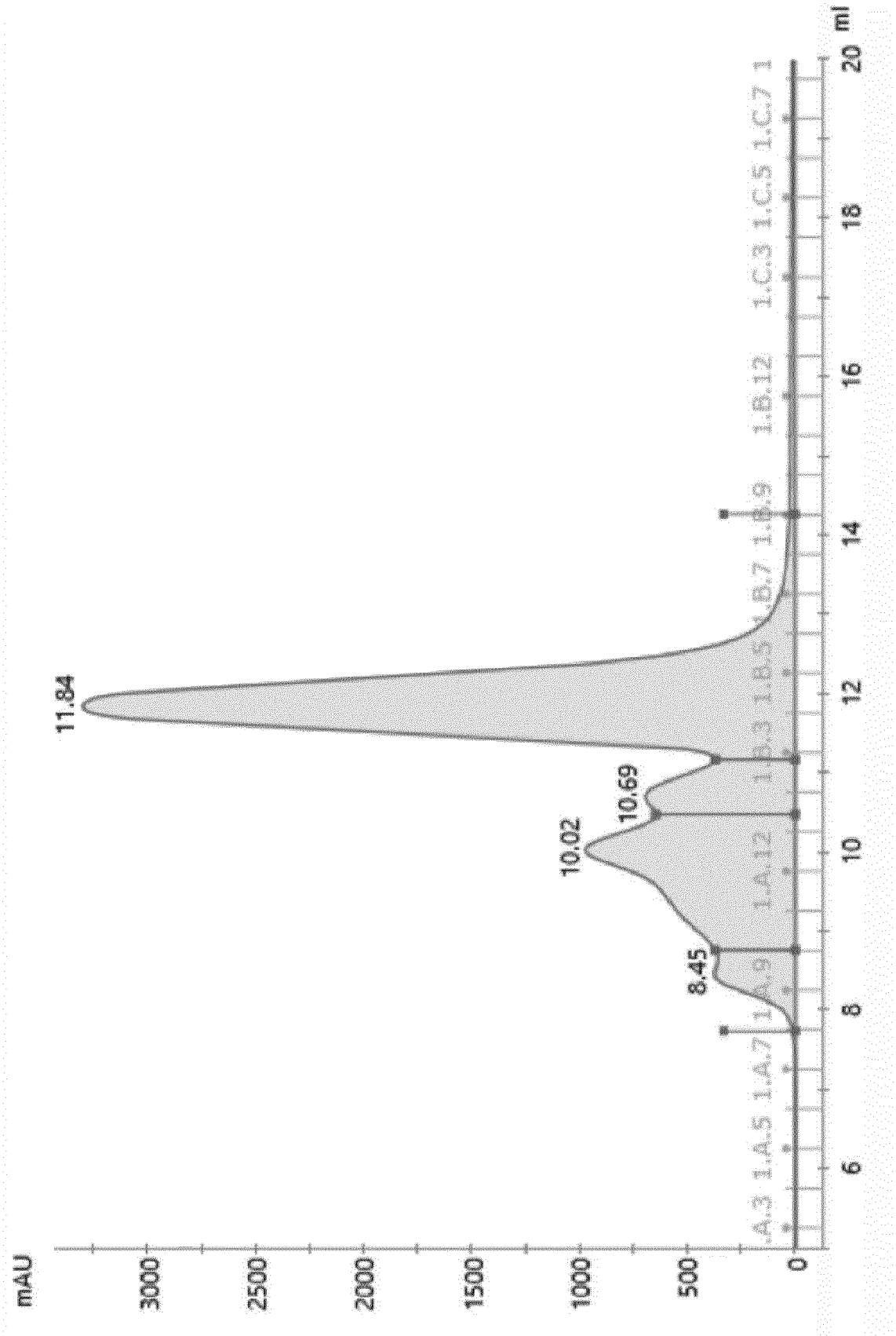

mAU
3000
2500
2000
1500
1000
500
0
ml
6
8
10
12
14
16
18
20
11.84
10.69
10.02
8.45
1.A.3
1.A.5
1.A.7
1.A.9
1.A.12
1.B.3
1.B.5
1.B.7
1.B.9
1.B.12
1.C.3
1.C.5
1.C.7
1

Figure 41B

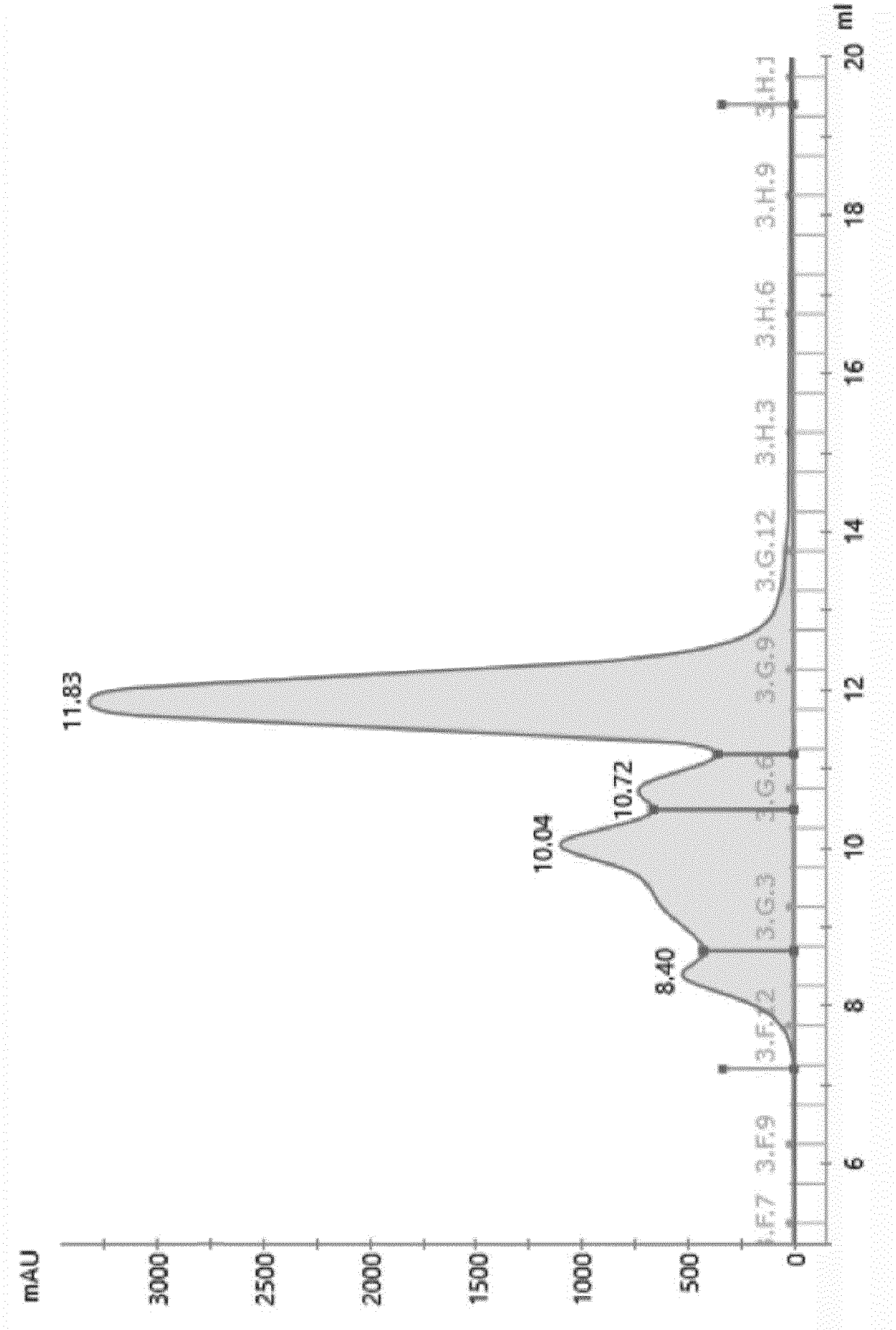

mAU
3000
2500
2000
1500
1000
500
0
ml
6
8
10
12
14
16
18
20
11,83
10,72
10,04
8,40
3.F.7
3.F.9
3.F.2
3.G.3
3.G.6
3.G.9
3.G.12
3.H.3
3.H.6
3.H.9
3.H.1

Figure 41C

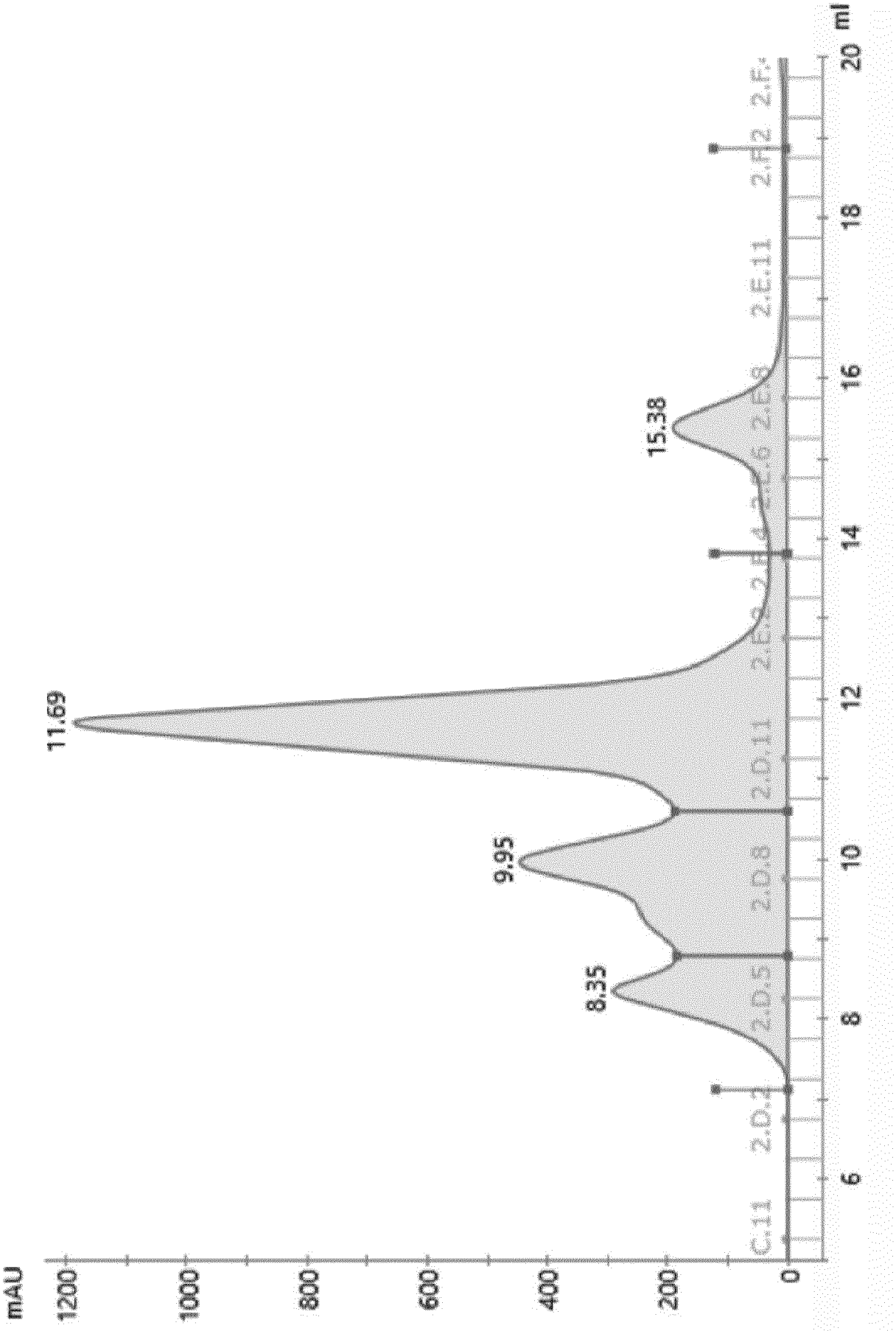

mAU
1200
1000
800
600
400
200
0
ml
6
8
10
12
14
16
18
20
11,69
9,95
8,35
15,38

Figure 41D

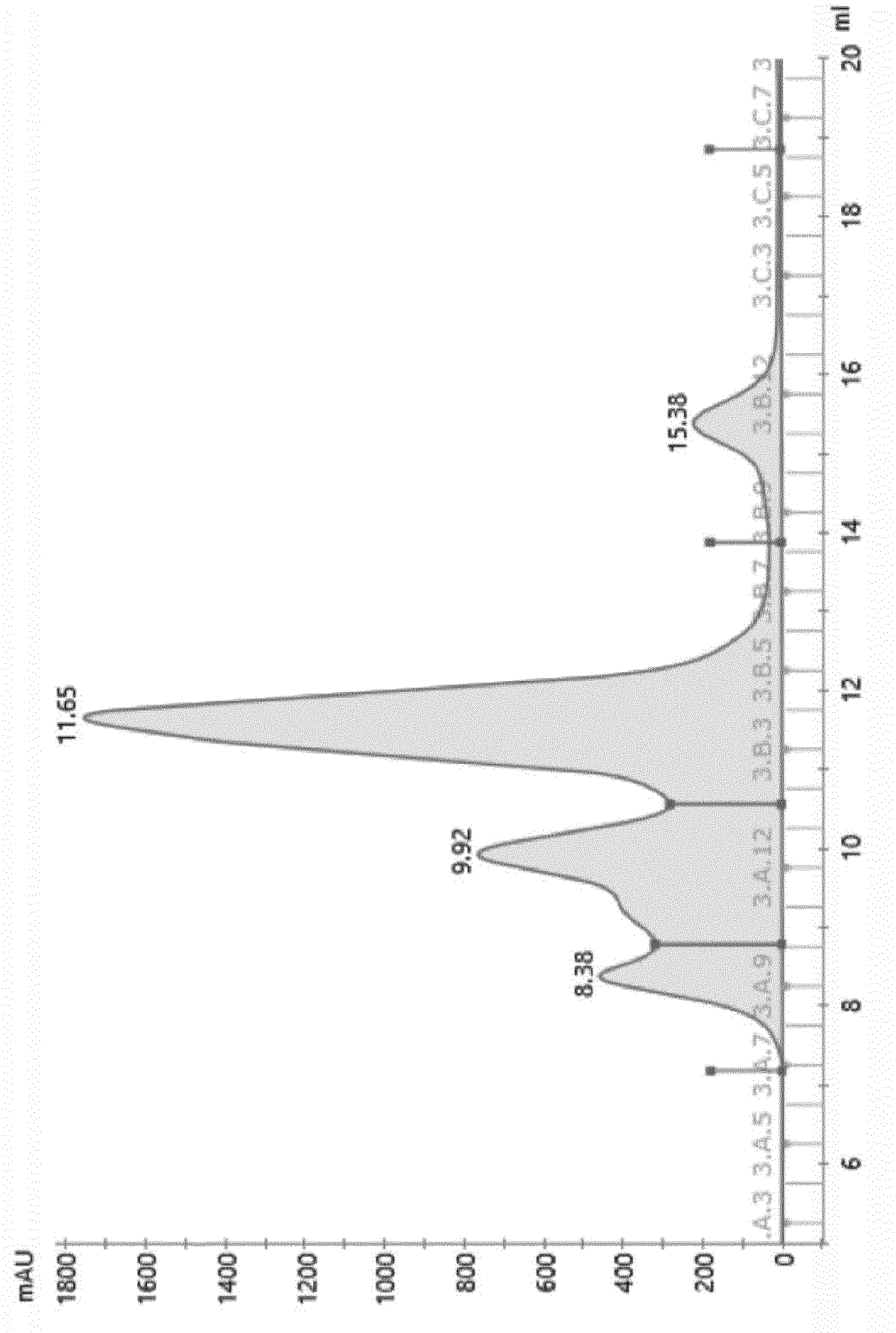

mAU
1800
1600
1400
1200
1000
800
600
400
200
0
ml
6
8
10
12
14
16
18
20
11.65
9.92
8.38
15.38
3.A.3 3.A.5 3.A.7 3.A.9 3.A.12 3.B.3 3.B.5 3.B.7 3.B.9 3.B.12 3.C.3 3.C.5 3.C.7

Figure 42A

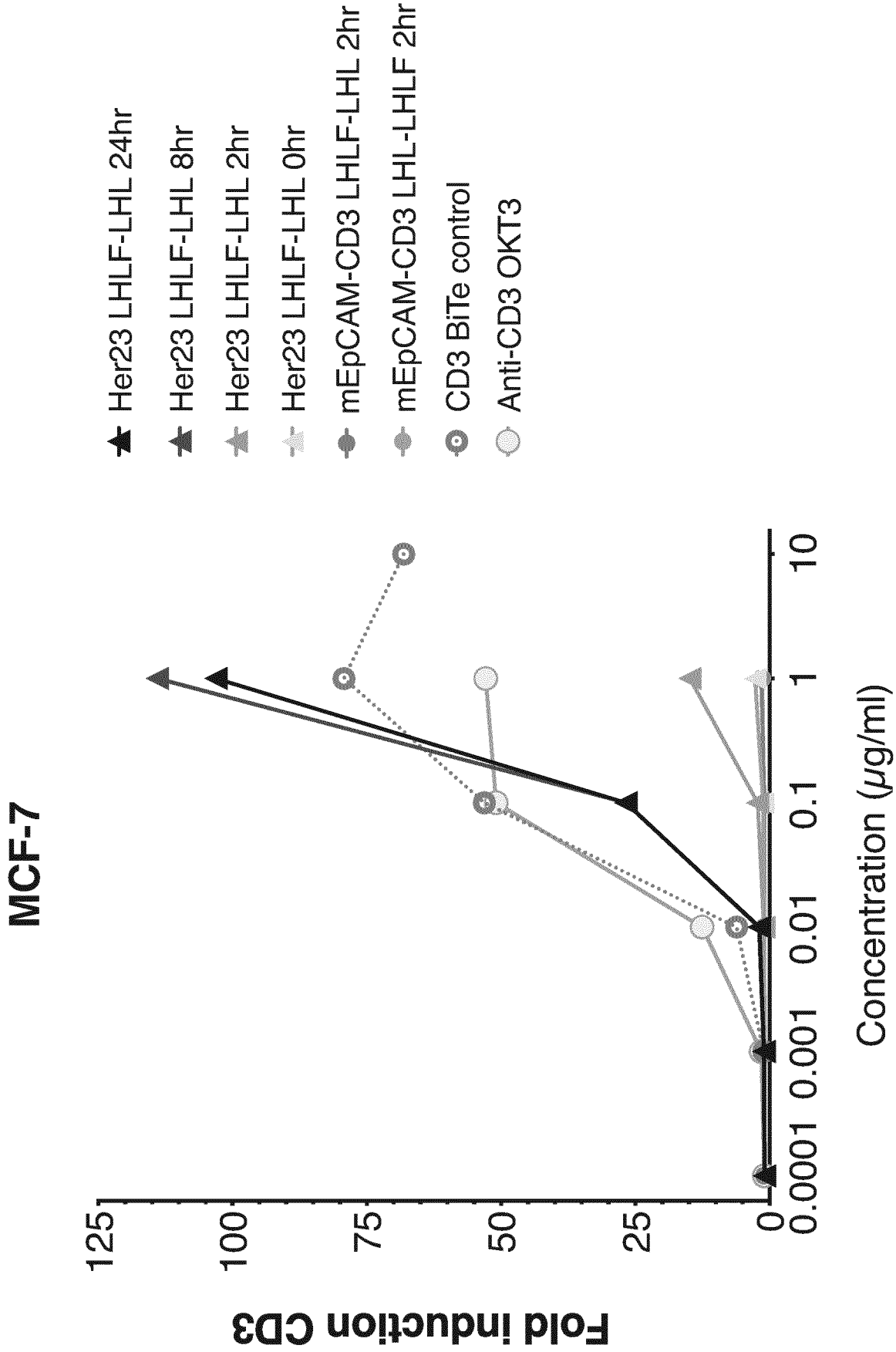

MCF-7
Fold induction CD3
125
100
75
50
25
0
0.0001
0.001
0.01
0.1
1
10
Concentration (µg/ml)
Her23 LHLF-LHL 24hr
Her23 LHLF-LHL 8hr
Her23 LHLF-LHL 2hr
Her23 LHLF-LHL 0hr
mEpCAM-CD3 LHLF-LHL 2hr
mEpCAM-CD3 LHL-LHLF 2hr
CD3 BiTe control
Anti-CD3 OKT3

