



(51) International Patent Classification:

A61K 38/00 (2006.01) C07K 7/00 (2006.01)
A61K 39/395 (2006.01) C07K 16/00 (2006.01)

(21) International Application Number:

PCT/US2017/012754

(22) International Filing Date:

9 January 2017 (09.01.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/276,803 8 January 2016 (08.01.2016) US
62/317,342 1 April 2016 (01.04.2016) US

(71) Applicant: **MEDITOPE BIOSCIENCES, INC.**
[US/US]; 177 E. Colorado Blvd, 2nd Floor, Pasadena, CA
91105 (US).

(72) Inventors: **DUMITRU, Calin**; c/o Meditope Biosciences,
Inc., 177 E. Colorado Blvd, 2nd Floor, Pasadena, CA
91105 (US). **GARDINER, Elisabeth, M.**; c/o Meditope
Biosciences, Inc., 177 E. Colorado Blvd, 2nd Floor, Pas-
adena, CA 91105 (US). **MCKENZIE, Robert, P.**; c/o
Meditope Biosciences, Inc., 177 E. Colorado Blvd, 2nd
Floor, Pasadena, CA 91105 (US). **MATHO, Michael, H.**;
c/o Meditope Biosciences, Inc., 177 E. Colorado Blvd, 2nd
Floor, Pasadena, CA 91105 (US).

(74) Agents: **TANNER, Lorna, L.** et al.; Sheppard Mullin
Richter & Hampton LLP, 379 Lytton Avenue, Palo Alto,
CA 94301-1479 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN,
KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG,
NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS,
RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY,
TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,
ZA, ZM, ZW.

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

Declarations under Rule 4.17:

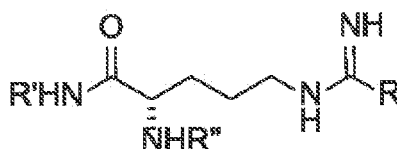
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: SELF-CROSSLINKING ANTIBODIES

Fig. 1



Modified Arg8

R = alkyl, substituted alkyl, aromatic or NHR'''
where R''' = alkyl, substituted alkyl, aromatic

(57) Abstract: Provided are self-crosslinking meditope-enabled antibodies. Also provided are methods for altering the distribution of a cell surface antigen using self-crosslinking meditope enabled antibodies, compositions for use in the methods, and methods of producing, using, testing, and screening the same, including therapeutic and diagnostic methods and uses.



SELF-CROSSLINKING ANTIBODIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/276,803, filed January 8, 2016, and to U.S. Provisional Application No. 62/317,342, filed April 1, 2016. The contents of both applications are incorporated by reference in their entirety herein.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 49JV_227262_WO_SEQ.txt, created January 9, 2017, which is 601 kilobytes in size. The information in the electronic format of the Sequence Listing is incorporated by reference in its entirety.

BACKGROUND

[0003] Monoclonal antibodies (mAbs) are used in a number of therapeutic, diagnostic, and research applications. Therapeutic and diagnostic areas include cancer, antiviral treatment, autoimmune and inflammatory disease, allergy, cardiovascular disease, osteoporosis, and rheumatology.

[0004] Protein engineering and other efforts have generated mAbs with improved efficacy and targeting (e.g., bispecific mAbs), improved localization, tissue penetration, and blood clearance (e.g., single chain Fab variable fragments (scFvs), diabodies, minibodies, and other fragments), and altered immunostimulatory, safety, toxicity, and/or pharmacokinetic/pharmacodynamics properties, such as those containing modified Fc regions (e.g., through mutation or glycosylation). mAbs have been reengineered to permit site-specific conjugation of small molecules for improved delivery (e.g., ThioMABs) or to irreversibly bind to their cognate epitope (e.g., infinite affinity mAbs). mAbs have also been developed to improve the circulation and presentation of bioactive peptides and other biologics (e.g., CovX-bodies). Conjugation to various agents has allowed targeted immunotherapy and diagnostic methods. Hetero-multimeric scFvs and scFvs or mAbs fused to avidin have been developed for pre-targeted therapy and to improve the detection limits for tumor imaging.