Figure 42B

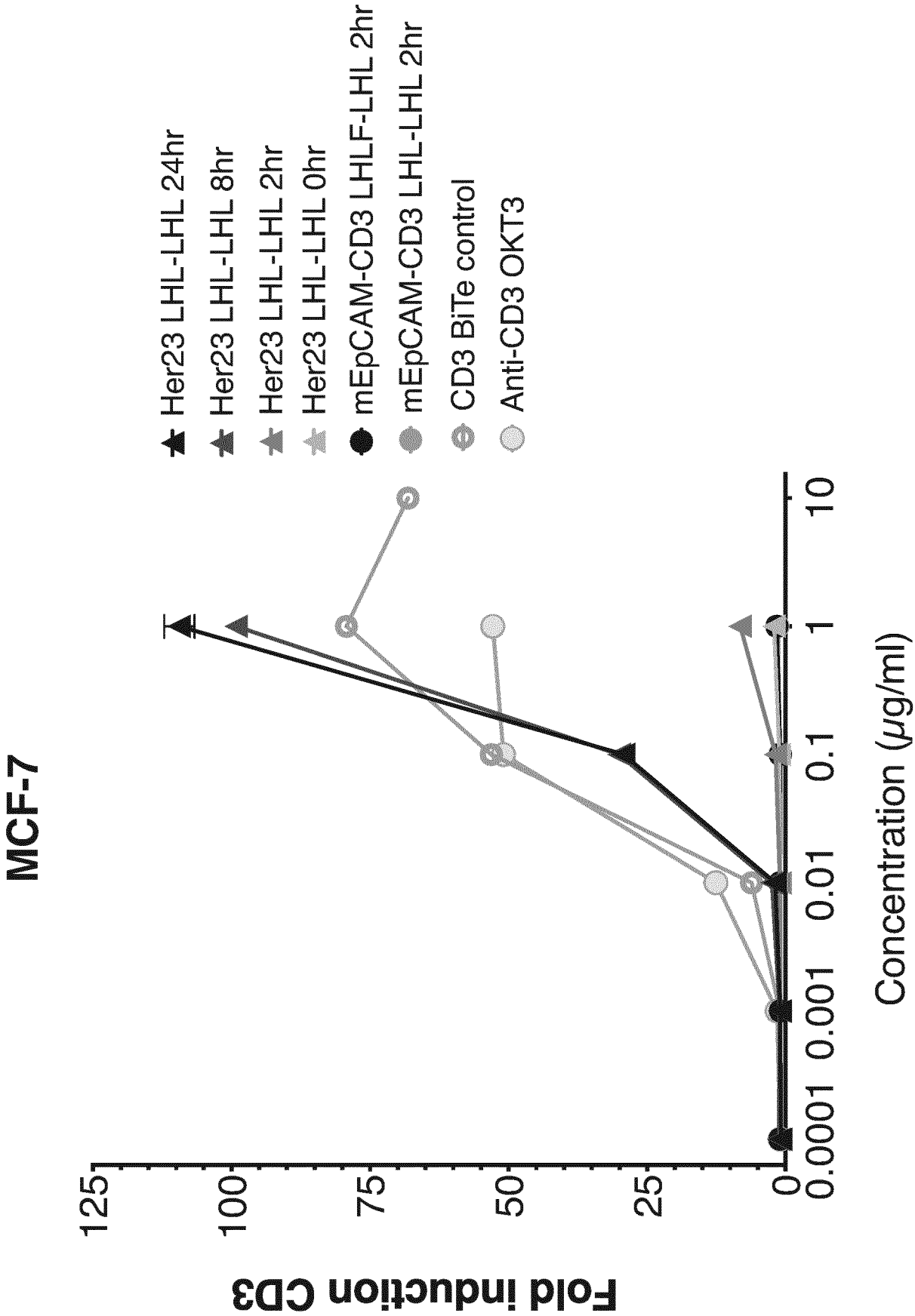

MCF-7
Fold induction CD3
125
100
75
50
25
0
0.0001
0.001
0.01
0.1
1
10
Concentration (µg/ml)
Her23 LHL-LHL 24hr
Her23 LHL-LHL 8hr
Her23 LHL-LHL 2hr
Her23 LHL-LHL 0hr
mEpCAM-CD3 LHLF-LHL 2hr
mEpCAM-CD3 LHL-LHL 2hr
CD3 BiTe control
Anti-CD3 OKT3

Figure 43A

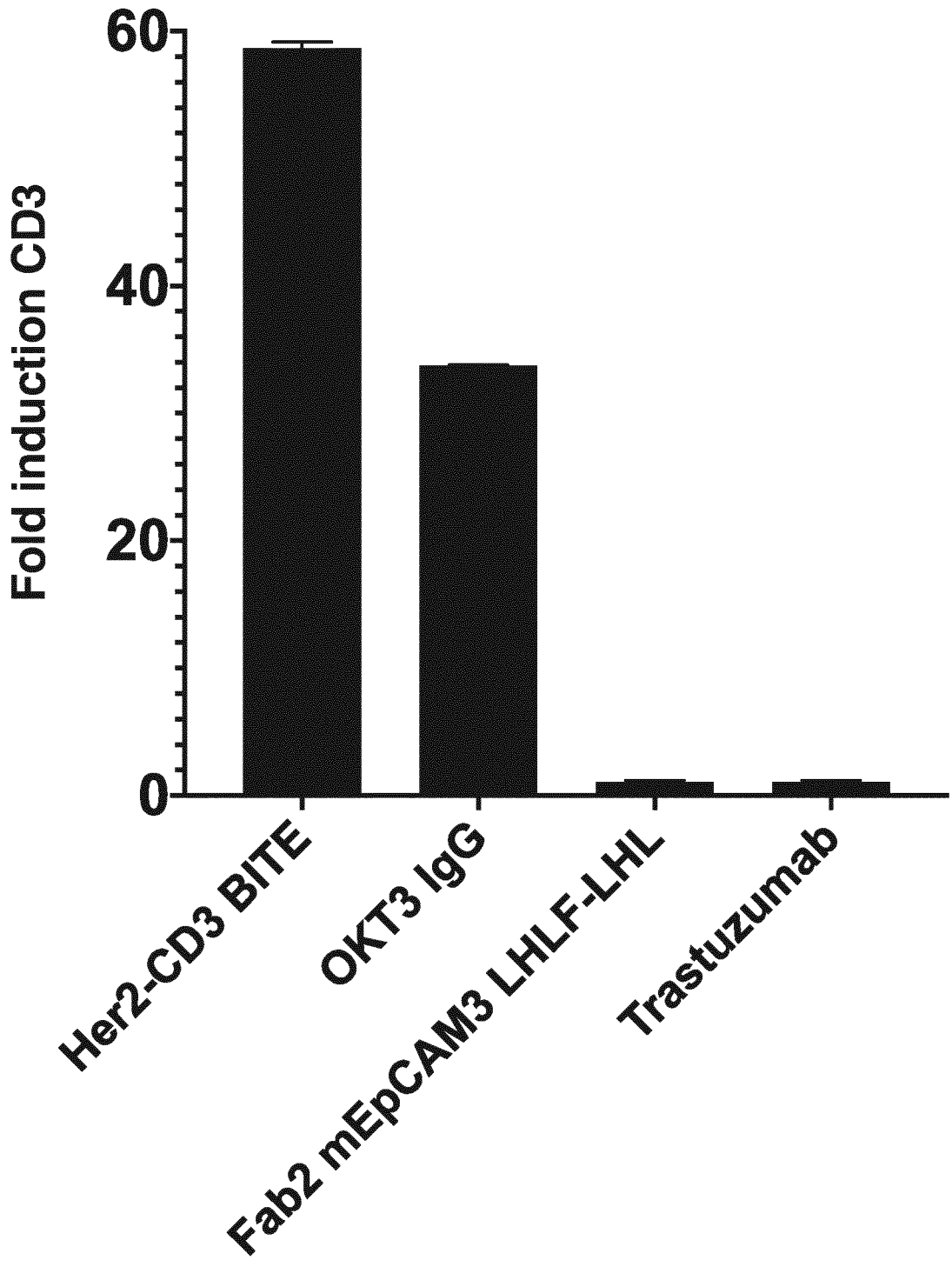

Fold induction CD3
60
40
20
0
Her2-CD3 BITE
OKT3 IgG
Fab2 mEpCAM3 LHLF-LHL
Trastuzumab

Figure 43B

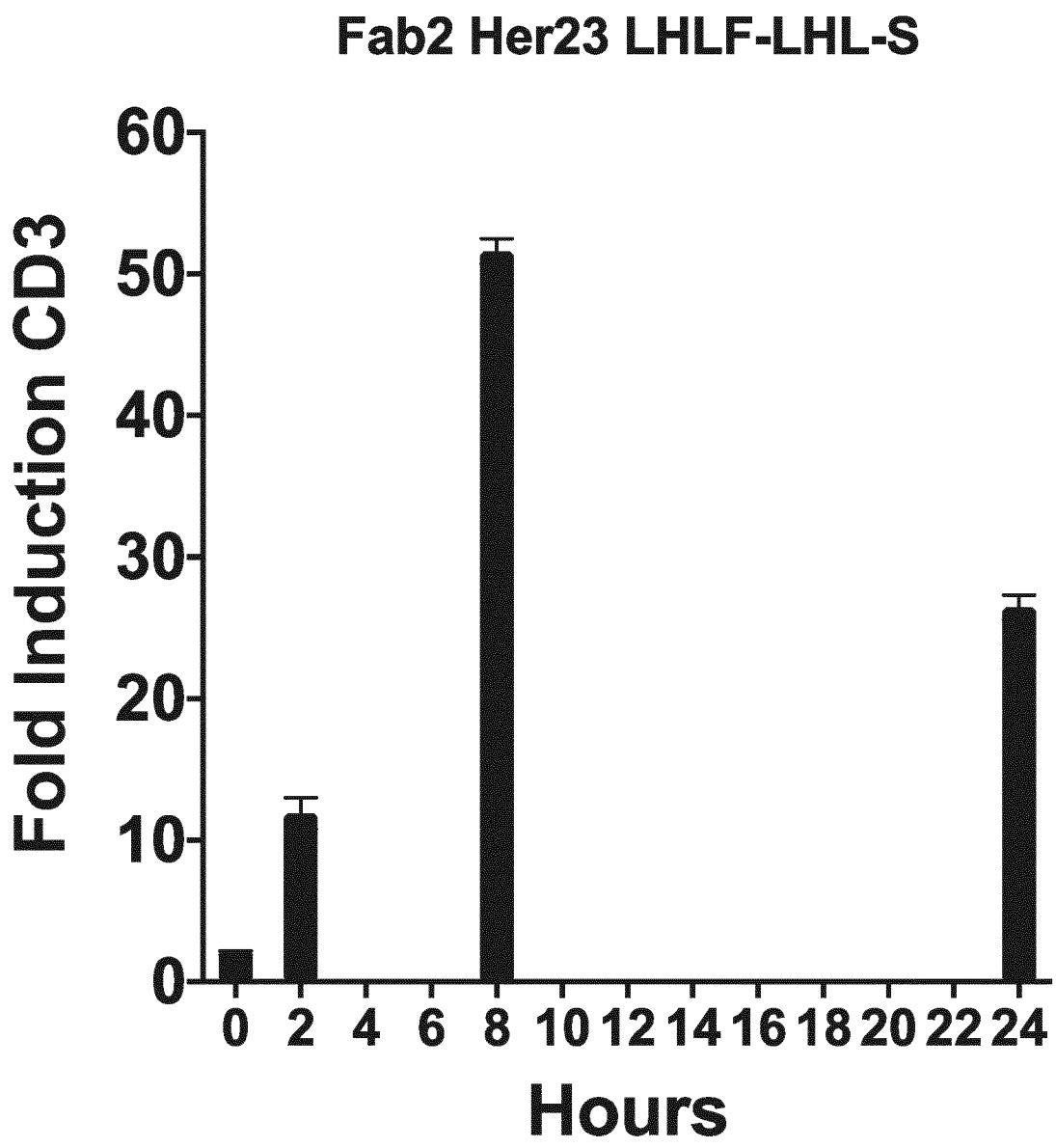

Fab2 Her23 LHLF-LHL-S
Fold Induction CD3
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Hours

Figure 43C

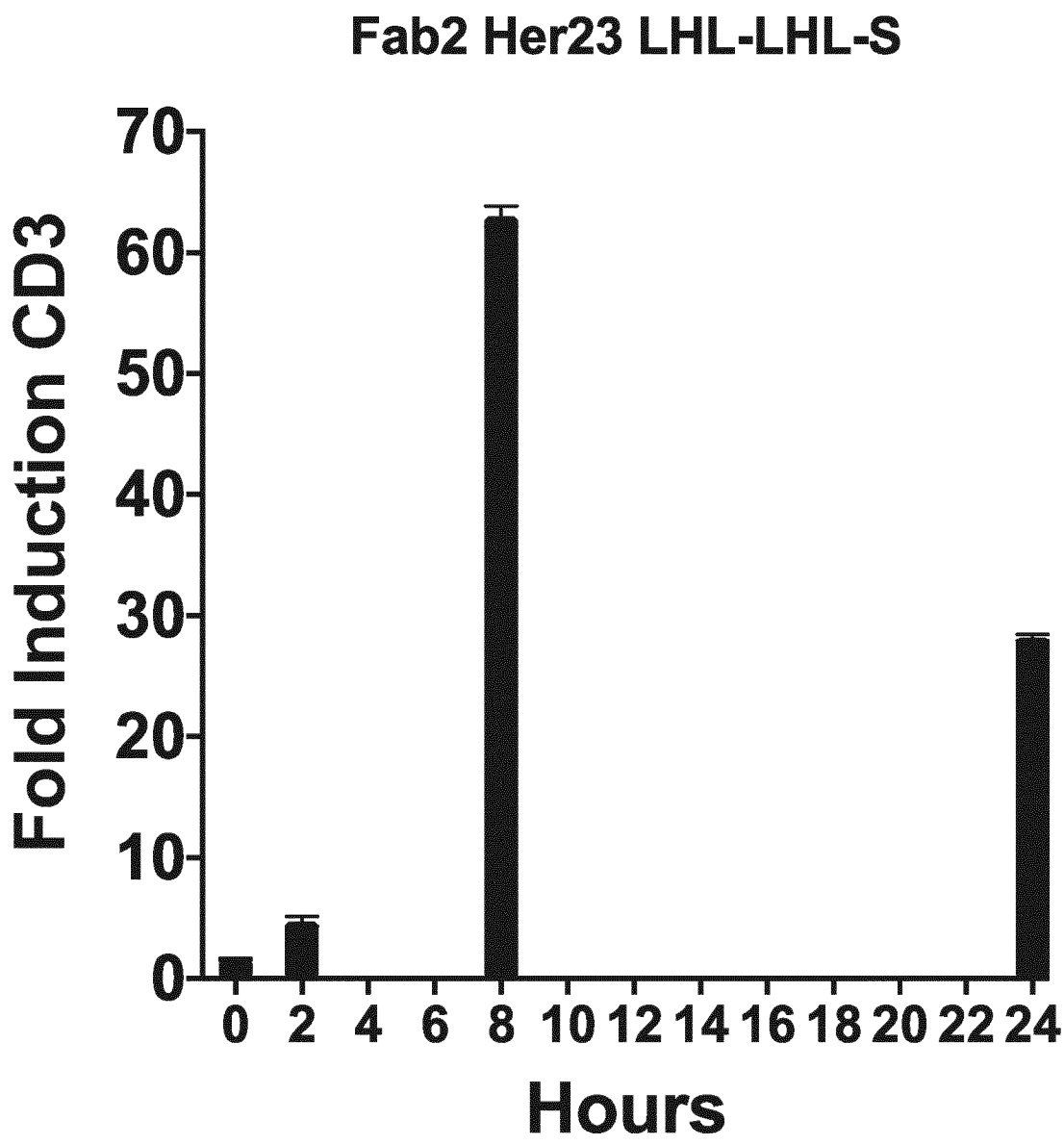

Fab2 Her23 LHL-LHL-S
Fold Induction CD3
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Hours

Figure 44A

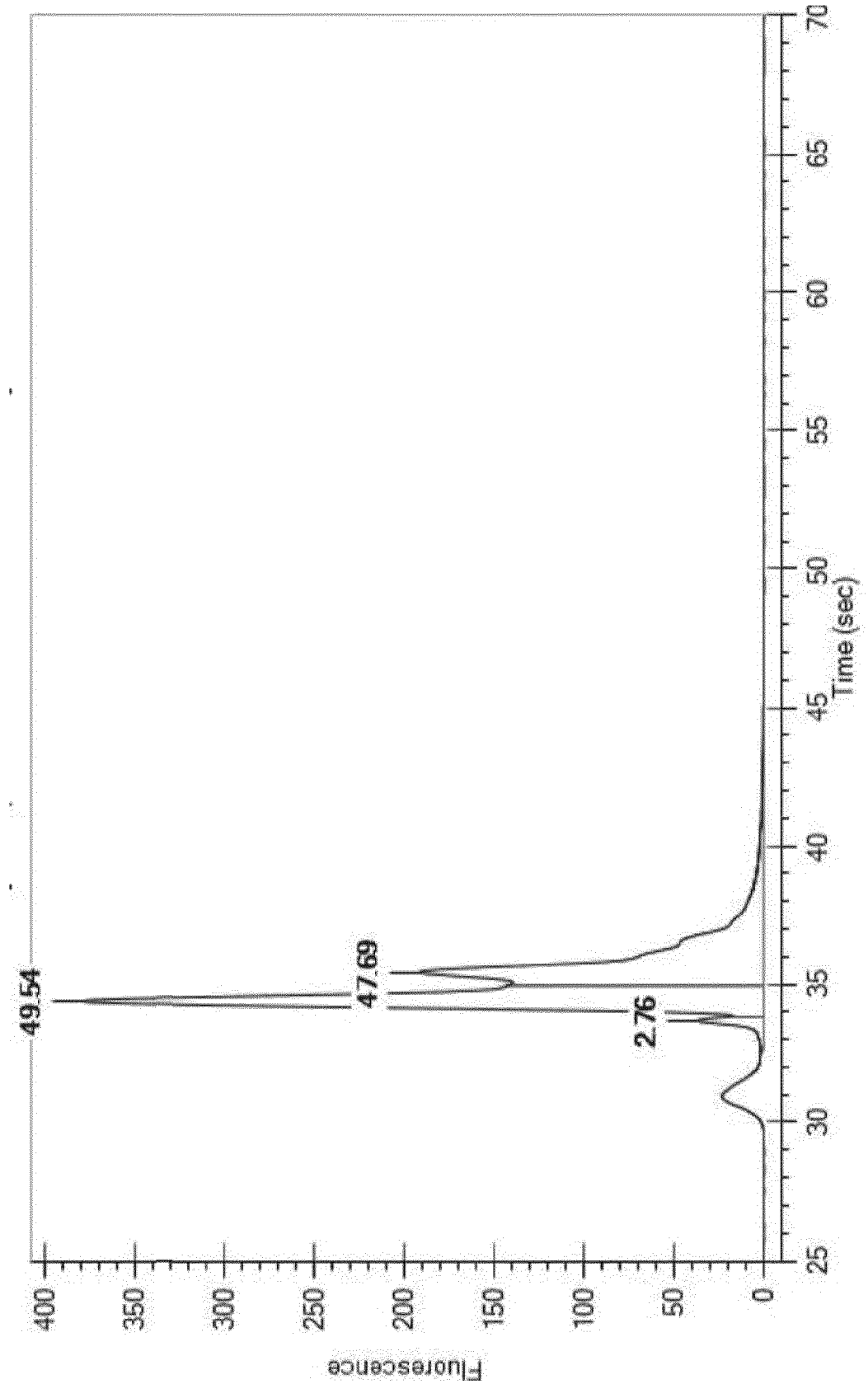

49.54
47.69
2.76
Fluorescence
Time (sec)
400
350
300
250
200
150
100
50
0
25
30
35
40
45
50
55
60
65
70

Figure 44B

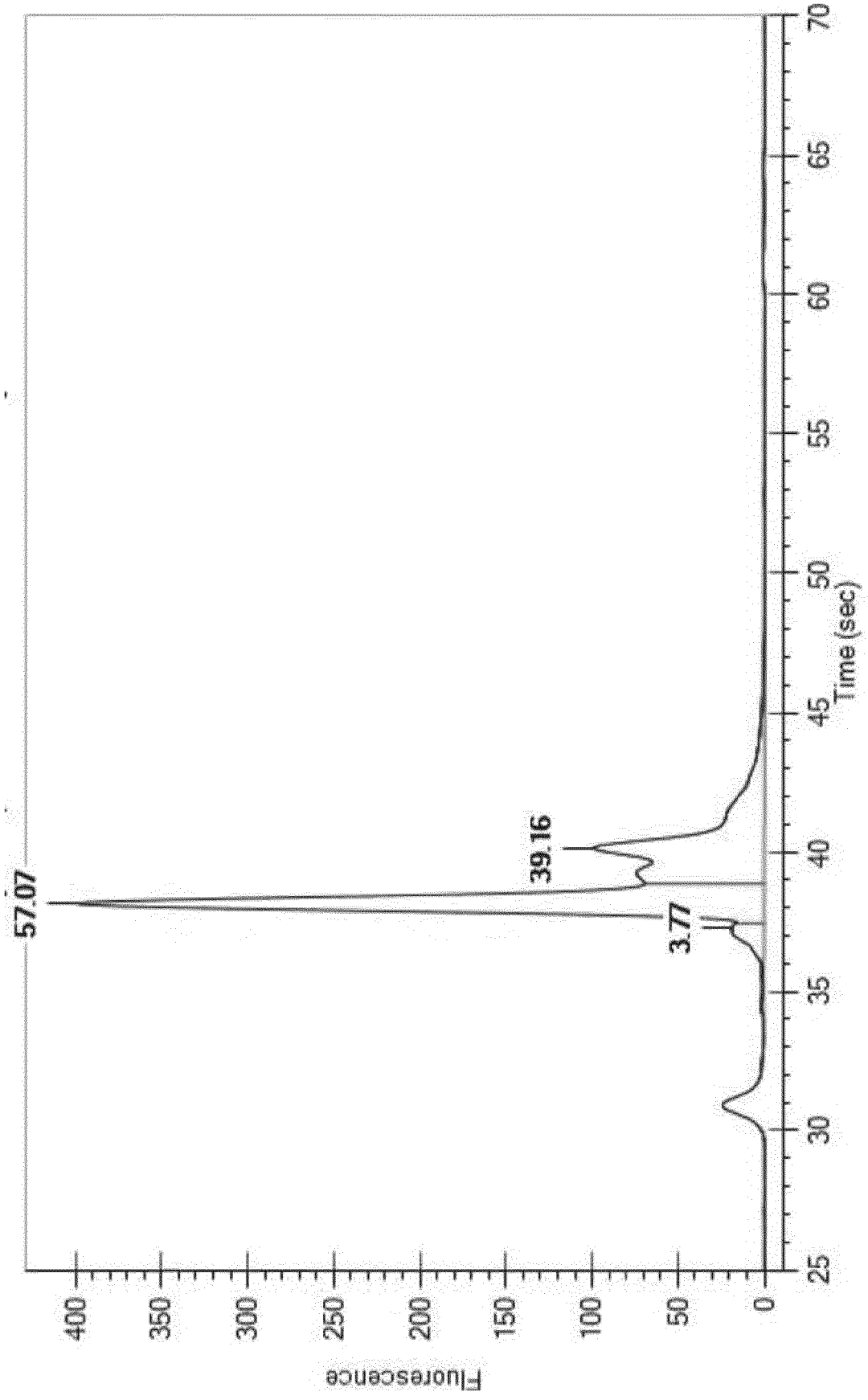

57.07
39.16
3.77
Fluorescence
Time (sec)
400
350
300
250
200
150
100
50
0
25
30
35
40
45
50
55
60
65
70

Figure 45A

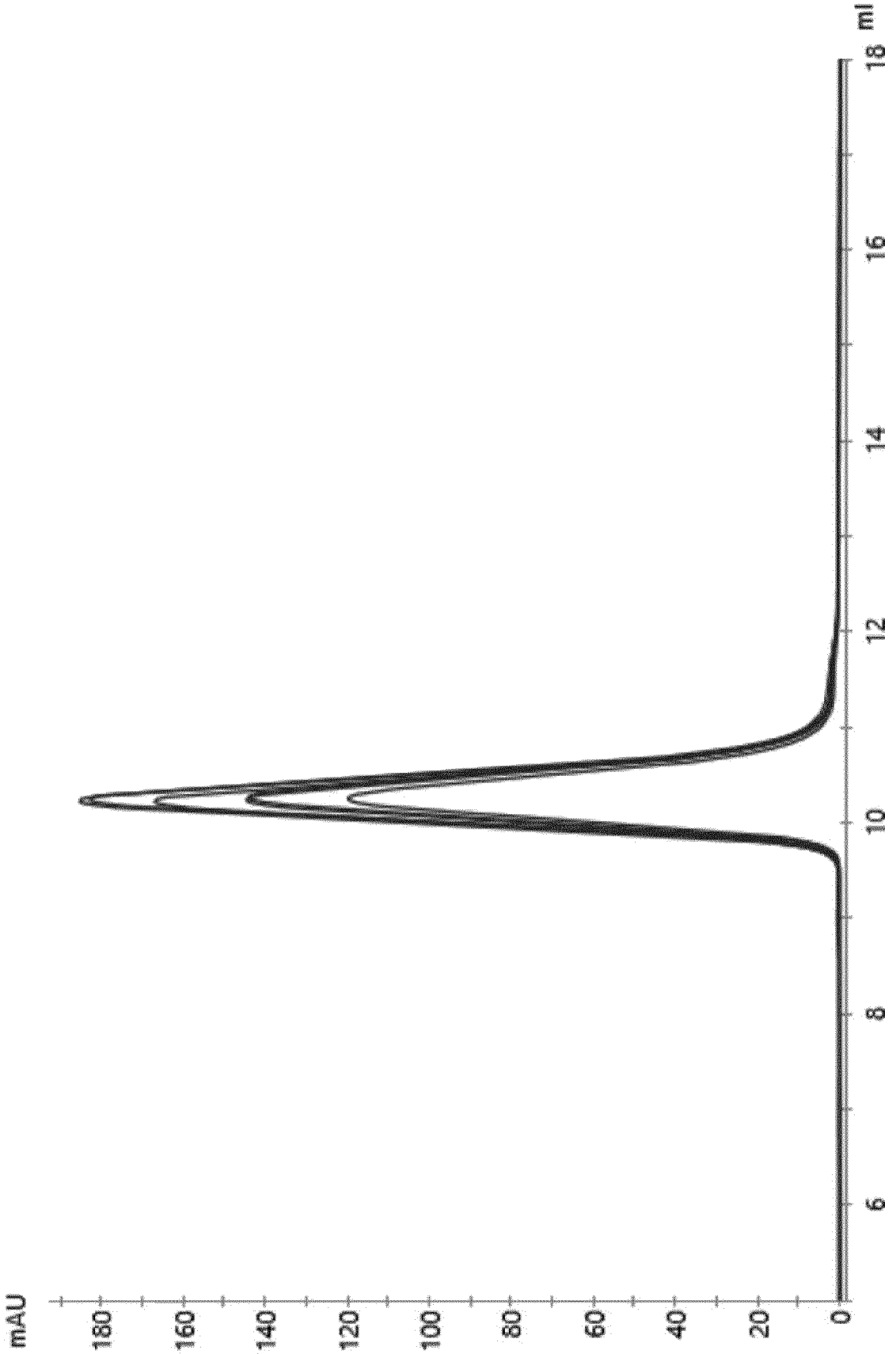


Figure 45B

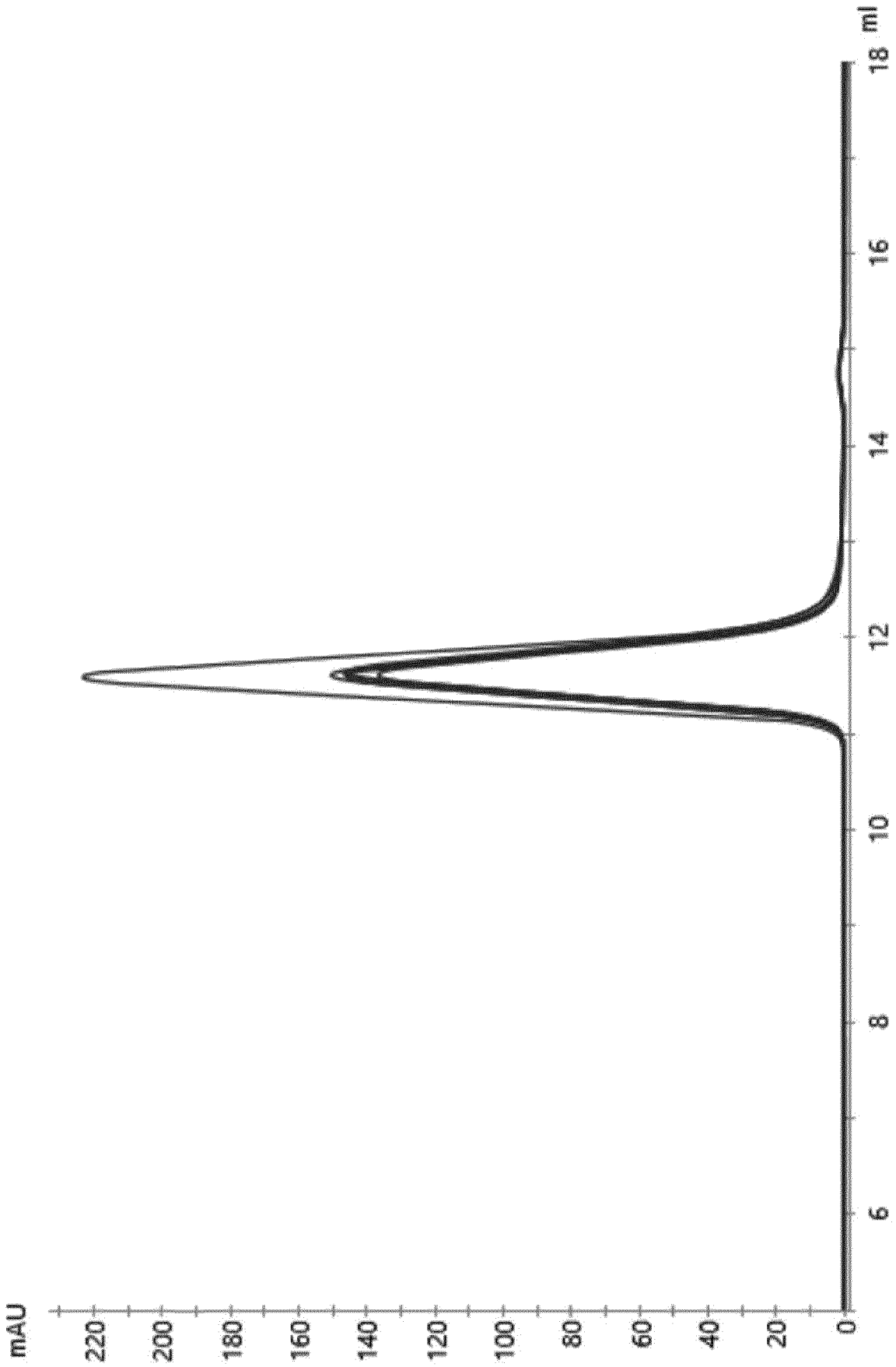


Figure 46

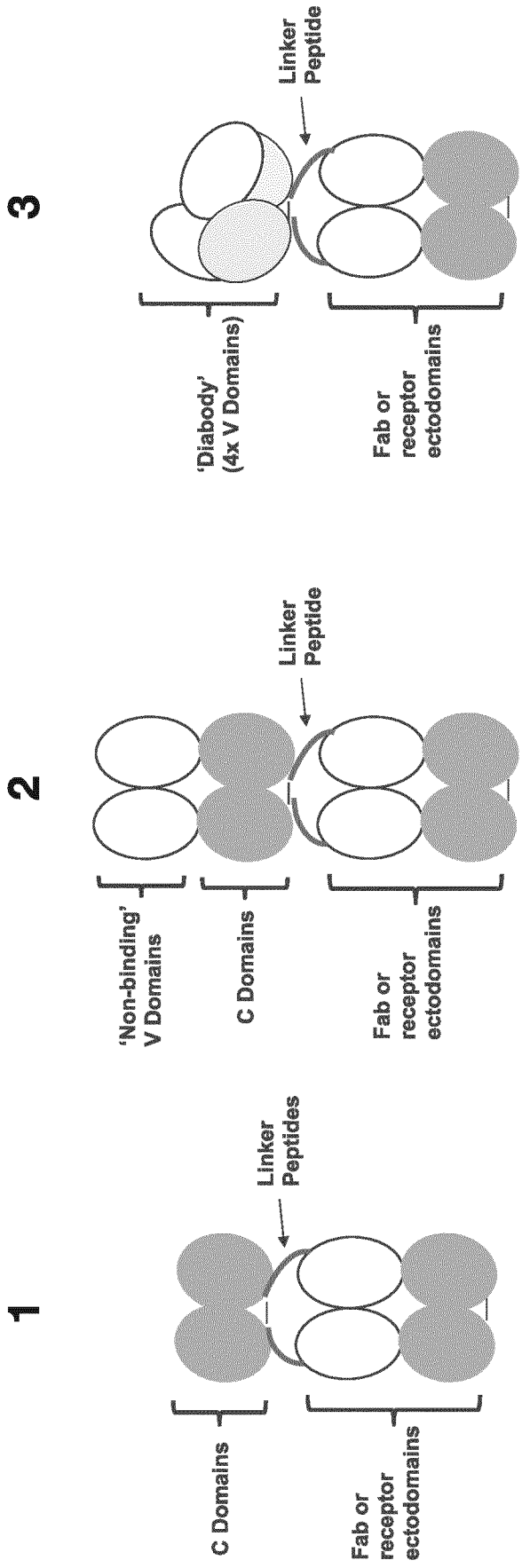

1
Linker Peptides
C Domains
Fab or receptor ectodomains
2
Linker Peptide
'Non-binding' V Domains
C Domains
Fab or receptor ectodomains
3
Linker Peptide
'Diabody' (4x V Domains)
Fab or receptor ectodomains

Figure 47A

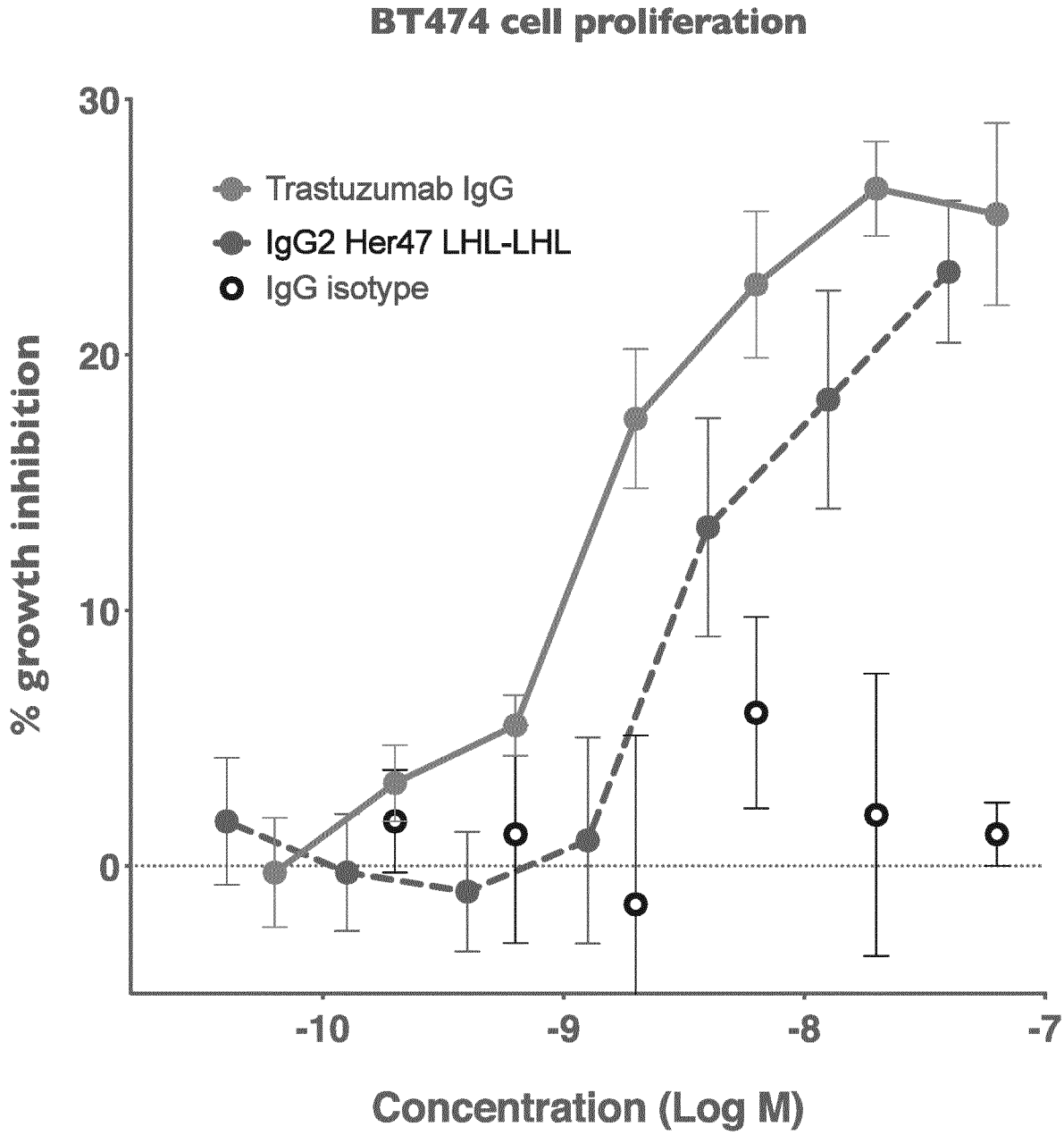

BT474 cell proliferation
Trastuzumab IgG
IgG2 Her47 LHL-LHL
IgG isotype
% growth inhibition
30
20
10
0
-10
-9
-8
-7
Concentration (Log M)

Figure 47B

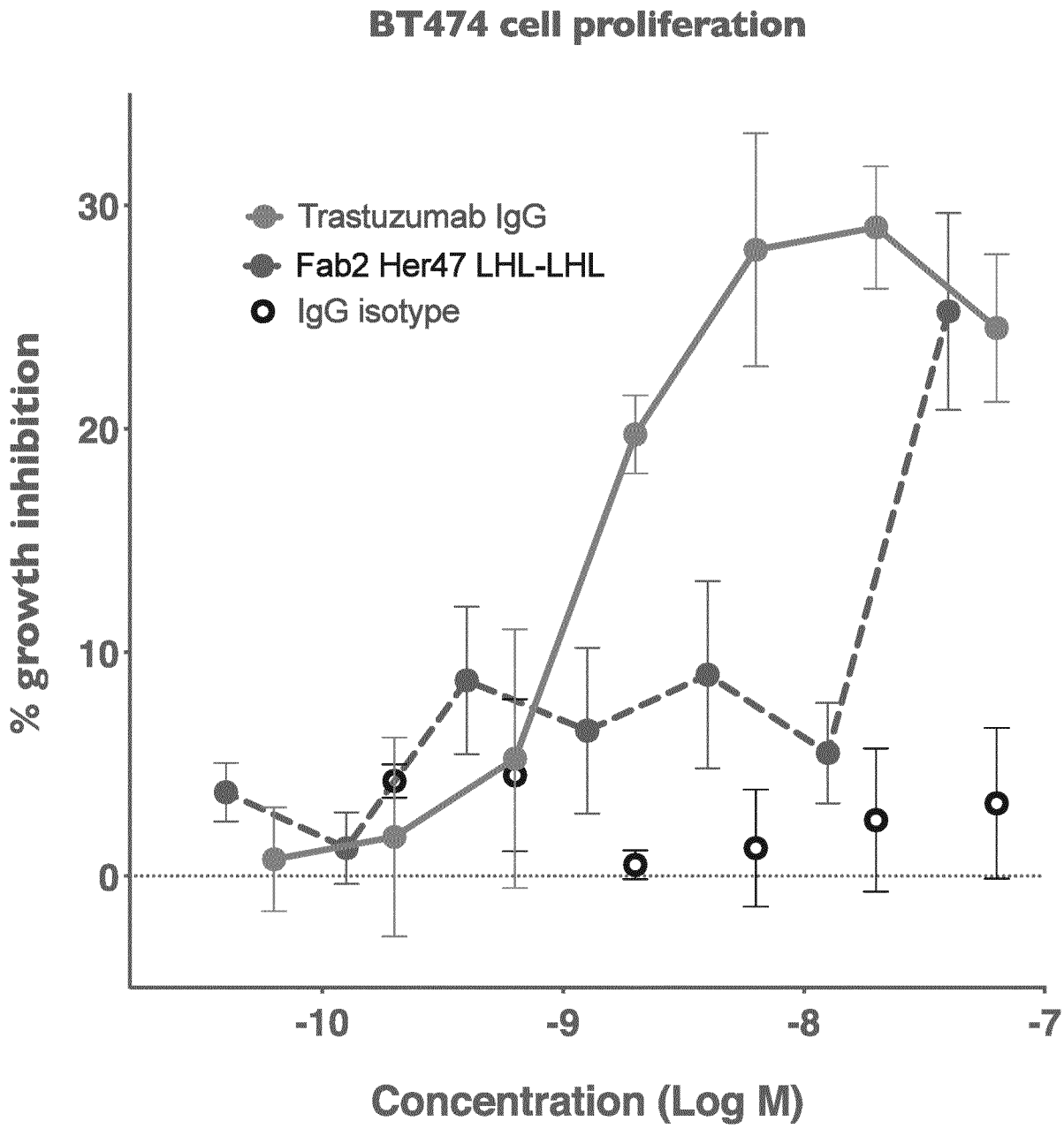

BT474 cell proliferation
Trastuzumab IgG
Fab2 Her47 LHL-LHL
IgG isotype
% growth inhibition
30
20
10
0
-10
-9
-8
-7
Concentration (Log M)

Figure 48A

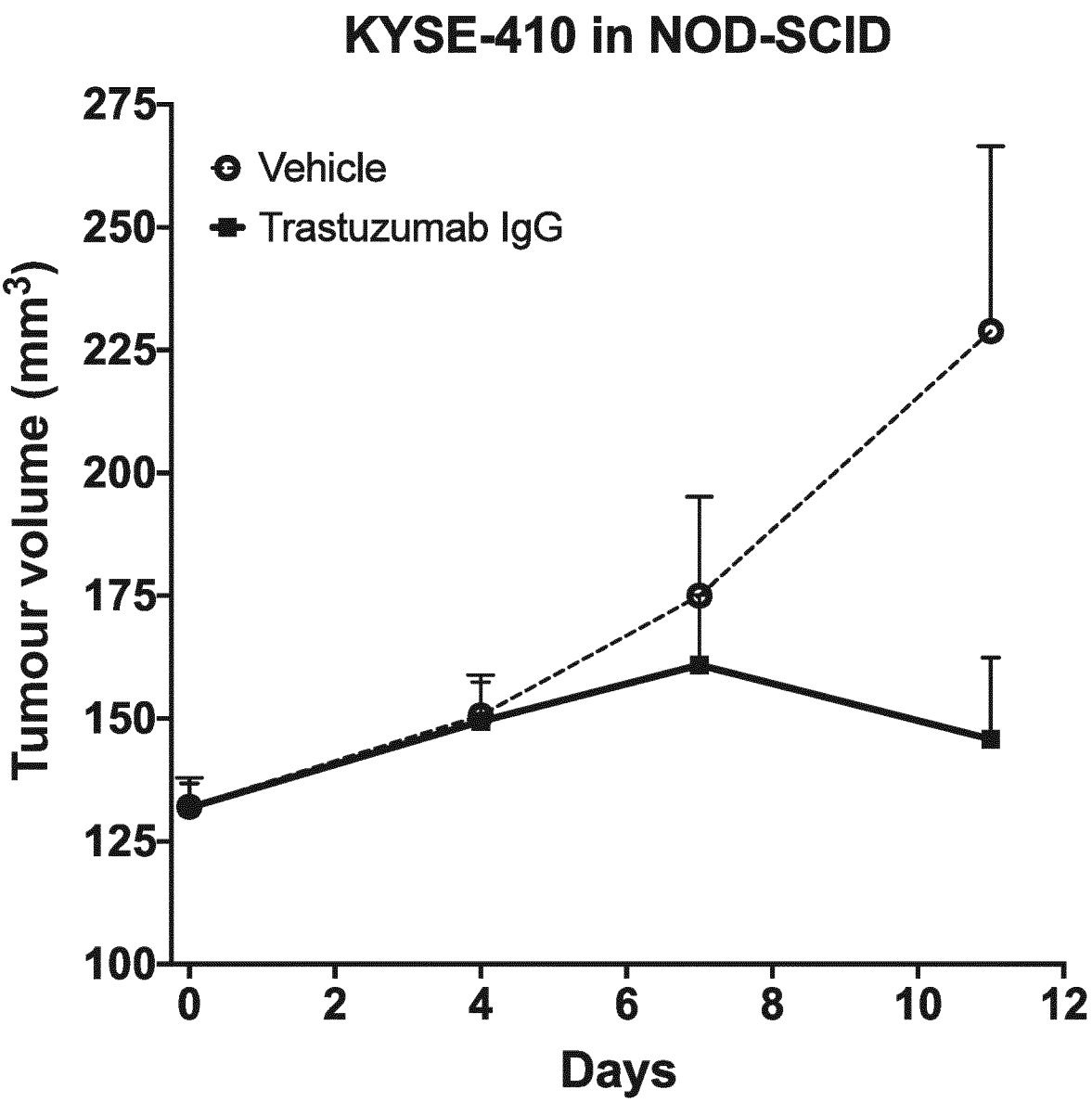

KYSE-410 in NOD-SCID
Vehicle
Trastuzumab IgG
Tumour volume (mm3)
275
250
225
200
175
150
125
100
0
2
4
6
8
10
12
Days