[0005] Although mAbs can be effective and have advantages over small molecule approaches, existing antibodies and methods have various limitations. These can include adverse side effects resulting from off-target interactions, and/or collateral damage due to, among other things, long circulation times of antibody-drug conjugates. Additionally, while some antibodies are capable of binding to an epitope on a cell-surface antigen effectively, they may require internalization by the cell to produce a desired or intended result. Merely binding to the cognate antigen may not be sufficient to elicit a therapeutic response. Increasing the rate of internalization of a cell surface antigen could improve the efficacy of an antibody or antibody therapy. In view of these shortcomings, there is a need for improved antibodies and associated compounds, including those providing improved efficacy, synergy, specificity, and safety for both new and existing antibodies, and methods and uses of the same. Provided herein are antibodies, compounds and compositions including peptides and other molecules, and related methods that address such needs.

SUMMARY

[0006] In some embodiments, provided herein is a recombinant mediotope enabled antibody or antigen binding fragment thereof, containing a heavy chain containing a heavy chain variable (VH) region, a heavy chain constant region (CH) or portion thereof, and a light chain containing a light chain variable (VL) region, wherein each chain includes an amino terminus, a mediotope binding site, a linker including a carboxy terminus, a rigid, alpha helical segment, a first flexible, unstructured segment, and an amino terminus, wherein the carboxy terminus of the linker is coupled to the amino terminus of the heavy chain or the light chain, and a cyclic peptide, wherein the cyclic peptide is coupled to the amino terminus of the linker, and wherein the cyclic peptide does not bind to the mediotope binding site.

[0007] In some embodiments, the carboxy terminus of the linker and the cyclic peptide are separated by a distance of between 10-120 angstroms, including between about 10-100 angstroms and between about 10-80 angstroms. In some embodiments, the rigid, alpha helical segment of the linker includes the carboxy terminus of the linker. In some embodiments, the first flexible, unstructured segment of the linker includes the amino terminus of the linker.

[0008] In some embodiments, the amino terminus of the light chain or heavy chain is coupled to a carboxy terminus of the rigid, alpha helical segment of the linker, a carboxy

terminus of the first flexible, unstructured segment of the linker is coupled to an amino terminus of the rigid, alpha helical segment of the linker, and the cyclic peptide is coupled to an amino terminus of the first flexible, unstructured segment of the linker.

[0009] In some embodiments, the linker further includes a second flexible, unstructured segment. In some embodiments, the second flexible, unstructured segment of the linker includes the carboxy terminus of the linker. In some embodiments, the amino terminus of the light chain or heavy chain is coupled to a carboxy terminus of the second flexible, unstructured segment of the linker, a carboxy terminus of the rigid, alpha helical segment of the linker is coupled to an amino terminus of the second flexible, unstructured segment of the linker, a carboxy terminus of the first flexible, unstructured segment of the linker is coupled to an amino terminus of the rigid, alpha helical segment of the linker, and the cyclic peptide is coupled to an amino terminus of the linker.

[0010] In some embodiments, the rigid alpha helical segment includes a sequence selected from the group consisting of SEQ ID NOS: 266-274. In some embodiments, the first flexible, unstructured segment of the linker includes SEQ ID NO: 265. In some embodiments, the second flexible, unstructured segment of the linker includes SEQ ID NO: 265.

[0011] In some embodiments, the cyclic peptide is capable of binding to a mediotope binding site of a second mediotope enabled antibody. In some embodiments, the cyclic peptide includes a mediotope. In some embodiments, the mediotope includes a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

5 X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X11 is Lys; and

10 X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

[0012] In some embodiments, the mediotope includes an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, and 207, or a cyclic peptide derived therefrom.