Figure 48B

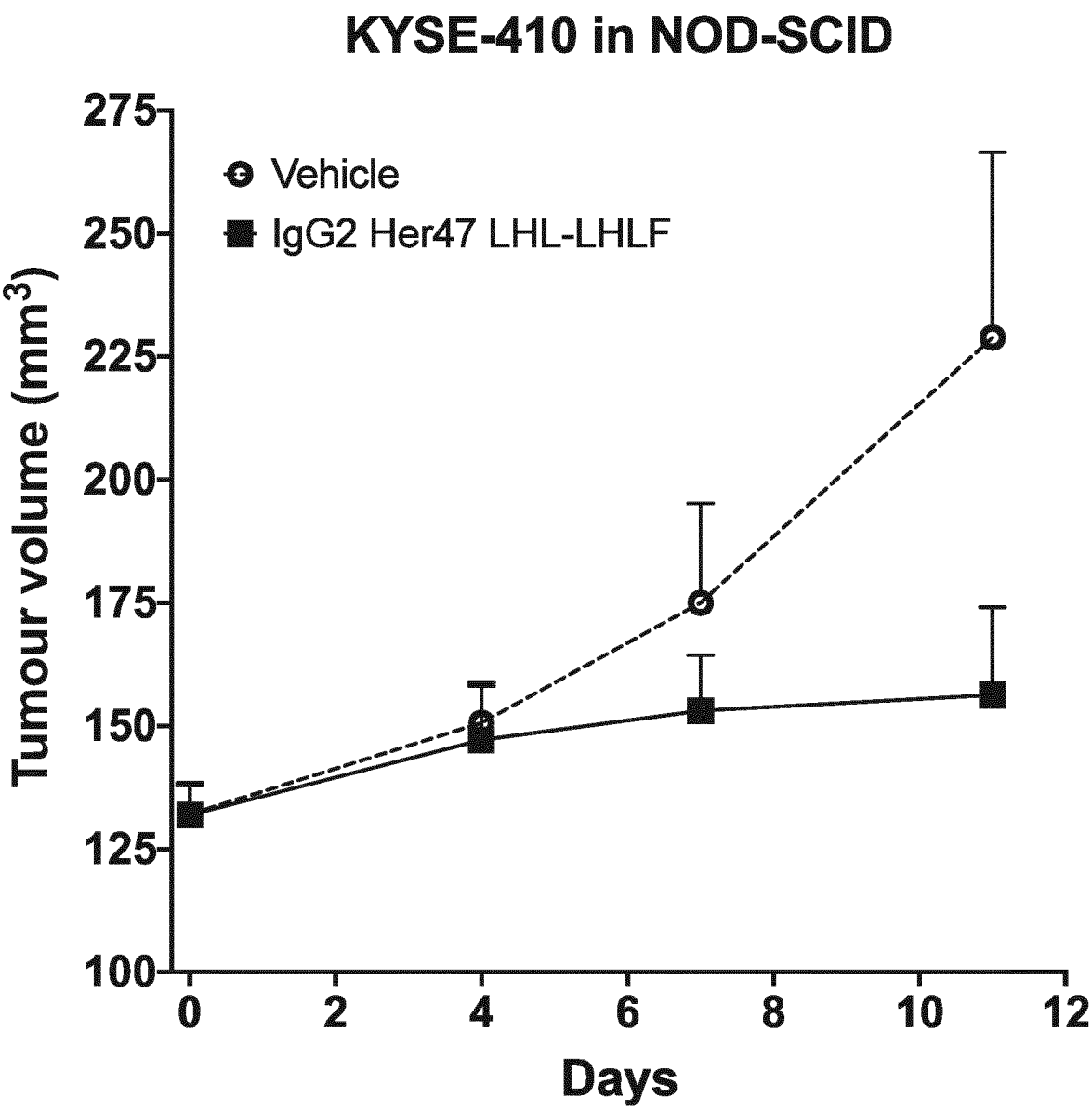

KYSE-410 in NOD-SCID
Vehicle
IgG2 Her47 LHL-LHLF
Tumour volume (mm3)
275
250
225
200
175
150
125
100
0
2
4
6
8
10
12
Days

Figure 48C

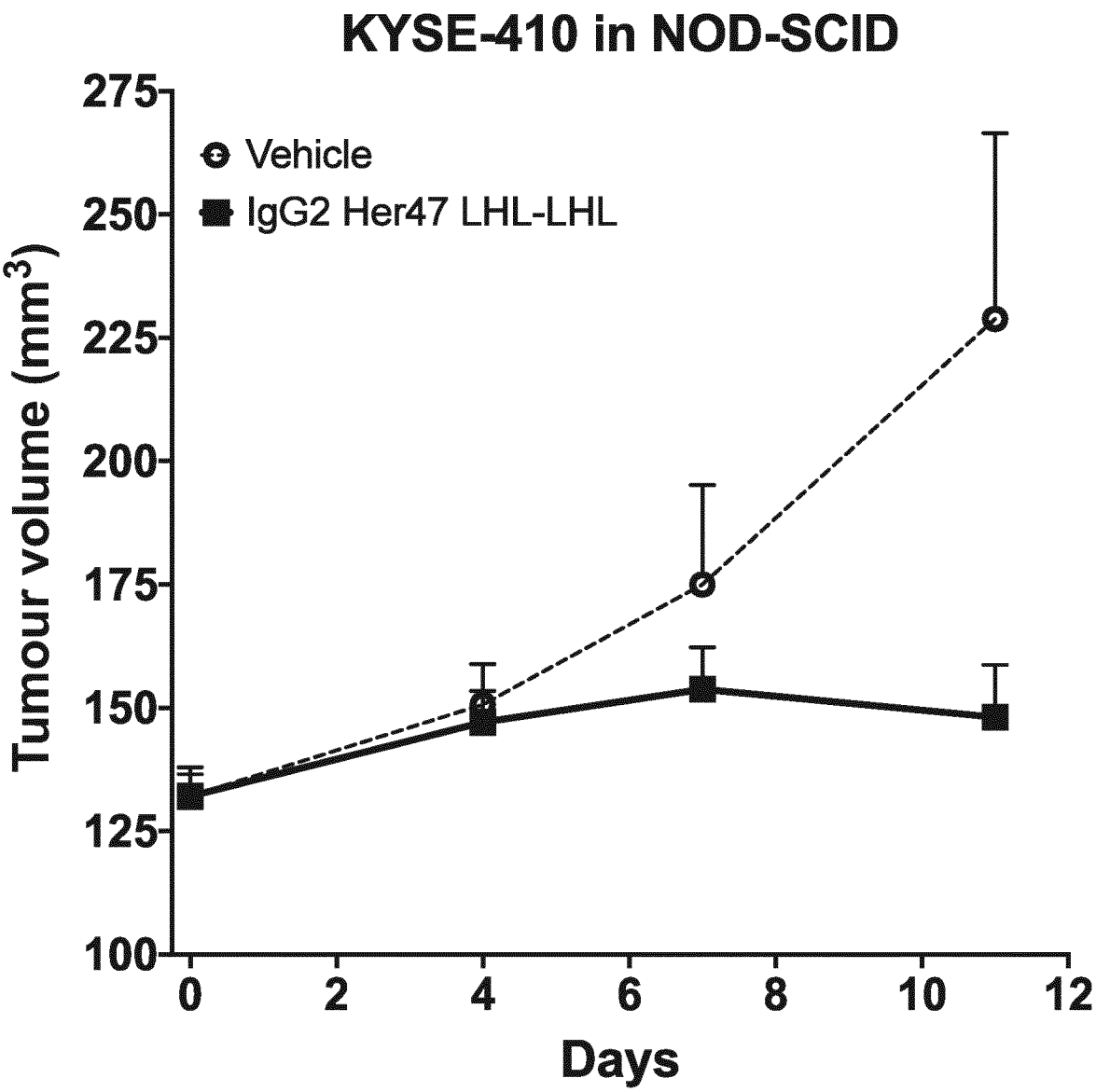

KYSE-410 in NOD-SCID
Vehicle
IgG2 Her47 LHL-LHL
Tumour volume (mm3)
275
250
225
200
175
150
125
100
0
2
4
6
8
10
12
Days

Figure 48D

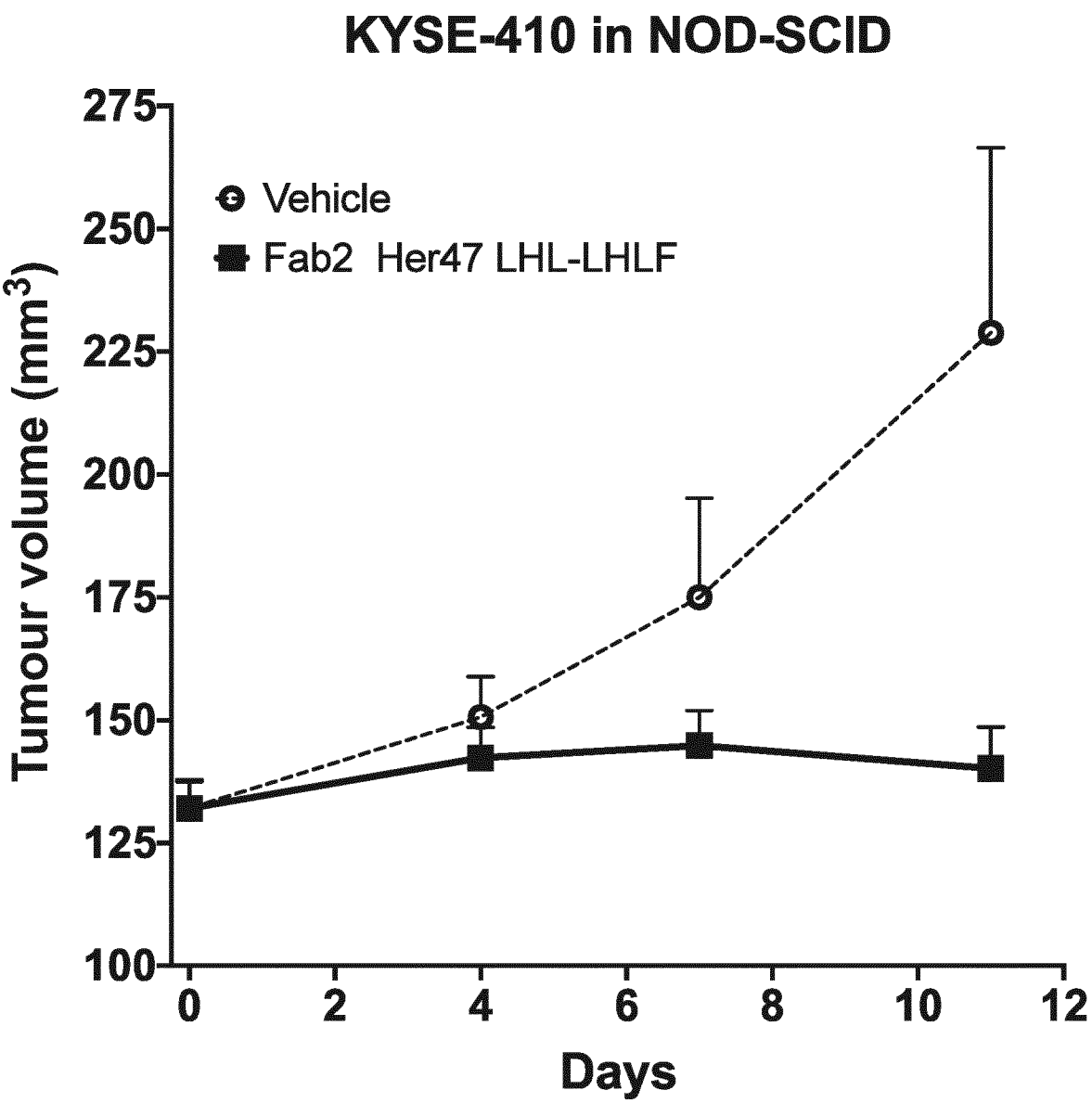

KYSE-410 in NOD-SCID
Vehicle
Fab2 Her47 LHL-LHLF
Tumour volume (mm3)
275
250
225
200
175
150
125
100
0
2
4
6
8
10
12
Days

Figure 48E

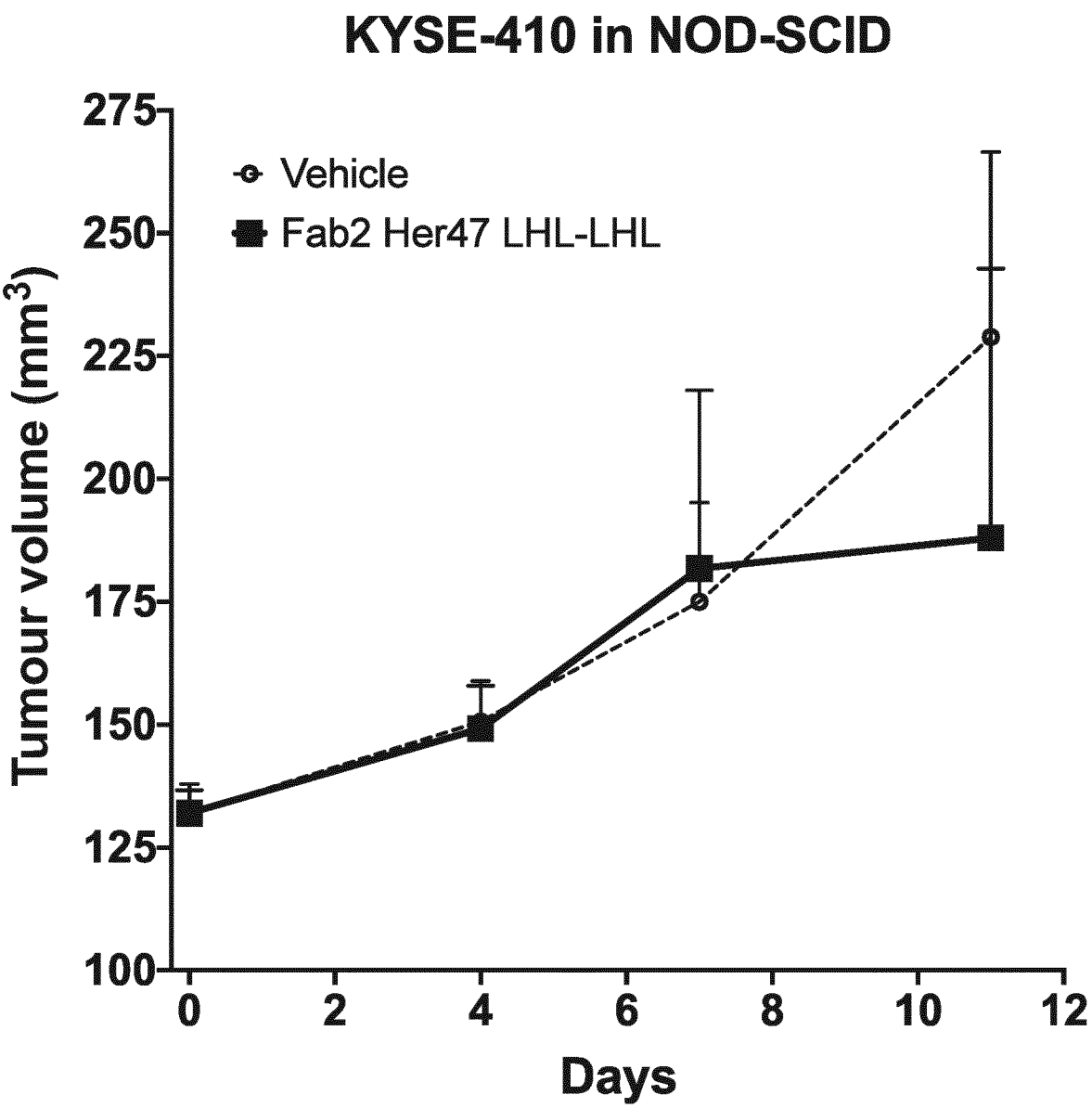

KYSE-410 in NOD-SCID
Vehicle
Fab2 Her47 LHL-LHL
Tumour volume (mm3)
275
250
225
200
175
150
125
100
0
2
4
6
8
10
12
Days

Figure 48F

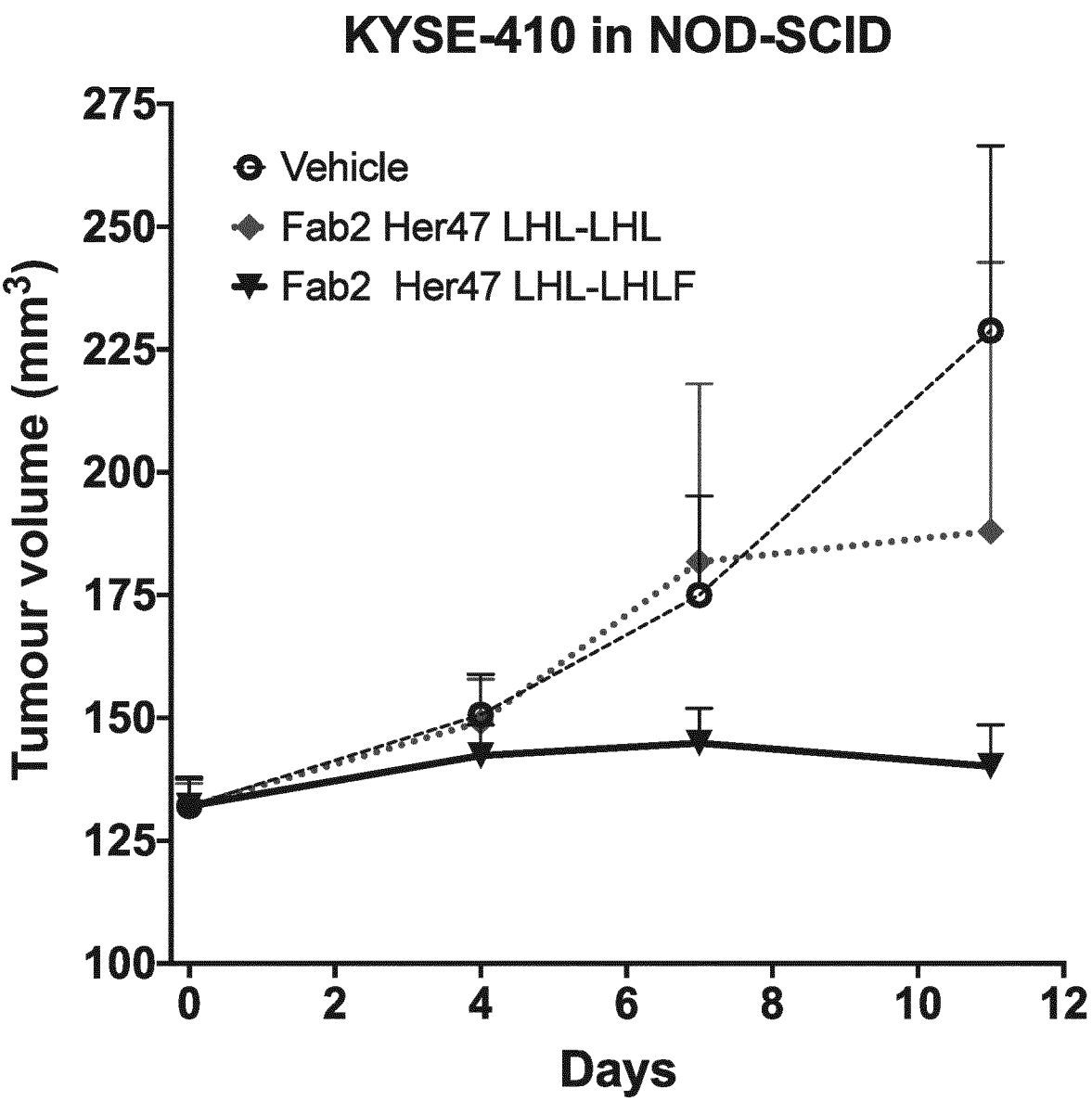
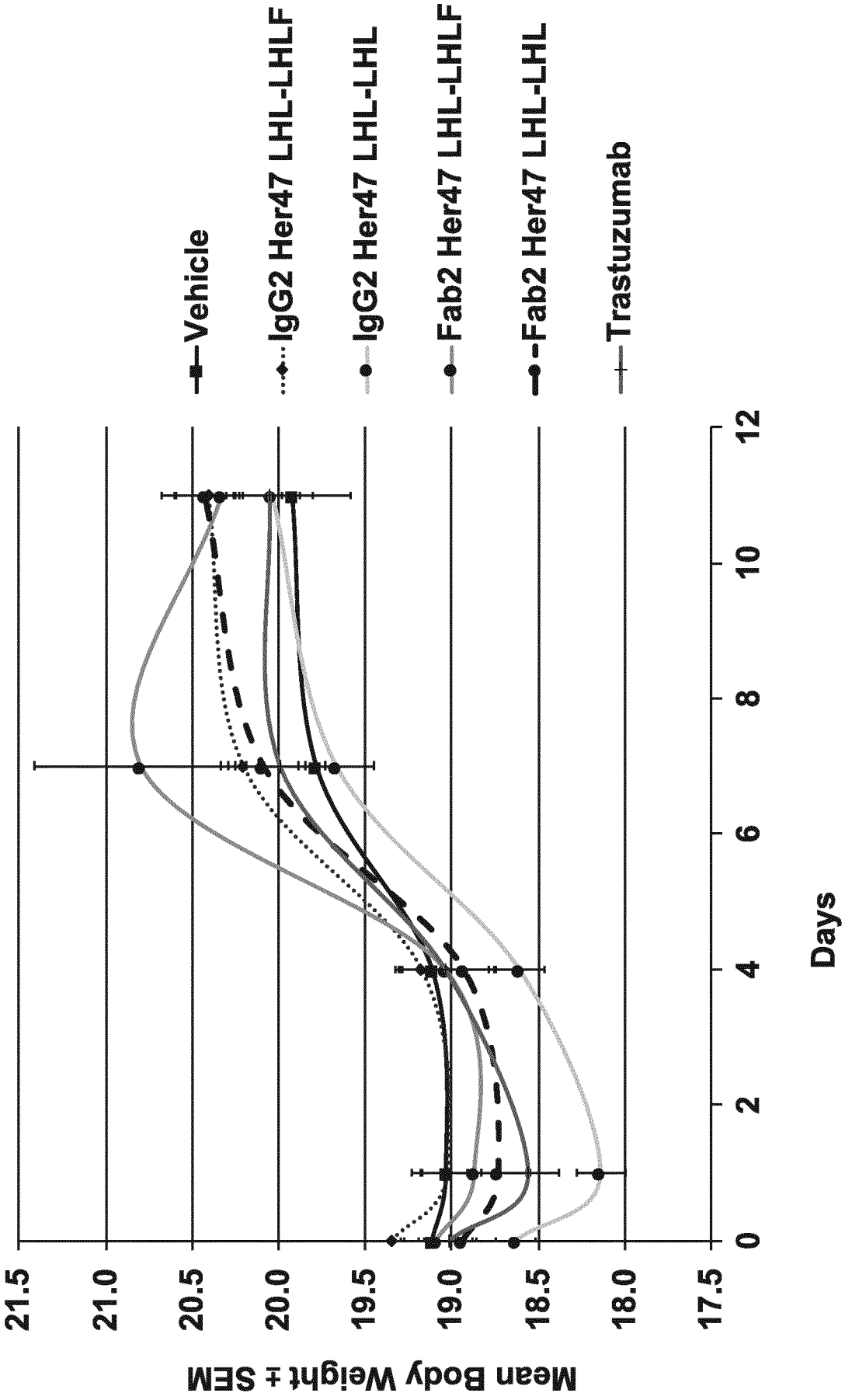