15 **[0013]** In some embodiments of the recombinant mediotope enabled antibody or antigen binding fragment thereof, the heavy chain variable (VH) region includes an amino acid sequence selected from the group consisting of SEQ ID NO: 260-261, the light chain variable (VL) region includes an amino acid sequence selected from the group consisting of SEQ ID NO: 258-259, the rigid, alpha helical segment includes an amino acid sequence selected from the group consisting of SEQ ID NO: 266-274, the first flexible, unstructured segment
20 includes an amino acid sequence of SEQ ID NO: 265, and the cyclic peptide includes an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide
25 derived therefrom.

[0014] In some embodiments, provided herein is a recombinant mediotope enabled antibody or antigen binding fragment thereof including a heavy chain including the amino acid sequence of SEQ ID NO: 255, 256, 277, 278, 279, 280, or 282.

30 **[0015]** In some embodiments, the mediotope enabled antibody or antigen binding fragment specifically binds to a cell surface antigen. In some embodiments, the mediotope enabled antibody or antigen binding fragment specifically binds to an antigen expressed by a disease

or condition of a cell or tissue thereof. In some embodiments, the disease or condition is a cancer.

[0016] In some embodiments, the mediotope enabled antibody or antigen binding fragment competes for antigen binding with, or binds to the same epitope as an antibody or antigen-binding fragment thereof selected from the group consisting of abagovomab, abciximab, 5 adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, 10 eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, fontolizumab, gemtuzumab, lintuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, 15 ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab, anrakinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab, mavrilimumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, and urelumab; or the mediotope-enabled antibody or fragment specifically binds to an antigen selected from the 20 group consisting of: CA-125, glycoprotein (GP) IIb/IIIa receptor, TNF-alpha, CD52, TAG-72, Carcinoembryonic antigen (CEA), interleukin-6 receptor (IL-6R), IL-2, interleukin-2 receptor a-chain (CD25), CD22, B-cell activating factor, interleukin-5 receptor (CD125), VEGF, VEGF-A, CD30, IL-1beta, prostate specific membrane antigen (PSMA), CD3, EpCAM, EGF receptor (EGFR), MUC1, human interleukin-2 receptor, Tac, RANK ligand, 25 C5 or other complement proteins, CD11a, alpha-v beta-3 integrin, HER2, neu, CD15, CD20, Interferon gamma, CD33, CA-IX, CTLA-4, IL-5, CD3 epsilon, CAM, Alpha-4-integrin, IgE, IgE Fc region, an RSV antigen, F (or fusion) protein of respiratory syncytial virus (RSV), NCA-90 (granulocyte cell antigen), IL-6, GD2, GD3, IL-12, IL-23, IL-17, CTAA16.88, beta-amyloid, IGF-1 receptor (IGF-1R), delta-like ligand 4 (DLL4), alpha subunit of granulocyte 30 macrophage colony stimulating factor receptor, hepatocyte growth factor, IFN-alpha, nerve growth factor, IL-13, CD326, CD19, PD-L1, CD47, and CD137.

[0017] In some embodiments, the meditope enabled antibody or antigen binding fragment is coupled to a therapeutic agent or diagnostic agent.

[0018] In some embodiments, the cyclic peptide is coupled to a therapeutic agent or diagnostic agent. In some embodiments, the therapeutic agent is selected from the group consisting of a chemotherapeutic agent, a therapeutic antibody, a toxin, a radioactive isotope, an enzyme, a chelator, a boron compound, a photoactive agent, a dye, a metal, a metal alloy, and a nanoparticle; or the diagnostic agent is an imaging agent selected from the group consisting of a fluorescent substance, a luminescent substance, a dye, and a radioactive isotope.

[0019] In some embodiments, provided herein is a method of crosslinking a first meditope enabled antibody or antigen binding fragment thereof and a second meditope enabled antibody or antigen binding fragment thereof, wherein the second meditope enabled antibody is any of the recombinant meditope enabled antibodies as described herein, the method including contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment thereof with a meditope of the second meditope enabled antibody, thereby resulting in crosslinking of the first and second meditope-enabled antibodies.