KYSE-410 in NOD-SCID
Vehicle
Fab2 Her47 LHL-LHL
Fab2 Her47 LHL-LHLF
Tumour volume (mm3)
275
250
225
200
175
150
125
100
0
2
4
6
8
10
12
Days

Figure 48G


Vehicle
IgG2 Her47 LHL-LHLF
IgG2 Her47 LHL-LHL
Fab2 Her47 LHL-LHLF
Fab2 Her47 LHL-LHL
Trastuzumab
Mean Body Weight ± SEM
21.5
21.0
20.5
20.0
19.5
19.0
18.5
18.0
17.5
0
2
4
6
8
10
12
Days

SEQUENCE LISTING

<110> ULTRAHUMAN SIX LIMITED

<120> ACTIVATABLE PROTEIN CONSTRUCTS AND USES THEREOF

<130> ULSL-002/04WO 332949-2010

<150> GB 2001196.1
<151> 2020-01-28

<150> GB 1917678.3
<151> 2019-12-04

<150> GB 1910254.0
<151> 2019-07-17

<150> GB 1906685.1
<151> 2019-05-13

<160> 112

<170> PatentIn version 3.5

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<213> Artificial Sequence

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<223> peptide linker

<400> 1

Gly Pro Ala Pro Glu Leu Leu
1 5

<210> 2
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 2

Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser
1 5 10

<210> 3
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 3

Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser
1 5 10

<210> 4
<211> 13

<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 4

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser
1 5 10

<210> 5
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 5

Pro Pro Cys Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser
1 5 10

<210> 6
<211> 678
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Heavy chain

<400> 6

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 Ser Tyr
20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

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

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly

```
    130                 135                 140

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

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

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

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

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Gly Gly
    210                 215                 220

Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro
225                 230                 235                 240

Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr
                245                 250                 255

Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu
            260                 265                 270

Trp Met Gly Ile Ile Asn Pro Val Asp Gly Asp Thr Asn Tyr Asn Pro
        275                 280                 285

Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr
    290                 295                 300

Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr
305                 310                 315                 320

Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp Arg Trp Gly Gln Gly Thr
                325                 330                 335

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
            340                 345                 350

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
        355                 360                 365

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
    370                 375                 380

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
385                 390                 395                 400

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
                405                 410                 415
```

```
Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
            420                 425                 430

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Gly
        435                 440                 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro
    450                 455                 460

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465                 470                 475                 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                485                 490                 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            500                 505                 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        515                 520                 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    530                 535                 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545                 550                 555                 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                565                 570                 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
            580                 585                 590

Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
        595                 600                 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    610                 615                 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625                 630                 635                 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
                645                 650                 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
            660                 665                 670

Leu Ser Leu Ser Pro Gly
        675
```

<210> 7
<211> 673
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Light chain

<400> 7

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


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


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


Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
    50                  55                  60


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


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


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


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


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


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


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


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


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


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Asp
    210                 215                 220


Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly Glu
225                 230                 235                 240
```

```
Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn
                245                 250                 255

Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro
            260                 265                 270

Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val Pro Asp
        275                 280                 285

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser
    290                 295                 300

Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Asn Thr
305                 310                 315                 320

His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
                325                 330                 335

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
            340                 345                 350

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
        355                 360                 365

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
    370                 375                 380

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
385                 390                 395                 400

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
                405                 410                 415

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
            420                 425                 430

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly
        435                 440                 445

Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
    450                 455                 460

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
465                 470                 475                 480

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
                485                 490                 495

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
            500                 505                 510
```

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
515 520 525

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
530 535 540

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
545 550 555 560

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
565 570 575

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
580 585 590

Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
595 600 605

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
610 615 620

Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp
625 630 635 640

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
645 650 655

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
660 665 670

Gly

<210> 8
<211> 683
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Heavy chain

<400> 8

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 Ser Tyr
20 25 30

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

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

```
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

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

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

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

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

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

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

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

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

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Gly Gly
    210                 215                 220

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala
225                 230                 235                 240

Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser
                245                 250                 255

Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met Pro
            260                 265                 270

Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val Asp Gly Asp
        275                 280                 285

Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp
    290                 295                 300

Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser
305                 310                 315                 320

Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp Arg
                325                 330                 335
```

```
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
            340                 345                 350

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
        355                 360                 365

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
    370                 375                 380

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
385                 390                 395                 400

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
                405                 410                 415

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
            420                 425                 430

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
        435                 440                 445

Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro
    450                 455                 460

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
465                 470                 475                 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
                485                 490                 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
            500                 505                 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
        515                 520                 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
    530                 535                 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545                 550                 555                 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
                565                 570                 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
            580                 585                 590

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
        595                 600                 605
```

```
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
    610                 615                 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625                 630                 635                 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
                645                 650                 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
            660                 665                 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        675                 680
```

<210> 9
<211> 678
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Light chain

<400> 9

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

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

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

Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
    50                  55                  60

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

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

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

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

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

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160
```

```
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

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

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly
    210                 215                 220

Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro
225                 230                 235                 240

Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
                245                 250                 255

Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys
            260                 265                 270

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu
        275                 280                 285

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
    290                 295                 300

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
305                 310                 315                 320

Cys Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys
                325                 330                 335

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

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
        355                 360                 365

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
    370                 375                 380

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
385                 390                 395                 400

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
                405                 410                 415

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
            420                 425                 430
```

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
435 440 445

Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
580 585 590

Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly
675

<210> 10
<211> 688
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Heavy chain

<400> 10

```
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 Ser Tyr
            20                  25                  30


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


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


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80


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


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


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


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


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


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


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


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


Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Gly Gly
    210                 215                 220


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu
225                 230                 235                 240


Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
                245                 250                 255
```

```
Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp
            260                 265                 270

Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn
        275                 280                 285

Pro Val Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val
    290                 295                 300

Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser
305                 310                 315                 320

Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
                325                 330                 335

Tyr Thr Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        355                 360                 365

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    370                 375                 380

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
385                 390                 395                 400

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                405                 410                 415

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            420                 425                 430

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        435                 440                 445

Lys Val Glu Pro Lys Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly Gly
    450                 455                 460

Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
465                 470                 475                 480

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                485                 490                 495

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            500                 505                 510

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        515                 520                 525

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
```

530 535 540

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
545 550 555 560

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
565 570 575

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
580 585 590

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp
595 600 605

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
610 615 620

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
625 630 635 640

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
645 650 655

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
660 665 670

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
675 680 685

<210> 11
<211> 680
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Light chain

<400> 11

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

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

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

Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
50 55 60

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

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

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

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

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

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

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

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

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly
    210                 215                 220

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser
225                 230                 235                 240

Pro Leu Ser Leu Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys
                245                 250                 255

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu His
            260                 265                 270

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys
        275                 280                 285

Val Ser Asn Arg Leu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly
    290                 295                 300

Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp
305                 310                 315                 320

Val Gly Val Tyr Tyr Cys Phe Gln Asn Thr His Thr Pro Arg Thr Phe
                325                 330                 335

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

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
```

355 360 365

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
370 375 380

Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu
385 390 395 400

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
405 410 415

Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
420 425 430

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

Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro
450 455 460

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
465 470 475 480

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
485 490 495

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
500 505 510

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
515 520 525

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
530 535 540

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
545 550 555 560

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
565 570 575

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
580 585 590

Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro
595 600 605

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
610 615 620

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
625 630 635 640

```
Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
                645                 650                 655


Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
            660                 665                 670


Lys Ser Leu Ser Leu Ser Pro Gly
        675                 680


<210>  12
<211>  4
<212>  PRT
<213>  Unknown

<220>
<223>  MMP peptide substrate sequence

<400>  12

Pro Leu Gly Leu
1


<210>  13
<211>  675
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 CMET/CD47 Light chain

<400>  13

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


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


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


Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
    50                  55                  60


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


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


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


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

```
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

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

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

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

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu
    210                 215                 220

Leu Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val
        275                 280                 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
            340                 345                 350

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
        355                 360                 365

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
    370                 375                 380

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
385                 390                 395                 400
```

```
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
                405                 410                 415


Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
            420                 425                 430


Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly
        435                 440                 445


Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
    450                 455                 460


Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
465                 470                 475                 480


Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
                485                 490                 495


His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
            500                 505                 510


Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
        515                 520                 525


Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
    530                 535                 540


Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
545                 550                 555                 560


Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
                565                 570                 575


Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
            580                 585                 590


Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
        595                 600                 605


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
    610                 615                 620


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr
625                 630                 635                 640


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
                645                 650                 655


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
            660                 665                 670


Ser Pro Gly
```

675

<210> 14
<211> 680
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Heavy chain

<400> 14

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 Ser Tyr
20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

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

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

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

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

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

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

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

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Pro Ala
210 215 220

```
Pro Glu Leu Leu Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
225                 230                 235                 240


Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                245                 250                 255


Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met Pro Gly Lys Gly
            260                 265                 270


Leu Glu Trp Met Gly Ile Ile Asn Pro Val Asp Gly Asp Thr Asn Tyr
        275                 280                 285


Asn Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile
    290                 295                 300


Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
305                 310                 315                 320


Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp Arg Trp Gly Gln
                325                 330                 335


Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
            340                 345                 350


Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
        355                 360                 365


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
    370                 375                 380


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
385                 390                 395                 400


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                405                 410                 415


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
            420                 425                 430


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
        435                 440                 445


Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro
    450                 455                 460


Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
465                 470                 475                 480


Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
                485                 490                 495


Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
```

```
            500                 505                 510

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
        515                 520                 525

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
    530                 535                 540

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
545                 550                 555                 560

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
                565                 570                 575

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
            580                 585                 590

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
        595                 600                 605

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
    610                 615                 620

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
625                 630                 635                 640

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
                645                 650                 655

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
            660                 665                 670

Lys Ser Leu Ser Leu Ser Pro Gly
        675                 680


<210>  15
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  peptide linker

<400>  15

Gly Gly Gly Gly Ser
1               5


<210>  16
<211>  684
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 CMET/CD47 Heavy chain
```

<400> 16

```
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 Ser Tyr
            20                  25                  30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

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

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

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

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

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

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

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

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

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Pro Ala
    210                 215                 220

Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly
225                 230                 235                 240

Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly
                245                 250                 255

Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met
            260                 265                 270
```

```
Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val Asp Gly
        275                 280                 285

Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala
    290                 295                 300

Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala
305                 310                 315                 320

Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp
                325                 330                 335

Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
            340                 345                 350

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
        355                 360                 365

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
    370                 375                 380

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
385                 390                 395                 400

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
                405                 410                 415

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
            420                 425                 430

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
        435                 440                 445

Lys Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys
    450                 455                 460

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
465                 470                 475                 480

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                485                 490                 495

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
            500                 505                 510

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        515                 520                 525

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    530                 535                 540
```

```
Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
545                 550                 555                 560


Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                565                 570                 575


Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            580                 585                 590


Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys
        595                 600                 605


Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
    610                 615                 620


Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
625                 630                 635                 640


Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
                645                 650                 655


Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
            660                 665                 670


His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        675                 680


<210>  17
<211>  679
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 CMET/CD47 Light chain

<400>  17

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


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


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


Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
    50                  55                  60


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


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

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

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

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

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

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

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

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu
    210                 215                 220

Leu Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu
225                 230                 235                 240

Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
                245                 250                 255

Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln
            260                 265                 270

Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
        275                 280                 285

Leu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    290                 295                 300

Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
305                 310                 315                 320

Tyr Cys Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr
                325                 330                 335

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

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
        355                 360                 365
```

```
Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
    370                 375                 380

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
385                 390                 395                 400

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
                405                 410                 415

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
            420                 425                 430

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
        435                 440                 445

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala
    450                 455                 460

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
465                 470                 475                 480

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                485                 490                 495

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
            500                 505                 510

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
        515                 520                 525

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
    530                 535                 540

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
545                 550                 555                 560

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
                565                 570                 575

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
            580                 585                 590

Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser
        595                 600                 605

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
    610                 615                 620

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val
625                 630                 635                 640

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
```

645 650 655

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
660 665 670

Ser Leu Ser Leu Ser Pro Gly
675

<210> 18
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Heavy chain

<400> 18

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

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

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

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

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Gly Gly Gly
    210                 215                 220

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

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

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

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

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

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

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

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

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

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

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

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445

Leu Ser Pro Gly
    450
```

<210> 19

<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 Light chain

<400> 19

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


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


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


Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu 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 Val Gly Val Tyr Tyr Cys Phe Gln Asn
                85                  90                  95


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


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


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


Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160


Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175


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


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


Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser
    210                 215                 220


Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225                 230                 235                 240
```

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


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


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


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


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


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


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


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


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


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


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


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            420                 425                 430


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


Pro Gly
    450


<210>  20
<211>  688
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Heavy chain

<400>  20

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 Asn Ile Lys Asp Thr
            20                  25                  30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
225                 230                 235                 240

Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys
                245                 250                 255

Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys Gln
            260                 265                 270

Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg
        275                 280                 285
```

```
Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr
    290                 295                 300

Thr Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
305                 310                 315                 320

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
                325                 330                 335

Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
            340                 345                 350

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        355                 360                 365

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    370                 375                 380

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
385                 390                 395                 400

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                405                 410                 415

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            420                 425                 430

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        435                 440                 445

Lys Val Glu Pro Lys Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly Gly
    450                 455                 460

Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
465                 470                 475                 480

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                485                 490                 495

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            500                 505                 510

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        515                 520                 525

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    530                 535                 540

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
545                 550                 555                 560

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
```

565 570 575

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
580 585 590

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp
595 600 605

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
610 615 620

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
625 630 635 640

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
645 650 655

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
660 665 670

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
675 680 685

<210> 21
<211> 668
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 21

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    210                 215                 220

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
225                 230                 235                 240

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
                245                 250                 255

Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
            260                 265                 270

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
        275                 280                 285

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
    290                 295                 300

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
305                 310                 315                 320

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

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
            340                 345                 350

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
        355                 360                 365

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
    370                 375                 380

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
```

385 390 395 400

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
405 410 415

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
420 425 430

Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys
435 440 445

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu
450 455 460

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
465 470 475 480

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
485 490 495

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
500 505 510

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
515 520 525

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
530 535 540

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
545 550 555 560

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
565 570 575

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys
580 585 590

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
595 600 605

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
610 615 620

Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
625 630 635 640

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
645 650 655

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665

<210> 22
<211> 683
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Heavy chain

<400> 22

```
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 Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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


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


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


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


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


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


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


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


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220


Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala
```

225 230 235 240

Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr
245 250 255

Phe Thr Arg Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly
260 265 270

Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr
275 280 285

Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser
290 295 300

Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala
305 310 315 320

Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr
325 330 335

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly
340 345 350

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
355 360 365

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
370 375 380

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
385 390 395 400

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
405 410 415

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
420 425 430

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
435 440 445

Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro
450 455 460

Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe
465 470 475 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
485 490 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
500 505 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
515 520 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
530 535 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545 550 555 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
565 570 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
580 585 590

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly
595 600 605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
610 615 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625 630 635 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
645 650 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
660 665 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
675 680

<210> 23
<211> 665
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 23

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

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

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

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gln Ile Val
210 215 220

Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val
225 230 235 240

Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr
245 250 255

Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser
260 265 270

Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly
275 280 285

Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala
290 295 300

Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser
305 310 315 320

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

```
Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
            340                 345                 350

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
        355                 360                 365

Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
    370                 375                 380

Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
385                 390                 395                 400

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
                405                 410                 415

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
            420                 425                 430

Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys
        435                 440                 445

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515                 520                 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530                 535                 540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545                 550                 555                 560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565                 570                 575

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
            580                 585                 590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595                 600                 605
```

```
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610                 615                 620

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625                 630                 635                 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645                 650                 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly
            660                 665
```

<210> 24
<211> 685
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Heavy chain

<400> 24

```
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 Asn Ile Lys Asp Thr
            20                  25                  30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
225                 230                 235                 240

Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly
                245                 250                 255

Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly
            260                 265                 270

Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr
        275                 280                 285

Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys
    290                 295                 300

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp
305                 310                 315                 320

Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu
                325                 330                 335

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
            340                 345                 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
        355                 360                 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
    370                 375                 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385                 390                 395                 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
                405                 410                 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
            420                 425                 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
        435                 440                 445
```

```
Pro Lys Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    450                 455                 460

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe
465                 470                 475                 480

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                485                 490                 495

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            500                 505                 510

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        515                 520                 525

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    530                 535                 540

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
545                 550                 555                 560

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                565                 570                 575

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            580                 585                 590

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val
        595                 600                 605

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    610                 615                 620

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
625                 630                 635                 640

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                645                 650                 655

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            660                 665                 670

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        675                 680                 685


<210>  25
<211>  663
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Light chain
```

<400> 25

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gln Ile Val Leu Thr
210 215 220

Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met
225 230 235 240

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln
245 250 255

Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
260 265 270

```
Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser
        275                 280                 285

Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr
    290                 295                 300

Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr
305                 310                 315                 320

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

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

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
        355                 360                 365

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
    370                 375                 380

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
385                 390                 395                 400

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
                405                 410                 415

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            420                 425                 430

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala
        435                 440                 445

Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
    450                 455                 460

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
465                 470                 475                 480

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
                485                 490                 495

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
            500                 505                 510

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
        515                 520                 525

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
    530                 535                 540
```

```
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
545                 550                 555                 560


Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
                565                 570                 575


Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser
            580                 585                 590


Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
        595                 600                 605


Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val
    610                 615                 620


Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
625                 630                 635                 640


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
                645                 650                 655


Ser Leu Ser Leu Ser Pro Gly
            660


<210>  26
<211>  689
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Heavy chain

<400>  26

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 Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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


Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110
```

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
225                 230                 235                 240

Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys
                245                 250                 255

Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys
            260                 265                 270

Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
        275                 280                 285

Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu
    290                 295                 300

Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
305                 310                 315                 320

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp
                325                 330                 335

His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
            340                 345                 350

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        355                 360                 365

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    370                 375                 380
```

```
Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
385                 390                 395                 400

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                405                 410                 415

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
            420                 425                 430

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
        435                 440                 445

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Gly Gly Gly Gly Ser Gly
    450                 455                 460

Gly Gly Gly Ser Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala
465                 470                 475                 480

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                485                 490                 495

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            500                 505                 510

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        515                 520                 525

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    530                 535                 540

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
545                 550                 555                 560

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                565                 570                 575

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            580                 585                 590

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        595                 600                 605

Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    610                 615                 620

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
625                 630                 635                 640

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                645                 650                 655

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
```

660 665 670

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
675 680 685

Gly

<210> 27
<211> 669
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 27

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

Ser Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro
225                 230                 235                 240

Gly Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr
                245                 250                 255

Met Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile
            260                 265                 270

Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly
        275                 280                 285

Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala
    290                 295                 300

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe
305                 310                 315                 320

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg Thr Val Ala Ala
                325                 330                 335

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
            340                 345                 350

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
        355                 360                 365

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
    370                 375                 380

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
                405                 410                 415

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
            420                 425                 430

Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        435                 440                 445

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe
    450                 455                 460

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
```

465 470 475 480

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
485 490 495

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
500 505 510

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
515 520 525

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
530 535 540

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
545 550 555 560

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
565 570 575

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
580 585 590

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
595 600 605

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
610 615 620

Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
625 630 635 640

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
645 650 655

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665

<210> 28
<211> 344
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG Her2/CD47 Heavy chain

<400> 28

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
225                 230                 235                 240

Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Thr
                245                 250                 255

Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met Pro Gly Lys Gly
            260                 265                 270

Leu Glu Trp Met Gly Ile Ile Asn Pro Val Asp Gly Asp Thr Asn Tyr
        275                 280                 285

Asn Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile
    290                 295                 300

Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala
```

305 310 315 320

Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp Arg Trp Gly Gln
325 330 335

Gly Thr Leu Val Thr Val Ser Ser
340

<210> 29
<211> 333
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG Her2/CD47 Light chain

<400> 29

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

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

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

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

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

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

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

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

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

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

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

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

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


Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Asp Ile Val
    210                 215                 220


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


Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr
                245                 250                 255


Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu
            260                 265                 270


Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val Pro Asp Arg Phe
        275                 280                 285


Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val
    290                 295                 300


Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Asn Thr His Thr
305                 310                 315                 320


Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                325                 330


<210>  30
<211>  346
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG Her2/CD47 Heavy chain

<400>  30

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 Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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

```
Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gln Val Gln Leu Val Gln Ser Gly Ala Glu
225                 230                 235                 240

Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly
                245                 250                 255

Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met Pro Gly
            260                 265                 270

Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val Asp Gly Asp Thr
        275                 280                 285

Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys
    290                 295                 300

Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp
305                 310                 315                 320

Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp Arg Trp
                325                 330                 335