[0020] In some embodiments, provided herein is a method for altering the distribution of a cell surface antigen, including contacting a cell including a cell surface antigen with a plurality of any of the recombinant meditope enabled antibodies or antigen binding fragments as described herein, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of binding to the cell surface antigen, and contacting a meditope binding site of a first meditope enabled antibody or antigen binding fragment thereof of the plurality of meditope enabled antibodies with a meditope from a second meditope enabled antibody from the plurality of meditope enabled antibodies, resulting in crosslinking of the first and second meditope-enabled antibodies, whereby crosslinking the first and second meditope enabled antibodies alters the distribution of the cell surface antigen.

[0021] In some embodiments, provided herein is a method for increasing co-localization of a cell surface antigen or cell surface receptor, including contacting a cell including a cell surface antigen with a plurality of any of the recombinant meditope enabled antibodies or antigen binding fragments provided herein, wherein the recombinant meditope enabled

antibodies or antigen binding fragments are capable of binding to the cell surface antigen, and contacting a mediotope binding site of a first mediotope enabled antibody or antigen binding fragment thereof of the plurality of mediotope enabled antibodies with a mediotope from a second mediotope enabled antibody from the plurality of mediotope enabled antibodies, resulting in crosslinking of the first and second mediotope-enabled antibodies, whereby crosslinking the first and second mediotope enabled antibodies increases the co-localization of the cell surface antigen or receptor.

[0022] In some embodiments, provided herein is a method for increasing cellular internalization of a mediotope enabled antibody, including contacting a cell including a cell surface antigen with a plurality of any of the recombinant mediotope enabled antibodies or antigen binding fragments provided herein, wherein the recombinant mediotope enabled antibodies or antigen binding fragments are capable of binding to the cell surface antigen, and contacting a mediotope binding site of a first mediotope enabled antibody or antigen binding fragment thereof of the plurality of mediotope enabled antibodies with a mediotope from a second mediotope enabled antibody from the plurality of mediotope enabled antibodies, resulting in crosslinking of the first and second mediotope-enabled antibodies, whereby crosslinking the first and second mediotope enabled antibodies increases cellular internalization of the first and second mediotope enabled antibodies bound to the cell surface antigen.

[0023] In some embodiments, provided herein is a method for increasing cellular internalization of a cell surface antigen, including contacting a cell including a cell surface antigen with a plurality of any of the recombinant mediotope enabled antibodies or antigen binding fragments provided herein, wherein the recombinant mediotope enabled antibodies or antigen binding fragments are capable of binding to the cell surface antigen; and contacting a mediotope binding site of a first mediotope enabled antibody or antigen binding fragment thereof of the plurality of mediotope enabled antibodies with a mediotope from a second mediotope enabled antibody from the plurality of mediotope enabled antibodies, resulting in crosslinking of the first and second mediotope-enabled antibodies, whereby crosslinking of the first and second mediotope enabled antibodies increases cellular internalization of the first and second cell surface antigen.

[0024] In some embodiments, provided herein is a method of increasing the efficacy of an antibody therapy, including administering to a subject in need thereof an effective amount

of a plurality of any of the recombinant meditope enabled antibodies or antigen binding fragments provided herein, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of binding to a cell surface antigen, contacting a cell including the cell surface antigen with a first recombinant meditope enabled antibody or fragment of the plurality of recombinant meditope enabled antibodies or antigen binding fragments, contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment with a meditope from a second meditope enabled antibody of the plurality of recombinant meditope enabled antibodies, resulting in crosslinking of the first and second meditope-enabled antibodies, whereby crosslinking the first and second antibodies increases the efficacy of the antibody therapy.

[0025] In some embodiments, provided herein is a method of decreasing a dosage of an antibody therapy needed to achieve a desired therapeutic effect in a subject including administering to a subject in need thereof an effective amount of a plurality of any of the recombinant meditope enabled antibodies or antigen binding fragments provided herein, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of binding to a cell surface antigen, contacting a cell including the cell surface antigen with a first recombinant meditope enabled antibody or fragment of the plurality of recombinant meditope enabled antibodies or antigen binding fragments, contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment with a meditope from a second meditope enabled antibody of the plurality of recombinant meditope enabled antibodies, resulting in crosslinking of the first and second antibodies, whereby crosslinking the first and second antibodies decreases the dosage of the antibody therapy needed to achieve the desired therapeutic effect in a subject.