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345
```

<210> 31
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG Her2/CD47 Light chain

<400> 31

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


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


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


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


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


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


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


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


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


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


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


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


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


Phe Asn Arg Gly Glu Cys Gly Gly Gly Ser Asp Ile Val Met Thr Gln
    210                 215                 220


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


Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu
                245                 250                 255
```

```
His Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr
            260                 265                 270


Lys Val Ser Asn Arg Leu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
        275                 280                 285


Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu
    290                 295                 300


Asp Val Gly Val Tyr Tyr Cys Phe Gln Asn Thr His Thr Pro Arg Thr
305                 310                 315                 320


Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
                325                 330


<210>  32
<211>  10
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  peptide linker

<400>  32

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10


<210>  33
<211>  15
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  peptide linker

<400>  33

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10                  15


<210>  34
<211>  350
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG Her2/CD47 Heavy chain

<400>  34

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 Asn Ile Lys Asp Thr
            20                  25                  30


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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln
225                 230                 235                 240

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
                245                 250                 255

Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg
            260                 265                 270

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val
        275                 280                 285

Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile
    290                 295                 300

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
305                 310                 315                 320
```

```
Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr
                325                 330                 335


Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350


<210>  35
<211>  337
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG Her2/CD47 Light chain

<400>  35

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


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


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


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


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


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


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


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


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


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


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


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


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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
210 215 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225 230 235 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
245 250 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
260 265 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val
275 280 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
290 295 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305 310 315 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
325 330 335

Lys

<210> 36
<211> 348
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 One Arm style Heavy chain

<400> 36

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 Ser Tyr
20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

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

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

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

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

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

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

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

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Pro Ala
210 215 220

Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly
225 230 235 240

Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly
245 250 255

Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg Gln Met
260 265 270

Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val Asp Gly
275 280 285

Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala
290 295 300

Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala
305 310 315 320

Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr Met Asp
325 330 335

Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
340 345

<210> 37
<211> 341

<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 CMET/CD47 One Arm style Light chain

<400> 37

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

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

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

Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
    50                  55                  60

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

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

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

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

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

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

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

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

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu
    210                 215                 220

Leu Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu
225                 230                 235                 240

Pro Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln
```

245 250 255

Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln
260 265 270

Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg
275 280 285

Leu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
290 295 300

Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr
305 310 315 320

Tyr Cys Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr
325 330 335

Lys Val Glu Ile Lys
340

<210> 38
<211> 353
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 One Arm style Heavy chain

<400> 38

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
225 230 235 240

Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys
245 250 255

Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys
260 265 270

Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
275 280 285

Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu
290 295 300

Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
305 310 315 320

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp
325 330 335

His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
340 345 350

Ser

<210> 39
<211> 331
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 One Arm style Light chain

<400> 39

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

Ser Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro
225                 230                 235                 240

Gly Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr
                245                 250                 255

Met Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile
            260                 265                 270
```

```
Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly
        275                 280                 285


Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala
    290                 295                 300


Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe
305                 310                 315                 320


Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
                325                 330


<210>  40
<211>  359
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3(34) One Arm style Heavy chain

<400>  40

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 Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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


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


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


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


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


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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Glu Val Lys Leu Leu Glu
225 230 235 240

Ser Gly Gly Gly Leu Val Gln Pro Lys Gly Ser Leu Lys Leu Ser Cys
245 250 255

Ala Ala Ser Gly Phe Thr Phe Asn Thr Tyr Ala Met Asn Trp Val Arg
260 265 270

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys
275 280 285

Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asp Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn
305 310 315 320

Asn Leu Lys Thr Glu Asp Thr Ala Met Tyr Tyr Cys Val Arg His Gly
325 330 335

Asn Phe Gly Asn Ser Tyr Val Ser Trp Phe Ala Tyr Trp Gly Gln Gly
340 345 350

Thr Leu Val Thr Val Ser Ser
355

<210> 41
<211> 334
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3(34) One Arm style Light chain

<400> 41

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

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

Glu Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Thr
                245                 250                 255

Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu Phe Thr
            260                 265                 270

Gly Leu Ile Gly Gly Thr Asn Lys Arg Ala Pro Gly Val Pro Ala Arg
        275                 280                 285

Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly
    290                 295                 300

Ala Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp Tyr Ser
305                 310                 315                 320
```

Asn Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
325 330

<210> 42
<211> 350
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Heavy chain

<400> 42

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

```
Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln
225                 230                 235                 240

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
                245                 250                 255

Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg
            260                 265                 270

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val
        275                 280                 285

Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile
    290                 295                 300

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
305                 310                 315                 320

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr
                325                 330                 335

Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350


<210>  43
<211>  337
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG2 Her2/CD47 Light chain

<400>  43

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

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
```

```
            100                 105                 110

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val
        275                 280                 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys
```

<210> 44
<211> 350
<212> PRT
<213> Artificial Sequence

<220>

<223> IgG2 Her2/CD47 Heavy chain

<400> 44

```
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 Asn Ile Lys Asp Thr
            20                  25                  30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln
225                 230                 235                 240

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
                245                 250                 255

Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg
```

260 265 270

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val
275 280 285

Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile
290 295 300

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
305 310 315 320

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr
325 330 335

Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
340 345 350

<210> 45
<211> 337
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 45

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly
210 215 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225 230 235 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
245 250 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
260 265 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val
275 280 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
290 295 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305 310 315 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
325 330 335

Lys

<210> 46
<211> 350
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Heavy chain

<400> 46

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln
225                 230                 235                 240

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
                245                 250                 255

Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg
            260                 265                 270

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val
        275                 280                 285

Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile
    290                 295                 300
```

```
Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
305                 310                 315                 320


Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr
                325                 330                 335


Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350


<210>  47
<211>  337
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG2 Her2/CD47 Light chain

<400>  47

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


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


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


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


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


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


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


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


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


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


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


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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly
210 215 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225 230 235 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
245 250 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
260 265 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser Gly Val
275 280 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
290 295 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305 310 315 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
325 330 335

Lys

<210> 48
<211> 352
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Heavy chain

<400> 48

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Pro
    210                 215                 220

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

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
                245                 250                 255

Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp
            260                 265                 270

Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn
        275                 280                 285

Pro Val Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val
    290                 295                 300

Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser
305                 310                 315                 320

Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
                325                 330                 335

Tyr Thr Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350
```

<210> 49
<211> 339
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 49

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


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


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


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


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


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


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


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


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


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


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


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


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


Phe Asn Arg Gly Glu Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
    210                 215                 220


Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val
225                 230                 235                 240
```

```
Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
                245                 250                 255

Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro
            260                 265                 270

Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser
        275                 280                 285

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    290                 295                 300

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
305                 310                 315                 320

Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val
                325                 330                 335

Glu Ile Lys
```

<210> 50
<211> 352
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Heavy chain

<400> 50

```
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 Asn Ile Lys Asp Thr
            20                  25                  30

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

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

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

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

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

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
```

```
         115                 120                 125

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Pro
    210                 215                 220

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

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
                245                 250                 255

Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp
            260                 265                 270

Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn
        275                 280                 285

Pro Val Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val
    290                 295                 300

Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser
305                 310                 315                 320

Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
                325                 330                 335

Tyr Thr Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350
```

<210> 51
<211> 339
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 51

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


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


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


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


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


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


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


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


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


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


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


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


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


Phe Asn Arg Gly Glu Cys Pro Pro Cys Pro Ala Pro Leu Gly Leu Gly
    210                 215                 220


Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val
225                 230                 235                 240


Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
                245                 250                 255


Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro
            260                 265                 270


Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser
```

275 280 285

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
290 295 300

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
305 310 315 320

Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val
325 330 335

Glu Ile Lys

<210> 52
<211> 352
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Heavy chain

<400> 52

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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


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


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


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Pro
    210                 215                 220


Pro Cys Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser Gln Val Gln Leu
225                 230                 235                 240


Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
                245                 250                 255


Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp
            260                 265                 270


Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn
        275                 280                 285


Pro Val Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val
    290                 295                 300


Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser
305                 310                 315                 320


Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
                325                 330                 335


Tyr Thr Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350


<210>  53
<211>  339
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG2 Her2/CD47 Light chain

<400>  53

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


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


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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
    210                 215                 220

Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val
225                 230                 235                 240

Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
                245                 250                 255

Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro
            260                 265                 270

Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser
        275                 280                 285

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    290                 295                 300

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
305                 310                 315                 320
```

```
Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val
                325                 330                 335


Glu Ile Lys



<210>  54
<211>  352
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG2 Her2/CD47 Heavy chain

<400>  54

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 Asn Ile Lys Asp Thr
            20                  25                  30


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


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


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


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


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


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


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


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


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


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


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

```
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Pro
    210                 215                 220

Pro Cys Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser Gln Val Gln Leu
225                 230                 235                 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile
                245                 250                 255

Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp
            260                 265                 270

Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn
        275                 280                 285

Pro Val Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val
    290                 295                 300

Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser
305                 310                 315                 320

Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly
                325                 330                 335

Tyr Thr Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350
```

<210> 55
<211> 339
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 55

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

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

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95
```

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Pro Pro Cys Pro Ala Pro Leu Gly Leu Gly
    210                 215                 220

Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val
225                 230                 235                 240

Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu
                245                 250                 255

Leu His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro
            260                 265                 270

Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Ser
        275                 280                 285

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    290                 295                 300

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
305                 310                 315                 320

Phe Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val
                325                 330                 335

Glu Ile Lys
```

```
<210>  56
<211>  327
<212>  PRT
```

<213> Homo sapiens

<400> 56

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


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


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80


Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110


Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140


Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205


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


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
```

260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 57
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> Human IgG4(S228P) immunoglobulin Fc region

<400> 57

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

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

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
325

<210> 58
<211> 330
<212> PRT
<213> Homo sapiens

<400> 58

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 59
<211> 330
<212> PRT

<213> Artificial Sequence

<220>
<223> Human IgG1-3M immunoglobulin Fc region

<400> 59

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15


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


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110


Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140


Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160


Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175


Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190


His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205


Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220


Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240


Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210>  60
<211>  326
<212>  PRT
<213>  Homo sapiens

<400>  60

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

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

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

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

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160
```

```
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175


Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190


Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205


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


Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240


Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                245                 250                 255


Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            260                 265                 270


Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        275                 280                 285


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    290                 295                 300


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320


Ser Leu Ser Pro Gly Lys
                325


<210>  61
<211>  330
<212>  PRT
<213>  Homo sapiens

<400>  61

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15


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


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80
```

```
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 62
<211> 329
<212> PRT

<213> Artificial Sequence

<220>
<223> Human IgG1-3M REEM allotype immunoglobulin Fc region

<400> 62

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
245 250 255

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
            260                 265                 270

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
        275                 280                 285

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
    290                 295                 300

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
305                 310                 315                 320

Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325

<210>  63
<211>  323
<212>  PRT
<213>  Homo sapiens

<400>  63

Met Trp Pro Leu Val Ala Ala Leu Leu Leu Gly Ser Ala Cys Cys Gly
1               5                   10                  15

Ser Ala Gln Leu Leu Phe Asn Lys Thr Lys Ser Val Glu Phe Thr Phe
            20                  25                  30

Cys Asn Asp Thr Val Val Ile Pro Cys Phe Val Thr Asn Met Glu Ala
        35                  40                  45

Gln Asn Thr Thr Glu Val Tyr Val Lys Trp Lys Phe Lys Gly Arg Asp
    50                  55                  60

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

Phe Ser Ser Ala Lys Ile Glu Val Ser Gln Leu Leu Lys Gly Asp Ala
                85                  90                  95

Ser Leu Lys Met Asp Lys Ser Asp Ala Val Ser His Thr Gly Asn Tyr
            100                 105                 110

Thr Cys Glu Val Thr Glu Leu Thr Arg Glu Gly Glu Thr Ile Ile Glu
        115                 120                 125

Leu Lys Tyr Arg Val Val Ser Trp Phe Ser Pro Asn Glu Asn Ile Leu
    130                 135                 140

Ile Val Ile Phe Pro Ile Phe Ala Ile Leu Leu Phe Trp Gly Gln Phe
145                 150                 155                 160
```

```
Gly Ile Lys Thr Leu Lys Tyr Arg Ser Gly Gly Met Asp Glu Lys Thr
                165                 170                 175


Ile Ala Leu Leu Val Ala Gly Leu Val Ile Thr Val Ile Val Ile Val
            180                 185                 190


Gly Ala Ile Leu Phe Val Pro Gly Glu Tyr Ser Leu Lys Asn Ala Thr
        195                 200                 205


Gly Leu Gly Leu Ile Val Thr Ser Thr Gly Ile Leu Ile Leu Leu His
    210                 215                 220


Tyr Tyr Val Phe Ser Thr Ala Ile Gly Leu Thr Ser Phe Val Ile Ala
225                 230                 235                 240


Ile Leu Val Ile Gln Val Ile Ala Tyr Ile Leu Ala Val Val Gly Leu
                245                 250                 255


Ser Leu Cys Ile Ala Ala Cys Ile Pro Met His Gly Pro Leu Leu Ile
            260                 265                 270


Ser Gly Leu Ser Ile Leu Ala Leu Ala Gln Leu Leu Gly Leu Val Tyr
        275                 280                 285


Met Lys Phe Val Ala Ser Asn Gln Lys Thr Ile Gln Pro Pro Arg Lys
    290                 295                 300


Ala Val Glu Glu Pro Leu Asn Ala Phe Lys Glu Ser Lys Gly Met Met
305                 310                 315                 320


Asn Asp Glu



<210>  64
<211>  323
<212>  PRT
<213>  Macaca fascicularis

<400>  64

Met Trp Pro Leu Val Ala Ala Leu Leu Leu Gly Ser Ala Cys Cys Gly
1               5                   10                  15


Ser Ala Gln Leu Leu Phe Asn Lys Thr Lys Ser Val Glu Phe Thr Phe
            20                  25                  30


Cys Asn Asp Thr Val Val Ile Pro Cys Phe Val Thr Asn Met Glu Ala
        35                  40                  45


Gln Asn Thr Thr Glu Val Tyr Val Lys Trp Lys Phe Lys Gly Arg Asp
    50                  55                  60


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

```
Phe Ser Ser Ala Lys Ile Glu Val Ser Gln Leu Leu Lys Gly Asp Ala
                85                  90                  95

Ser Leu Lys Met Asp Lys Ser Asp Ala Val Ser His Thr Gly Asn Tyr
            100                 105                 110

Thr Cys Glu Val Thr Glu Leu Thr Arg Glu Gly Glu Thr Ile Ile Glu
        115                 120                 125

Leu Lys Tyr Arg Val Val Ser Trp Phe Ser Pro Asn Glu Asn Ile Leu
    130                 135                 140

Ile Val Ile Phe Pro Ile Phe Ala Ile Leu Leu Phe Trp Gly Gln Phe
145                 150                 155                 160

Gly Ile Lys Thr Leu Lys Tyr Arg Ser Gly Gly Met Asp Glu Lys Thr
                165                 170                 175

Ile Ala Leu Leu Val Ala Gly Leu Met Ile Thr Val Ile Val Ile Val
            180                 185                 190

Gly Ala Ile Leu Phe Val Pro Gly Glu Tyr Ser Leu Lys Asn Ala Thr
        195                 200                 205

Gly Leu Gly Leu Ile Val Thr Ser Thr Gly Ile Leu Ile Leu Leu His
    210                 215                 220

Tyr Tyr Val Phe Ser Thr Ala Ile Gly Leu Thr Ser Phe Val Ile Ala
225                 230                 235                 240

Ile Leu Val Ile Gln Val Ile Ala Tyr Ile Leu Ala Val Val Gly Leu
                245                 250                 255

Ser Leu Cys Ile Ala Ala Cys Ile Pro Met His Gly Pro Leu Leu Ile
            260                 265                 270

Ser Gly Leu Ser Ile Leu Ala Leu Ala Gln Leu Leu Gly Leu Val Tyr
        275                 280                 285

Met Lys Phe Val Ala Ser Asn Gln Lys Thr Ile Gln Pro Pro Arg Lys
    290                 295                 300

Ala Val Glu Glu Pro Leu Asn Ala Phe Lys Glu Ser Lys Gly Met Met
305                 310                 315                 320

Asn Asp Glu
```

<210> 65
<211> 5
<212> PRT

<213> Artificial Sequence

<220>
<223> immunoglobulin constant region

<400> 65

Arg Asp Glu Leu Thr
1 5

<210> 66
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> immunoglobulin constant region

<400> 66

Arg Glu Glu Met
1

<210> 67
<211> 1390
<212> PRT
<213> Homo sapiens

<400> 67

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
1 5 10 15

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

Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
35 40 45

Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
50 55 60

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

Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
85 90 95

Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
100 105 110

Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
115 120 125

Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
130 135 140

Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys

145 150 155 160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
165 170 175

Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
180 185 190

Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro Asp
195 200 205

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

Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
225 230 235 240

Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
245 250 255

Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
260 265 270

Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
275 280 285

His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
290 295 300

Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
305 310 315 320

Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
325 330 335

Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
340 345 350

Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
355 360 365

Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
370 375 380

Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385 390 395 400

Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
405 410 415

Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
420 425 430

```
Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
        435                 440                 445

Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
    450                 455                 460

Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
465                 470                 475                 480

Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
                485                 490                 495

Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
            500                 505                 510

Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
        515                 520                 525

Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
    530                 535                 540

Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile
545                 550                 555                 560

Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu
                565                 570                 575

Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg
            580                 585                 590

Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu
        595                 600                 605

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys
    610                 615                 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile
625                 630                 635                 640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp
                645                 650                 655

Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly
            660                 665                 670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg
        675                 680                 685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn
    690                 695                 700
```

```
Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe
705                 710                 715                 720

Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe
                725                 730                 735

Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser
            740                 745                 750

Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu Asn
        755                 760                 765

Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg
    770                 775                 780

Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys
785                 790                 795                 800

Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys
                805                 810                 815

Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp
            820                 825                 830

Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val
        835                 840                 845

Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp
    850                 855                 860

Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys
865                 870                 875                 880

Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val
                885                 890                 895

Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys
            900                 905                 910

Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp
        915                 920                 925

Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser Thr Ala
    930                 935                 940

Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg Lys Gln
945                 950                 955                 960

Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His
                965                 970                 975
```

```
Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr
            980                 985                 990


Thr Glu Met Val Ser Asn Glu Ser  Val Asp Tyr Arg Ala  Thr Phe Pro
        995                 1000                1005


Glu Asp  Gln Phe Pro Asn Ser  Ser Gln Asn Gly Ser  Cys Arg Gln
    1010                1015                1020


Val Gln  Tyr Pro Leu Thr Asp  Met Ser Pro Ile Leu  Thr Ser Gly
    1025                1030                1035


Asp Ser  Asp Ile Ser Ser Pro  Leu Leu Gln Asn Thr  Val His Ile
    1040                1045                1050


Asp Leu  Ser Ala Leu Asn Pro  Glu Leu Val Gln Ala  Val Gln His
    1055                1060                1065


Val Val  Ile Gly Pro Ser Ser  Leu Ile Val His Phe  Asn Glu Val
    1070                1075                1080


Ile Gly  Arg Gly His Phe Gly  Cys Val Tyr His Gly  Thr Leu Leu
    1085                1090                1095


Asp Asn  Asp Gly Lys Lys Ile  His Cys Ala Val Lys  Ser Leu Asn
    1100                1105                1110


Arg Ile  Thr Asp Ile Gly Glu  Val Ser Gln Phe Leu  Thr Glu Gly
    1115                1120                1125


Ile Ile  Met Lys Asp Phe Ser  His Pro Asn Val Leu  Ser Leu Leu
    1130                1135                1140


Gly Ile  Cys Leu Arg Ser Glu  Gly Ser Pro Leu Val  Val Leu Pro
    1145                1150                1155


Tyr Met  Lys His Gly Asp Leu  Arg Asn Phe Ile Arg  Asn Glu Thr
    1160                1165                1170


His Asn  Pro Thr Val Lys Asp  Leu Ile Gly Phe Gly  Leu Gln Val
    1175                1180                1185


Ala Lys  Gly Met Lys Tyr Leu  Ala Ser Lys Lys Phe  Val His Arg
    1190                1195                1200


Asp Leu  Ala Ala Arg Asn Cys  Met Leu Asp Glu Lys  Phe Thr Val
    1205                1210                1215


Lys Val  Ala Asp Phe Gly Leu  Ala Arg Asp Met Tyr  Asp Lys Glu
    1220                1225                1230


Tyr Tyr  Ser Val His Asn Lys  Thr Gly Ala Lys Leu  Pro Val Lys
```

```
    1235                1240                1245

Trp Met  Ala Leu Glu Ser Leu  Gln Thr Gln Lys Phe  Thr Thr Lys
    1250                1255                1260

Ser Asp  Val Trp Ser Phe Gly  Val Leu Leu Trp Glu  Leu Met Thr
    1265                1270                1275

Arg Gly  Ala Pro Pro Tyr Pro  Asp Val Asn Thr Phe  Asp Ile Thr
    1280                1285                1290

Val Tyr  Leu Leu Gln Gly Arg  Arg Leu Leu Gln Pro  Glu Tyr Cys
    1295                1300                1305

Pro Asp  Pro Leu Tyr Glu Val  Met Leu Lys Cys Trp  His Pro Lys
    1310                1315                1320

Ala Glu  Met Arg Pro Ser Phe  Ser Glu Leu Val Ser  Arg Ile Ser
    1325                1330                1335

Ala Ile  Phe Ser Thr Phe Ile  Gly Glu His Tyr Val  His Val Asn
    1340                1345                1350

Ala Thr  Tyr Val Asn Val Lys  Cys Val Ala Pro Tyr  Pro Ser Leu
    1355                1360                1365

Leu Ser  Ser Glu Asp Asn Ala  Asp Asp Glu Val Asp  Thr Arg Pro
    1370                1375                1380

Ala Ser  Phe Trp Glu Thr Ser
    1385                1390


<210>  68
<211>  1381
<212>  PRT
<213>  Macaca fascicularis

<400>  68

Met Lys Ala Pro Ala Val Leu Val Pro Gly Ile Leu Val Leu Leu Phe
1               5                   10                  15

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

Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
        35                  40                  45

Glu Thr Ala Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
    50                  55                  60

Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
65                  70                  75                  80
```

```
Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
                85                  90                  95

Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
            100                 105                 110

Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
        115                 120                 125

Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
    130                 135                 140

Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
145                 150                 155                 160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Asn Gln Cys Pro Asp Cys Val
                165                 170                 175

Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
            180                 185                 190

Ile Asn Phe Phe Val Gly Asn Thr Ile Asn Ser Ser Tyr Phe Pro His
        195                 200                 205

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

Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
225                 230                 235                 240

Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Ile His Ala Phe Glu Ser Asn
                245                 250                 255

Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asn Ala Gln
            260                 265                 270

Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Leu Asn Ser Gly Leu
        275                 280                 285

His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
    290                 295                 300

Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
305                 310                 315                 320

Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
                325                 330                 335

Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
            340                 345                 350
```

```
Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
        355                 360                 365

Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
    370                 375                 380

Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385                 390                 395                 400

Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
                405                 410                 415

Arg Ala Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
            420                 425                 430

Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Val Lys Gly
        435                 440                 445

Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
    450                 455                 460

Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
465                 470                 475                 480

Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Pro Leu
                485                 490                 495

Asn Gln Asn Gly Tyr Thr Leu Val Val Thr Gly Lys Lys Ile Thr Lys
            500                 505                 510

Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
        515                 520                 525

Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
    530                 535                 540

Cys Val Arg Ser Glu Glu Cys Pro Ser Gly Thr Trp Thr Gln Gln Ile
545                 550                 555                 560

Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Thr Ser Ala Pro Leu Glu
                565                 570                 575

Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg
            580                 585                 590

Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu
        595                 600                 605

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys
    610                 615                 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile
```

625 630 635 640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp
645 650 655

Pro Ile Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly
660 665 670

Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg
675 680 685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn
690 695 700

Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe
705 710 715 720

Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe
725 730 735

Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser
740 745 750

Phe Ile Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn Leu His
755 760 765

Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala Gly Arg
770 775 780

Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile Ile Cys
785 790 795 800

Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro Leu Lys
805 810 815

Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr Phe Asp
820 825 830

Leu Ile Tyr Val His Asn Pro Val Phe Lys Pro Phe Glu Lys Pro Val
835 840 845

Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly Asn Asp
850 855 860

Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly Asn Lys
865 870 875 880

Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys Thr Val
885 890 895

Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu Trp Lys
900 905 910

```
Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln Pro Asp
        915                 920                 925


Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser Ile Ala
    930                 935                 940


Leu Leu Leu Leu Leu Gly Leu Phe Leu Trp Leu Lys Lys Arg Lys Gln
945                 950                 955                 960


Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His
                965                 970                 975


Thr Pro His Leu Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr
            980                 985                 990


Thr Glu Met Val Ser Asn Glu Ser  Val Asp Tyr Arg Ala  Thr Phe Pro
        995                 1000                1005


Glu Asp  Gln Phe Pro Asn Ser  Ser Gln Asn Gly Ser  Cys Arg Gln
    1010                1015                1020


Val Gln  Tyr Pro Leu Thr Asp  Met Ser Pro Ile Leu  Thr Ser Gly
    1025                1030                1035


Asp Ser  Asp Ile Ser Ser Pro  Leu Leu Gln Asn Thr  Val His Ile
    1040                1045                1050


Asp Leu  Ser Ala Leu Asn Pro  Glu Leu Val Gln Ala  Val Gln His
    1055                1060                1065


Val Val  Ile Gly Pro Ser Ser  Leu Ile Val His Phe  Asn Glu Val
    1070                1075                1080


Ile Gly  Arg Gly His Phe Gly  Cys Val Tyr His Gly  Thr Leu Leu
    1085                1090                1095


Asp Asn  Asp Gly Lys Lys Ile  His Cys Ala Val Lys  Ser Leu Asn
    1100                1105                1110


Arg Ile  Thr Asp Ile Gly Glu  Val Ser Gln Phe Leu  Thr Glu Gly
    1115                1120                1125


Ile Ile  Met Lys Asp Phe Ser  His Pro Asn Val Leu  Ser Leu Leu
    1130                1135                1140


Gly Ile  Cys Leu Arg Ser Glu  Gly Ser Pro Leu Val  Val Leu Pro
    1145                1150                1155


Tyr Met  Lys His Gly Asp Leu  Arg Asn Phe Ile Arg  Asn Glu Thr
    1160                1165                1170
```

```
His Asn  Pro Thr Val Lys Asp  Leu Ile Gly Phe Gly  Leu Gln Val
    1175                1180                1185


Ala Lys  Gly Met Lys Tyr Leu  Ala Ser Lys Lys Phe  Val His Arg
    1190                1195                1200


Asp Leu  Ala Ala Arg Asn Cys  Met Leu Asp Glu Lys  Phe Thr Val
    1205                1210                1215


Lys Val  Ala Asp Phe Gly Leu  Ala Arg Asp Met Tyr  Asp Lys Glu
    1220                1225                1230


Tyr Tyr  Ser Val His Asn Lys  Thr Gly Ala Lys Leu  Pro Val Lys
    1235                1240                1245


Trp Met  Ala Leu Glu Ser Leu  Gln Thr Gln Lys Phe  Thr Thr Lys
    1250                1255                1260


Ser Asp  Val Trp Ser Phe Gly  Val Leu Leu Trp Glu  Leu Met Thr
    1265                1270                1275


Arg Gly  Ala Pro Pro Tyr Pro  Asp Val Asn Thr Phe  Asp Ile Thr
    1280                1285                1290


Val Tyr  Leu Leu Gln Gly Arg  Arg Leu Leu Gln Pro  Glu Tyr Cys
    1295                1300                1305


Pro Asp  Pro Leu Tyr Glu Val  Met Leu Lys Cys Trp  His Pro Lys
    1310                1315                1320


Ala Glu  Met Arg Pro Ser Phe  Ser Glu Leu Val Ser  Arg Ile Ser
    1325                1330                1335


Ala Ile  Phe Ser Thr Phe Ile  Gly Glu His Tyr Val  His Val Asn
    1340                1345                1350


Ala Thr  Tyr Val Asn Val Lys  Cys Val Ala Pro Tyr  Pro Ser Leu
    1355                1360                1365


Leu Ser  Ser Glu Asp Asn Ala  Asp Asp Glu Val Asp  Thr
    1370                1375                1380


<210>  69
<211>  11
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  peptide linker

<400>  69

Gly Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
1               5                   10
```

<210> 70
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 70

Gly Pro Ala Pro Leu Gly Leu Gly Gly Pro Ser
1 5 10

<210> 71
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 71

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
1 5 10

<210> 72
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 72

Pro Pro Cys Pro Ala Pro Leu Gly Leu Gly Gly Pro Ser
1 5 10

<210> 73
<211> 694
<212> PRT
<213> Art Seq Fc-Her2/CD3(34) Heavy chain

<400> 73

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe
1 5 10 15

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
20 25 30

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
35 40 45

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
50 55 60

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
65 70 75 80

```
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                85                  90                  95

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            100                 105                 110

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        115                 120                 125

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val
    130                 135                 140

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

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

Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            180                 185                 190

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        195                 200                 205

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Pro Ala
    210                 215                 220

Pro Leu Gly Leu Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
225                 230                 235                 240

Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
                245                 250                 255

Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ala
            260                 265                 270

Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly
        275                 280                 285

Tyr Thr Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala
    290                 295                 300

Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala
305                 310                 315                 320

Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe
                325                 330                 335

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350
```

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
        355                 360                 365

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
    370                 375                 380

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
385                 390                 395                 400

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
                405                 410                 415

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
            420                 425                 430

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
        435                 440                 445

Lys Val Glu Pro Lys Ser Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly
    450                 455                 460

Gly Ser Glu Val Lys Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
465                 470                 475                 480

Lys Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn
                485                 490                 495

Thr Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
            500                 505                 510

Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr
        515                 520                 525

Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln
    530                 535                 540

Ser Ile Leu Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala
545                 550                 555                 560

Met Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser
                565                 570                 575

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
            580                 585                 590

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
        595                 600                 605

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
    610                 615                 620
```

```
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
625                 630                 635                 640


Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
                645                 650                 655


Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
            660                 665                 670


Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
        675                 680                 685


Val Glu Pro Lys Ser Cys
    690


<210>  74
<211>  672
<212>  PRT
<213>  Art Seq Fc-Her2/CD3(34) Light chain

<400>  74

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe
1               5                   10                  15


Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            20                  25                  30


Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        35                  40                  45


Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    50                  55                  60


Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
65                  70                  75                  80


Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                85                  90                  95


Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            100                 105                 110


Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        115                 120                 125


Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val
    130                 135                 140


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


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

```
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            180                 185                 190

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        195                 200                 205

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Pro Ala
    210                 215                 220

Pro Leu Gly Leu Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro
225                 230                 235                 240

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln
                245                 250                 255

Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro
            260                 265                 270

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr
        275                 280                 285

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    290                 295                 300

Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Phe Cys
305                 310                 315                 320

Gln His Phe Asp His Leu Pro Leu Ala Phe Gly Gly Gly Thr Lys Val
                325                 330                 335

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

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
        355                 360                 365

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
    370                 375                 380

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
385                 390                 395                 400

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
                405                 410                 415

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
            420                 425                 430

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Pro
        435                 440                 445
```

```
Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Ala Val Val Thr Gln Glu
    450                 455                 460

Ser Ala Leu Thr Thr Ser Pro Gly Glu Thr Val Thr Leu Thr Cys Arg
465                 470                 475                 480

Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln
                485                 490                 495

Glu Lys Pro Asp His Leu Phe Thr Gly Leu Ile Gly Gly Thr Asn Lys
            500                 505                 510

Arg Ala Pro Gly Val Pro Ala Arg Phe Ser Gly Ser Leu Ile Gly Asp
        515                 520                 525

Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln Thr Glu Asp Glu Ala Ile
    530                 535                 540

Tyr Phe Cys Ala Leu Trp Tyr Ser Asn Leu Trp Val Phe Gly Gly Gly
545                 550                 555                 560

Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr
                565                 570                 575

Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu
            580                 585                 590

Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp
        595                 600                 605

Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro
    610                 615                 620

Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu
625                 630                 635                 640

Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr
                645                 650                 655

His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
            660                 665                 670


<210>  75
<211>  350
<212>  PRT
<213>  Art Seq Fab2 CMET/CMET One Arm style Heavy chain

<400>  75

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 Ser Tyr
```

```
            20                  25                  30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

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

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

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

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

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

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

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

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

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly Pro Ala
    210                 215                 220

Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly
225                 230                 235                 240

Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala
                245                 250                 255

Ser Gly Tyr Thr Phe Thr Ser Tyr Thr Met His Trp Val Arg Gln Ala
            260                 265                 270

Pro Gly Gln Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser Gly Gly
        275                 280                 285

Ser Thr Ser Tyr Ala Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg
    290                 295                 300
```

```
Asp Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser
305                 310                 315                 320


Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gln Glu Ile Thr Thr Glu
                325                 330                 335


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
            340                 345                 350


<210>  76
<211>  340
<212>  PRT
<213>  Art Seq Fab2 CMET/CMET One Arm style Light chain

<400>  76

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


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


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


Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu Ser Gly Ile Pro Asp
    50                  55                  60


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


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


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


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


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


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


Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175


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

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


Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu
    210                 215                 220


Leu Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu
225                 230                 235                 240


Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln
                245                 250                 255


Ser Val Ser Ser Tyr Ala Asn Ser Tyr Leu His Trp Tyr Gln Gln Lys
            260                 265                 270


Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Arg Gly Ser Thr Arg Glu
        275                 280                 285


Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
    290                 295                 300


Thr Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr
305                 310                 315                 320


Cys Gln Gln Ser Lys Ser Glu Pro Leu Thr Phe Gly Gly Gly Thr Lys
                325                 330                 335


Val Glu Ile Lys
            340


<210>  77
<211>  1255
<212>  PRT
<213>  Homo sapiens

<400>  77

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1               5                   10                  15


Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
            20                  25                  30


Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
        35                  40                  45


Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
    50                  55                  60


Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65                  70                  75                  80


Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
                85                  90                  95
```

```
Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
            100                 105                 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
        115                 120                 125

Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser
    130                 135                 140

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145                 150                 155                 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
                165                 170                 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
            180                 185                 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
        195                 200                 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
    210                 215                 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225                 230                 235                 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
                245                 250                 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
            260                 265                 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
        275                 280                 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
    290                 295                 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305                 310                 315                 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
                325                 330                 335

Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu
            340                 345                 350

Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys
        355                 360                 365
```

```
Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp
    370                 375                 380

Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe
385                 390                 395                 400

Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro
                405                 410                 415

Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg
            420                 425                 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
        435                 440                 445

Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
    450                 455                 460

Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val
465                 470                 475                 480

Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr
                485                 490                 495

Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His
            500                 505                 510

Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys
        515                 520                 525

Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys
    530                 535                 540

Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys
545                 550                 555                 560

Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys
                565                 570                 575

Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp
            580                 585                 590

Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu
        595                 600                 605

Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln
    610                 615                 620

Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys
625                 630                 635                 640
```

```
Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Ile Ser
                645                 650                 655

Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly
            660                 665                 670

Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg
        675                 680                 685

Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly
    690                 695                 700

Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu
705                 710                 715                 720

Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys
                725                 730                 735

Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile
            740                 745                 750

Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu
        755                 760                 765

Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg
    770                 775                 780

Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu
785                 790                 795                 800

Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg
                805                 810                 815

Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly
            820                 825                 830

Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala
        835                 840                 845

Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe
    850                 855                 860

Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp
865                 870                 875                 880

Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg
                885                 890                 895

Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val
            900                 905                 910

Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala
```

915 920 925

Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro
930 935 940

Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met
945 950 955 960

Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe
965 970 975

Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu
980 985 990

Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu
995 1000 1005

Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr
1010 1015 1020

Leu Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly
1025 1030 1035

Ala Gly Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg
1040 1045 1050

Ser Gly Gly Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu
1055 1060 1065

Glu Ala Pro Arg Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser
1070 1075 1080

Asp Val Phe Asp Gly Asp Leu Gly Met Gly Ala Ala Lys Gly Leu
1085 1090 1095

Gln Ser Leu Pro Thr His Asp Pro Ser Pro Leu Gln Arg Tyr Ser
1100 1105 1110

Glu Asp Pro Thr Val Pro Leu Pro Ser Glu Thr Asp Gly Tyr Val
1115 1120 1125

Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val Asn Gln Pro
1130 1135 1140

Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro Leu Pro
1145 1150 1155

Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Pro Lys Thr Leu
1160 1165 1170

Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val Phe Ala Phe Gly
1175 1180 1185

```
Gly Ala  Val Glu Asn Pro Glu  Tyr Leu Thr Pro Gln  Gly Gly Ala
    1190                1195                1200


Ala Pro  Gln Pro His Pro Pro  Pro Ala Phe Ser Pro  Ala Phe Asp
    1205                1210                1215


Asn Leu  Tyr Tyr Trp Asp Gln  Asp Pro Pro Glu Arg  Gly Ala Pro
    1220                1225                1230


Pro Ser  Thr Phe Lys Gly Thr  Pro Thr Ala Glu Asn  Pro Glu Tyr
    1235                1240                1245


Leu Gly  Leu Asp Val Pro Val
    1250                1255


<210>  78
<211>  1406
<212>  PRT
<213>  Macaca fascicularis

<400>  78

Met Ala Glu Ser Pro Ala Ser Ala Phe Arg Asp Ser Leu Arg Lys Ser
1               5                   10                  15


Val Arg Thr Ala Ala Gly Asn Pro Gly Val Pro Glu Leu Gly Gly Thr
            20                  25                  30


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


Thr Pro Arg Leu Val Gly Met Gln Leu Glu Gly Ala Ser Trp Glu Arg
    50                  55                  60


Ala Cys Ser Gln Ser Gln Glu Glu Glu Glu Val Glu Glu Glu Gly Cys
65                  70                  75                  80


Leu Arg Lys Tyr Lys Asn Glu Val Val Glu Leu Arg Phe Pro Ser Ile
                85                  90                  95


Gly Thr Gly Glu Thr Arg Gly Ala Pro Trp Ala Ala Val Arg Pro Phe
            100                 105                 110


Pro Arg Gly Ser Phe Arg Arg Arg Ala Pro Gly Pro His Pro Ser Pro
        115                 120                 125


His Pro Ala Pro His Ala Leu Pro Ala Gly Ser Ser Arg Ser His Gly
    130                 135                 140


Ala Gly Ala Ala Val Ser Thr Met Glu Leu Ala Ala Trp Tyr Arg Trp
145                 150                 155                 160
```

```
Gly Leu Leu Leu Ala Leu Leu Pro Pro Gly Ala Thr Gly Thr Gln Val
                165                 170                 175

Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser Pro Glu Thr
            180                 185                 190

His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln Val Val Gln
        195                 200                 205

Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser Leu Ser Phe
    210                 215                 220

Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile Ala His Asn
225                 230                 235                 240

Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val Arg Gly Thr
                245                 250                 255

Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp Asn Gly Asp
            260                 265                 270

Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro Gly Gly Leu
        275                 280                 285

Arg Glu Leu Gln Leu Arg Ser Leu Thr Glu Ile Leu Lys Gly Gly Val
    290                 295                 300

Leu Ile Gln Arg Asn Pro Gln Leu Cys Tyr Gln Asp Thr Ile Leu Trp
305                 310                 315                 320

Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr Leu Ile Asp
                325                 330                 335

Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Val Cys Lys Gly
            340                 345                 350

Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser Leu Thr Arg
        355                 360                 365

Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro Leu Pro Thr
    370                 375                 380

Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly Pro Lys His
385                 390                 395                 400

Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly Ile Cys Glu
                405                 410                 415

Leu His Cys Pro Ala Leu Val Thr Tyr Asn Thr Asp Thr Phe Glu Ser
            420                 425                 430

Met Pro Asn Pro Glu Gly Arg Tyr Thr Phe Gly Ala Ser Cys Val Thr
```

435 440 445

Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser Cys Thr Leu
450 455 460

Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp Gly Thr Gln
465 470 475 480

Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys Tyr Gly Leu
485 490 495

Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser Ala Asn Ile
500 505 510

Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu Ala Phe Leu
515 520 525

Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala Pro Leu Gln
530 535 540

Pro Glu Gln Leu Arg Val Phe Glu Thr Leu Glu Glu Ile Thr Gly Tyr
545 550 555 560

Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu Ser Val Leu
565 570 575

Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn Gly Ala Tyr
580 585 590

Ser Leu Thr Leu Gln Gly Leu Gly Ile Ser Trp Leu Gly Leu Arg Ser
595 600 605

Leu Arg Glu Leu Gly Ser Gly Leu Ala Leu Ile His His Asn Thr Arg
610 615 620

Leu Cys Phe Val His Thr Val Pro Trp Asp Gln Leu Phe Arg Asn Pro
625 630 635 640

His Gln Ala Leu Leu His Thr Ala Asn Arg Pro Glu Asp Glu Cys Val
645 650 655

Gly Glu Gly Leu Ala Cys His Gln Leu Cys Ala Arg Gly His Cys Trp
660 665 670

Gly Pro Gly Pro Thr Gln Cys Val Asn Cys Ser Gln Phe Leu Arg Gly
675 680 685

Gln Glu Cys Val Glu Glu Cys Arg Val Leu Gln Gly Leu Pro Arg Glu
690 695 700

Tyr Val Asn Ala Arg His Cys Leu Pro Cys His Pro Glu Cys Gln Pro
705 710 715 720

```
Gln Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp Gln Cys Val
                725                 730                 735

Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala Arg Cys Pro
            740                 745                 750

Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp Lys Phe Pro
        755                 760                 765

Asp Glu Glu Gly Thr Cys Gln Ser Cys Pro Ile Asn Cys Thr His Ser
    770                 775                 780

Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu Gln Arg Ala Ser
785                 790                 795                 800

Pro Leu Thr Ser Ile Ile Ser Ala Val Val Gly Ile Leu Leu Val Val
                805                 810                 815

Val Leu Gly Val Val Phe Gly Ile Leu Ile Lys Arg Arg Gln Gln Lys
            820                 825                 830

Ile Arg Lys Tyr Thr Met Arg Arg Leu Leu Gln Glu Thr Glu Leu Val
        835                 840                 845

Glu Pro Leu Thr Pro Ser Gly Ala Met Pro Asn Gln Ala Gln Met Arg
    850                 855                 860

Ile Leu Lys Glu Thr Glu Leu Arg Lys Val Lys Val Leu Gly Ser Gly
865                 870                 875                 880

Ala Phe Gly Thr Val Tyr Lys Gly Ile Trp Ile Pro Asp Gly Glu Asn
                885                 890                 895

Val Lys Ile Pro Val Ala Ile Lys Val Leu Arg Glu Asn Thr Ser Pro
            900                 905                 910

Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Gly Val
        915                 920                 925

Gly Ser Pro Tyr Val Ser Arg Leu Leu Gly Ile Cys Leu Thr Ser Thr
    930                 935                 940

Val Gln Leu Val Thr Gln Leu Met Pro Tyr Gly Cys Leu Leu Asp His
945                 950                 955                 960

Val Arg Glu Asn Arg Gly Arg Leu Gly Ser Gln Asp Leu Leu Asn Trp
                965                 970                 975

Cys Met Gln Ile Ala Lys Gly Met Ser Tyr Leu Glu Asp Val Arg Leu
            980                 985                 990
```

```
Val His Arg Asp Leu Ala Ala Arg  Asn Val Leu Val Lys  Ser Pro Asn
        995                 1000                1005


His Val  Lys Ile Thr Asp Phe  Gly Leu Ala Arg Leu  Leu Asp Ile
    1010                1015                1020


Asp Glu  Thr Glu Tyr His Ala  Asp Gly Gly Lys Val  Pro Ile Lys
    1025                1030                1035


Trp Met  Ala Leu Glu Ser Ile  Leu Arg Arg Arg Phe  Thr His Gln
    1040                1045                1050


Ser Asp  Val Trp Ser Tyr Gly  Val Thr Val Trp Glu  Leu Met Thr
    1055                1060                1065


Phe Gly  Ala Lys Pro Tyr Asp  Gly Ile Pro Ala Arg  Glu Ile Pro
    1070                1075                1080


Asp Leu  Leu Glu Lys Gly Glu  Arg Leu Pro Gln Pro  Pro Ile Cys
    1085                1090                1095


Thr Ile  Asp Val Tyr Met Ile  Met Val Lys Cys Trp  Met Ile Asp
    1100                1105                1110


Ser Glu  Cys Arg Pro Arg Phe  Arg Glu Leu Val Ser  Glu Phe Ser
    1115                1120                1125


Arg Met  Ala Arg Asp Pro Gln  Arg Phe Val Val Ile  Gln Asn Glu
    1130                1135                1140


Asp Leu  Gly Pro Ala Ser Pro  Leu Asp Ser Thr Phe  Tyr Arg Ser
    1145                1150                1155


Leu Leu  Glu Asp Asp Asp Met  Gly Asp Leu Val Asp  Ala Glu Glu
    1160                1165                1170


Tyr Leu  Val Pro Gln Gln Gly  Phe Phe Cys Pro Asp  Pro Ala Pro
    1175                1180                1185


Gly Thr  Gly Gly Met Val His  His Arg His Arg Ser  Ser Ser Thr
    1190                1195                1200


Arg Ser  Gly Gly Gly Asp Leu  Thr Leu Gly Leu Glu  Pro Ser Glu
    1205                1210                1215