[0026] In some embodiments, the first and second meditope enabled antibodies are the same or different. In some embodiments, at least one of the first or second meditope enabled antibodies or antigen-binding fragments specifically bind to an antigen expressed by a disease or condition of a cell or tissue thereof. In some embodiments, the disease or condition is a cancer. In some embodiments, the cell surface antigen is a receptor capable of receptor-mediated endocytosis.

[0027] In some embodiments, the cell surface antigen includes a plurality of cell surface antigens. In some embodiments, a first cell surface antigen of the plurality of cell surface antigens is different than a second cell surface antigen of the plurality of cell surface antigens,

and the first recombinant meditope enabled antibody specifically binds to the first cell surface antigen and the second recombinant meditope enabled antibody specifically binds to the second cell surface antigen. In some embodiments, a first cell surface molecule includes the first cell surface antigen and the second cell surface antigen. In some embodiments, a first
5 cell surface molecule includes the first cell surface antigen and a second cell surface molecule includes the second cell surface antigen.

[0028] In some embodiments, the method includes contacting a meditope binding site of the second meditope enabled antibody or fragment with a meditope of a third meditope enabled antibody or fragment, wherein the third meditope enabled antibody or fragment is
10 any of the recombinant meditope enabled antibodies or fragments thereof provided herein, thereby resulting in crosslinking of the second and third meditope-enabled antibodies.

[0029] In some embodiments, provided herein is a method of inhibiting the crosslinking of a first meditope enabled antibody or antigen binding fragment thereof and a second meditope enabled antibody or antigen binding fragment thereof, wherein the second meditope enabled antibody is one of any of the recombinant meditope enabled antibodies or fragments ,
15 the method including contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment thereof with a free meditope, thereby inhibiting a meditope of the second meditope enabled antibody from contacting the meditope binding site of the first meditope enabled antibody, resulting in inhibiting the crosslinking of the first and
20 second meditope-enabled antibodies.

[0030] In some embodiments, provided herein is a method of reducing the crosslinking of a first meditope enabled antibody or antigen binding fragment thereof and a second meditope enabled antibody or antigen binding fragment thereof, wherein the second meditope enabled antibody is one of any of the recombinant meditope enabled antibodies or antigen binding
25 fragments thereof described herein, the method including contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment thereof with a free meditope, thereby reducing the ability of a meditope of the second meditope enabled antibody to contact the meditope binding site of the first meditope enabled antibody, resulting in reducing the crosslinking of the first and second meditope-enabled antibodies.

[0031] In some embodiments, provided herein is a method of disrupting the crosslinking of a first meditope enabled antibody or antigen binding fragment thereof and a second

meditope enabled antibody or antigen binding fragment thereof, wherein the second meditope enabled antibody is one of any of the recombinant meditope enabled antibodies or antigen binding fragments thereof described herein, the method including contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment thereof with a free meditope, thereby displacing a meditope of the second meditope enabled antibody from the meditope binding site of the first meditope enabled antibody, resulting in disrupting the crosslinking of the first and second meditope-enabled antibodies.

[0032] In some embodiments, provided herein is a method of reversing the crosslinking of a first meditope enabled antibody or antigen binding fragment thereof and a second meditope enabled antibody or antigen binding fragment thereof, wherein the second meditope enabled antibody is one of any of the recombinant meditope enabled antibodies or antigen binding fragments described herein, the method including contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment thereof with a free meditope, thereby displacing a meditope of the second meditope enabled antibody from the meditope binding site of the first meditope enabled antibody, resulting in reversing the crosslinking of the first and second meditope-enabled antibodies.