Glu Glu  Ala Pro Arg Ser Pro  Arg Ala Pro Ser Glu  Gly Thr Gly
    1220                1225                1230


Ser Asp  Val Phe Asp Gly Asp  Leu Gly Met Gly Ala  Ala Lys Gly
    1235                1240                1245
```

```
Leu Gln  Ser Leu Pro Ala His  Asp Pro Ser Pro Leu  Gln Arg Tyr
    1250                 1255                 1260


Ser Glu  Asp Pro Thr Val Pro  Leu Pro Ser Glu Thr  Asp Gly Tyr
    1265                 1270                 1275


Val Ala  Pro Leu Thr Cys Ser  Pro Gln Pro Glu Tyr  Val Asn Gln
    1280                 1285                 1290


Pro Asp  Val Arg Pro Gln Pro  Pro Ser Pro Gln Glu  Gly Pro Leu
    1295                 1300                 1305


Ser Pro  Ala Arg Pro Thr Gly  Ala Thr Leu Glu Arg  Pro Lys Thr
    1310                 1315                 1320


Leu Ser  Pro Gly Lys Asn Gly  Val Val Lys Asp Val  Phe Ala Phe
    1325                 1330                 1335


Gly Gly  Ala Val Glu Asn Pro  Glu Tyr Leu Ala Pro  Arg Gly Gly
    1340                 1345                 1350


Ala Ala  Pro Gln Pro His Leu  Pro Pro Ala Phe Ser  Pro Ala Phe
    1355                 1360                 1365


Asp Asn  Leu Tyr Tyr Trp Asp  Gln Asp Pro Ser Glu  Arg Gly Ala
    1370                 1375                 1380


Pro Pro  Ser Thr Phe Lys Gly  Thr Pro Thr Ala Glu  Asn Pro Glu
    1385                 1390                 1395


Tyr Leu  Gly Leu Asp Val Pro  Val
    1400                 1405


<210>  79
<211>  206
<212>  PRT
<213>  Homo sapiens

<400>  79

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1               5                  10                  15


Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
            20                  25                  30


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


Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Gln His Asn Asp Lys Asn
    50                  55                  60


Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His
65                  70                  75                  80
```

```
Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr Val
                85                  90                  95

Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu Tyr
            100                 105                 110

Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met Ser
        115                 120                 125

Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu Leu
    130                 135                 140

Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys Pro
145                 150                 155                 160

Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn Lys
                165                 170                 175

Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg Lys
            180                 185                 190

Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
        195                 200                 205


<210>  80
<211>  198
<212>  PRT
<213>  Macaca fascicularis

<400>  80

Met Gln Ser Gly Thr Arg Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1               5                   10                  15

Ile Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Ser Ile Thr
            20                  25                  30

Gln Thr Pro Tyr Gln Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
        35                  40                  45

Cys Ser Gln His Leu Gly Ser Glu Ala Gln Trp Gln His Asn Gly Lys
    50                  55                  60

Asn Lys Glu Asp Ser Gly Asp Arg Leu Phe Leu Pro Glu Phe Ser Glu
65                  70                  75                  80

Met Glu Gln Ser Gly Tyr Tyr Val Cys Tyr Pro Arg Gly Ser Asn Pro
                85                  90                  95

Glu Asp Ala Ser His His Leu Tyr Leu Lys Ala Arg Val Cys Glu Asn
            100                 105                 110
```

Cys Met Glu Met Asp Val Met Ala Val Ala Thr Ile Val Ile Val Asp
115 120 125

Ile Cys Ile Thr Leu Gly Leu Leu Leu Leu Val Tyr Tyr Trp Ser Lys
130 135 140

Asn Arg Lys Ala Lys Ala Lys Pro Val Thr Arg Gly Ala Gly Ala Gly
145 150 155 160

Gly Arg Gln Arg Gly Gln Asn Lys Glu Arg Pro Pro Pro Val Pro Asn
165 170 175

Pro Asp Tyr Glu Pro Ile Arg Lys Gly Gln Gln Asp Leu Tyr Ser Gly
180 185 190

Leu Asn Gln Arg Arg Ile
195

<210> 81
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 81

Gly Pro Ala Pro Glu Ala Ala Gly Ala Gly Ser
1 5 10

<210> 82
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 82

Gly Pro Ala Asp Asp Asp Asp Lys Ser Gly Ser
1 5 10

<210> 83
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 83

Gly Pro Ala Leu Val Pro Arg Gly Ser Gly Ser
1 5 10

<210> 84
<211> 12
<212> PRT

<213> Artificial Sequence

<220>
<223> peptide linker

<400> 84

Gly Pro Gly Pro Phe Gly Arg Ser Ala Gly Gly Pro
1 5 10

<210> 85
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 85

Gly Pro Ala Pro Leu Glu Ala Asp Ala Gly Ser
1 5 10

<210> 86
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 86

Gly Pro Ala Pro Glu Ala Arg Arg Gly Gly Ser
1 5 10

<210> 87
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> peptide linker

<400> 87

Gly Pro Ala Pro Glu Gly Glu Ala Arg Gly Ser
1 5 10

<210> 88
<211> 678
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 IgG1-DAA Her2/CD47 Heavy chain

<400> 88

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Leu Gly Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln
225                 230                 235                 240

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
                245                 250                 255

Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg
            260                 265                 270

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val
        275                 280                 285

Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile
    290                 295                 300
```

```
Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
305                 310                 315                 320

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr
                325                 330                 335

Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
            340                 345                 350

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
        355                 360                 365

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
    370                 375                 380

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
385                 390                 395                 400

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
                405                 410                 415

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
            420                 425                 430

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
        435                 440                 445

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
    450                 455                 460

Pro Pro Val Ala Gly Pro Asp Val Phe Leu Phe Pro Pro Lys Pro Lys
465                 470                 475                 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                485                 490                 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            500                 505                 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        515                 520                 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    530                 535                 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu
545                 550                 555                 560

Pro Ala Pro Ile Ala Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                565                 570                 575
```

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly
675

<210> 89
<211> 444
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 IgG1-DAA Her2/CD47 Light chain

<400> 89

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
        275                 280                 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
            340                 345                 350

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
        355                 360                 365

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
    370                 375                 380

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
385                 390                 395                 400
```

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
405 410 415

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
420 425 430

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
435 440

<210> 90
<211> 678
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 IgG1-DAA Her2/CD47 Heavy chain

<400> 90

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Val Gln
225                 230                 235                 240

Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys
                245                 250                 255

Lys Gly Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Ile Phe Trp Val Arg
            260                 265                 270

Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Val
        275                 280                 285

Asp Gly Asp Thr Asn Tyr Asn Pro Ser Phe Gln Gly Gln Val Thr Ile
    290                 295                 300

Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu
305                 310                 315                 320

Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Gly Gly Tyr Thr
                325                 330                 335

Met Asp Arg Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
            340                 345                 350

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
        355                 360                 365

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
    370                 375                 380

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
385                 390                 395                 400

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
                405                 410                 415

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
            420                 425                 430

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
        435                 440                 445

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
    450                 455                 460
```

```
Pro Pro Val Ala Gly Pro Asp Val Phe Leu Phe Pro Pro Lys Pro Lys
465                 470                 475                 480


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                485                 490                 495


Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            500                 505                 510


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        515                 520                 525


Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    530                 535                 540


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu
545                 550                 555                 560


Pro Ala Pro Ile Ala Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                565                 570                 575


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
            580                 585                 590


Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
        595                 600                 605


Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    610                 615                 620


Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625                 630                 635                 640


Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
                645                 650                 655


Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
            660                 665                 670


Leu Ser Leu Ser Pro Gly
        675


<210>  91
<211>  444
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG2 IgG1-DAA Her2/CD47 Light chain

<400>  91

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly
    210                 215                 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
        275                 280                 285
```

```
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
            340                 345                 350

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
        355                 360                 365

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
    370                 375                 380

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
385                 390                 395                 400

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
                405                 410                 415

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
            420                 425                 430

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
        435                 440


<210>  92
<211>  337
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  IgG2 Her2/CD47 Light chain

<400>  92

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

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

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

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

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

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Asp Asp Asp Asp Lys Ser Gly
    210                 215                 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
        275                 280                 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys
```

<210> 93
<211> 337
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 93

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


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


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


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


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


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


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


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


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


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


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


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


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


Phe Asn Arg Gly Glu Cys Gly Pro Ala Leu Val Pro Arg Gly Ser Gly
    210                 215                 220


Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240
```

```
Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
        275                 280                 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys
```

<210> 94
<211> 338
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 94

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Gly Pro Phe Gly Arg Ser Ala Gly
    210                 215                 220

Gly Pro Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr
225                 230                 235                 240

Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu
                245                 250                 255

His Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly
            260                 265                 270

Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly
        275                 280                 285

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
    290                 295                 300

Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe
305                 310                 315                 320

Gln Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu
                325                 330                 335

Ile Lys
```

<210> 95
<211> 337
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 95

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
```

```
1               5                   10                  15

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Glu Ala Asp Ala Gly
    210                 215                 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
        275                 280                 285
```

```
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
                325                 330                 335

Lys
```

<210> 96
<211> 337
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 96

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

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

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

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

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

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

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

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

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

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

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
```

165 170 175

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Ala Arg Arg Gly Gly
210 215 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225 230 235 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
245 250 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
260 265 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
275 280 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
290 295 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305 310 315 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
325 330 335

Lys

<210> 97
<211> 337
<212> PRT
<213> Artificial Sequence

<220>
<223> IgG2 Her2/CD47 Light chain

<400> 97

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Gly Glu Ala Arg Gly
    210                 215                 220

Ser Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro
225                 230                 235                 240

Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His
                245                 250                 255

Ser Asn Gly Tyr Asn Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln
            260                 265                 270

Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val
        275                 280                 285

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys
    290                 295                 300

Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln
305                 310                 315                 320

Asn Thr His Thr Pro Arg Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
```

325 330 335

Lys

<210> 98
<211> 674
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Heavy chain

<400> 98

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

```
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220


Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
225                 230                 235                 240


Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys
                245                 250                 255


Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys
            260                 265                 270


Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
        275                 280                 285


Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu
    290                 295                 300


Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
305                 310                 315                 320


Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp
                325                 330                 335


His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
            340                 345                 350


Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        355                 360                 365


Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    370                 375                 380


Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
385                 390                 395                 400


Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                405                 410                 415


Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
            420                 425                 430


Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
        435                 440                 445


Lys Lys Val Glu Pro Lys Ser Cys Gly Pro Ala Pro Glu Ala Ala Gly
    450                 455                 460


Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
465                 470                 475                 480


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
```

485 490 495

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
500 505 510

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
515 520 525

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
530 535 540

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
545 550 555 560

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
565 570 575

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
580 585 590

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
595 600 605

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
610 615 620

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
625 630 635 640

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
645 650 655

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
660 665 670

Pro Gly

<210> 99
<211> 656
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 99

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly
    210                 215                 220

Ser Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro
225                 230                 235                 240

Gly Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr
                245                 250                 255

Met Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile
            260                 265                 270

Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly
        275                 280                 285

Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala
    290                 295                 300

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe
```

305 310 315 320

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
325 330 335

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
340 345 350

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
355 360 365

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
370 375 380

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
405 410 415

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
420 425 430

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Ala Ala Gly Ala Pro
435 440 445

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
450 455 460

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
465 470 475 480

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
485 490 495

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
500 505 510

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
515 520 525

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
530 535 540

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
545 550 555 560

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp
565 570 575

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
580 585 590

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
595 600 605

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
610 615 620

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
625 630 635 640

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
645 650 655

<210> 100
<211> 674
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Heavy chain

<400> 100

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val

165 170 175

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Val Gln Leu Gln Gln
225 230 235 240

Ser Gly Ala Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys
245 250 255

Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys
260 265 270

Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser
275 280 285

Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu
290 295 300

Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu
305 310 315 320

Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp
325 330 335

His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
340 345 350

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
355 360 365

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
370 375 380

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
385 390 395 400

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
405 410 415

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
420 425 430

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
435 440 445

```
Lys Lys Val Glu Pro Lys Ser Cys Gly Pro Ala Pro Glu Ala Ala Gly
    450                 455                 460

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
465                 470                 475                 480

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
                485                 490                 495

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            500                 505                 510

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
        515                 520                 525

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    530                 535                 540

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
545                 550                 555                 560

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                565                 570                 575

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
            580                 585                 590

Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        595                 600                 605

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
    610                 615                 620

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
625                 630                 635                 640

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                645                 650                 655

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            660                 665                 670

Pro Gly
```

<210> 101
<211> 656
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 101

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

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

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

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

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

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

Ser Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro
225                 230                 235                 240

Gly Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr
                245                 250                 255

Met Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile
            260                 265                 270
```

```
Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly
        275                 280                 285

Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala
    290                 295                 300

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe
305                 310                 315                 320

Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
                325                 330                 335

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
            340                 345                 350

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
        355                 360                 365

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
    370                 375                 380

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
                405                 410                 415

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
            420                 425                 430

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Ala Ala Gly Ala Pro
        435                 440                 445

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    450                 455                 460

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
465                 470                 475                 480

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                485                 490                 495

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
            500                 505                 510

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        515                 520                 525

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    530                 535                 540
```

```
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
545                 550                 555                 560


Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Trp
                565                 570                 575


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            580                 585                 590


Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
        595                 600                 605


Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
    610                 615                 620


Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
625                 630                 635                 640


Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                645                 650                 655


<210>  102
<211>  665
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Heavy chain

<400>  102

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


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


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


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


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


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


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


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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly
    210                 215                 220

Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly
225                 230                 235                 240

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg
                245                 250                 255

Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp
            260                 265                 270

Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys
        275                 280                 285

Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
    290                 295                 300

Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
305                 310                 315                 320

Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln
                325                 330                 335

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
            340                 345                 350

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
        355                 360                 365

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
    370                 375                 380

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
385                 390                 395                 400
```

```
Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                405                 410                 415

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
            420                 425                 430

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
        435                 440                 445

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515                 520                 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530                 535                 540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545                 550                 555                 560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565                 570                 575

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
            580                 585                 590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595                 600                 605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610                 615                 620

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625                 630                 635                 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645                 650                 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly
            660                 665
```

<210> 103
<211> 665
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 103

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 Asn Ile Lys Asp Thr
20 25 30

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

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

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

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

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

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

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

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

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

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

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

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
210 215 220

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

```
Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr
                245                 250                 255

Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
            260                 265                 270

Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala
        275                 280                 285

Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser Tyr
    290                 295                 300

Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr
305                 310                 315                 320

Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys
                325                 330                 335

Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
            340                 345                 350

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
        355                 360                 365

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
    370                 375                 380

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
385                 390                 395                 400

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
                405                 410                 415

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
            420                 425                 430

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
        435                 440                 445

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510
```

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
515 520 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
530 535 540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545 550 555 560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
565 570 575

Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr
580 585 590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
595 600 605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
610 615 620

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625 630 635 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
645 650 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665

<210> 104
<211> 665
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Heavy chain

<400> 104

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
    210                 215                 220

Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly
225                 230                 235                 240

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg
                245                 250                 255

Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp
            260                 265                 270

Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys
        275                 280                 285

Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
    290                 295                 300

Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
305                 310                 315                 320

Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln
                325                 330                 335

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
            340                 345                 350
```

```
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
        355                 360                 365


Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
    370                 375                 380


Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
385                 390                 395                 400


Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                405                 410                 415


Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
            420                 425                 430


Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
        435                 440                 445


Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480


Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495


Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510


Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515                 520                 525


His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530                 535                 540


Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545                 550                 555                 560


Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565                 570                 575


Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
            580                 585                 590


Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595                 600                 605


Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610                 615                 620


Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
```

625 630 635 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
645 650 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665

<210> 105
<211> 665
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Light chain

<400> 105

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 Asn Ile Lys Asp Thr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

```
Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
    210                 215                 220

Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Ile Val Leu Thr Gln
225                 230                 235                 240

Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met Thr
                245                 250                 255

Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys
            260                 265                 270

Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala
        275                 280                 285

Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser Tyr
    290                 295                 300

Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr Tyr
305                 310                 315                 320

Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys
                325                 330                 335

Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
            340                 345                 350

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
        355                 360                 365

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
    370                 375                 380

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
385                 390                 395                 400

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
                405                 410                 415

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
            420                 425                 430

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly
        435                 440                 445

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
```

465 470 475 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
485 490 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
500 505 510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
515 520 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
530 535 540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545 550 555 560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
565 570 575

Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr
580 585 590

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
595 600 605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
610 615 620

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625 630 635 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
645 650 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665

<210> 106
<211> 665
<212> PRT
<213> Artificial Sequence

<220>
<223> Fab2 Her2/CD3 Heavy chain

<400> 106

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Thr Val Ser Ile Glu Cys Leu Ala Ser Glu Gly Ile Ser Asn Asp
20 25 30

```
Leu Ala Trp Tyr Gln Gln Lys Ser Gly Lys Ser Pro Gln Leu Leu Ile
        35                  40                  45

Tyr Ala Thr Ser Arg Leu Gln Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Arg Tyr Ser Leu Lys Ile Ser Gly Met Gln Pro
65                  70                  75                  80

Glu Asp Glu Ala Asp Tyr Phe Cys Gln Gln Ser Tyr Lys Tyr Pro Trp
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Leu Gly Leu Gly Gly Gly
    210                 215                 220

Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly
225                 230                 235                 240

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg
                245                 250                 255

Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp
            260                 265                 270

Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys
        275                 280                 285

Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
    290                 295                 300

Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
```

```
305                 310                 315                 320

Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln
                325                 330                 335

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
            340                 345                 350

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
        355                 360                 365

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
    370                 375                 380

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
385                 390                 395                 400

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                405                 410                 415

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
            420                 425                 430

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
        435                 440                 445

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515                 520                 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530                 535                 540

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545                 550                 555                 560

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565                 570                 575

Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
            580                 585                 590
```

```
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595                 600                 605

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610                 615                 620

Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625                 630                 635                 640

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645                 650                 655

Gln Lys Ser Leu Ser Leu Ser Pro Gly
            660                 665


<210>  107
<211>  666
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Light chain

<400>  107

Glu Val Gln Leu Ala Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Met Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
            20                  25                  30

Pro Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Thr Ser Gly Gly Ser Thr Tyr Tyr Arg Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Thr Arg Thr Leu Tyr Ile Leu Arg Val Phe Tyr Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Val Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
```

145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Ile Val Leu Thr
225 230 235 240

Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met
245 250 255

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln
260 265 270

Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
275 280 285

Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser
290 295 300

Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr
305 310 315 320

Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr
325 330 335

Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
340 345 350

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
355 360 365

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
370 375 380

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
385 390 395 400

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
405 410 415

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
420 425 430

```
Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
        435                 440                 445

Gly Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
    450                 455                 460

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
465                 470                 475                 480

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                485                 490                 495

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
            500                 505                 510

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
        515                 520                 525

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    530                 535                 540

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
545                 550                 555                 560

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
                565                 570                 575

Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe
            580                 585                 590

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        595                 600                 605

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    610                 615                 620

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
625                 630                 635                 640

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                645                 650                 655

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
            660                 665


<210>  108
<211>  665
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Heavy chain
```

<400> 108

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Thr Val Ser Ile Glu Cys Leu Ala Ser Glu Gly Ile Ser Asn Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Ser Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Ala Thr Ser Arg Leu Gln Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Arg Tyr Ser Leu Lys Ile Ser Gly Met Gln Pro
65 70 75 80

Glu Asp Glu Ala Asp Tyr Phe Cys Gln Gln Ser Tyr Lys Tyr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly
210 215 220

Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Arg Pro Gly
225 230 235 240

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg
245 250 255

Tyr Thr Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp
260 265 270

```
Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys
        275                 280                 285

Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
    290                 295                 300

Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
305                 310                 315                 320

Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln
                325                 330                 335

Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
            340                 345                 350

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
        355                 360                 365

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
    370                 375                 380

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
385                 390                 395                 400

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
                405                 410                 415

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
            420                 425                 430

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Gly
        435                 440                 445

Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
    450                 455                 460

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
465                 470                 475                 480

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                485                 490                 495

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
            500                 505                 510

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
        515                 520                 525

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    530                 535                 540
```

```
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
545                 550                 555                 560


Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
                565                 570                 575


Leu Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr
            580                 585                 590


Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        595                 600                 605


Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    610                 615                 620


Leu Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
625                 630                 635                 640


Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                645                 650                 655


Gln Lys Ser Leu Ser Leu Ser Pro Gly
            660                 665


<210>  109
<211>  666
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Fab2 Her2/CD3 Light chain

<400>  109

Glu Val Gln Leu Ala Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15


Ser Met Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Phe
            20                  25                  30


Pro Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu Glu Trp Val
        35                  40                  45


Ala Thr Ile Ser Thr Ser Gly Gly Ser Thr Tyr Tyr Arg Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser Thr Leu Tyr
65                  70                  75                  80


Leu Gln Met Asn Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95


Thr Arg Thr Leu Tyr Ile Leu Arg Val Phe Tyr Phe Asp Tyr Trp Gly
            100                 105                 110
```

```
Gln Gly Val Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
                165                 170                 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
            180                 185                 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
        195                 200                 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
    210                 215                 220

Gly Pro Ala Pro Glu Leu Leu Gly Gly Gly Ser Gln Ile Val Leu Thr
225                 230                 235                 240

Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val Thr Met
                245                 250                 255

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln
            260                 265                 270

Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
        275                 280                 285

Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly Thr Ser
    290                 295                 300

Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala Thr Tyr
305                 310                 315                 320

Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr
                325                 330                 335

Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
            340                 345                 350

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
        355                 360                 365

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
    370                 375                 380
```

```
Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
385                 390                 395                 400

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
                405                 410                 415

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
            420                 425                 430

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
        435                 440                 445

Gly Pro Ala Pro Glu Ala Ala Gly Ala Pro Ser Val Phe Leu Phe Pro
    450                 455                 460

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
465                 470                 475                 480

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                485                 490                 495

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
            500                 505                 510

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
        515                 520                 525

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    530                 535                 540

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
545                 550                 555                 560

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
                565                 570                 575

Glu Leu Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe
            580                 585                 590

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        595                 600                 605

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    610                 615                 620

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
625                 630                 635                 640

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                645                 650                 655
```

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
660 665

<210> 110
<211> 7
<212> PRT
<213> Unknown

<220>
<223> intact MMP-cleavage site

<400> 110

Ser Cys Gly Pro Ala Pro Glu
1 5

<210> 111
<211> 6
<212> PRT
<213> Unknown

<220>
<223> cleaved MMP-cleavage site

<400> 111

Ser Cys Gly Pro Ala Pro
1 5

<210> 112
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> hinge sequence

<400> 112

Glu Leu Leu Gly
1