[0033] In some embodiments, provided herein is a method of treatment, including administering an effective amount of any of the recombinant meditope enabled antibodies or antigen binding fragments described herein to a subject having a disease or condition. In some embodiments, the disease or condition is cancer. In some embodiments, the method further includes administering a chemotherapeutic agent to the subject.

[0034] In some embodiments, provided herein is a use of any of the recombinant meditope enabled antibodies or antigen binding fragments thereof provided herein in the manufacture of a medicament for the treatment of a disease or condition. In some embodiments, provided herein is a use of a combination of any of the antibody drug conjugates described herein and a chemotherapeutic agent in the manufacture of a medicament for the treatment a disease or condition. In some embodiments, the disease or condition is cancer.

[0035] In some embodiments, a method of reducing the effects of a meditope-enabled self-crosslinking antibody on a subject who has been administered the antibody includes

administering free meditope to the subject. In some embodiments, the free meditope includes a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

- 5 X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;
- X2 is Gln or null;
- X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;
- 10 X4 is Asp or Asn;
- X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;
- X6 is Ser or Cys;
- X7 is Thr, Ser or Cys;
- 15 X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;
- X9 is Arg or Ala;
- X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-
- 20 containing residue;
- X11 is Lys; and
- X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

[0036] In some embodiments, the free meditope includes an amino acid sequence
 25 selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom.

[0037] In some embodiments, the method includes administering free meditope to the subject a plurality of times, optionally 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times.

30 **[0038]** In some embodiments, the half-life of the free meditope is the same or about the same as the half-life of the meditope-enabled self-crosslinking antibody. In some embodiments, the half-life of the free meditope is longer than the half-life of the meditope-

enabled self-crosslinking antibody. In some embodiments, the half-life of the free mediotope is shorter than the half-life of the mediotope-enabled self-crosslinking antibody.

[0039] In some embodiments, provided herein is a method of temporally controlling the effects of a mediotope-enabled self-crosslinking antibody including administering a mediotope-enabled self-crosslinking antibody to a subject in need thereof, administering one or more free mediotopes to the subject, wherein the free mediotope binds to a mediotope binding site on the mediotope-enabled self-crosslinking antibody, thereby reducing the ability of the antibody to self-crosslink.

[0040] In some embodiments, the step of administering one or more free mediotopes to the subject occurs after the step of administering the mediotope-enabled self-crosslinking antibody. In some embodiments, the method further includes administering one or more free mediotopes a plurality of times. In some embodiments, the administering one or more free mediotopes a plurality of times takes place over a period of minutes, hours, days, months, or years. In some embodiments, the half-life of the one or more free mediotopes is shorter than the half-life of the mediotope-enabled self-crosslinking antibody.

[0041] In some embodiments, the method further includes cessation of the administration of one or more free mediotopes, thereby restoring the ability of the antibody to self-crosslink as the levels of free mediotopes decrease. In some embodiments, the method further includes the restoration of the administration of one or more free mediotopes one or more times, wherein the free mediotope binds to a mediotope binding site on the mediotope-enabled self-crosslinking antibody, thereby reducing the ability of the antibody to self-crosslink.

[0042] In some embodiments, provided herein is a nucleic acid molecule including a sequence of nucleotides encoding a recombinant mediotope enabled antibody or antigen binding fragment thereof provided herein. In some embodiments, the nucleic acid further includes a sequence of nucleotides encoding a free mediotope. In some embodiments, the free mediotope includes a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

5 X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

10 X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

15 X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

[0043] In some embodiments, the free meditope includes an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 20 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom. In some embodiments, the free meditope encoded by the nucleic acid molecule is capable of binding to the meditope binding site on the recombinant meditope enabled antibody or antigen binding fragment thereof encoded by the nucleic acid molecule.

25 [0044] In some embodiments, the nucleic acid further includes at least one promoter operatively linked to control expression of the recombinant meditope enabled antibody or antigen binding fragment thereof. In some embodiments, the nucleic acid further includes at least one promoter operatively linked to control expression of the recombinant meditope enabled antibody or antigen binding fragment thereof and the free meditope. In some 30 embodiments, the sequence of nucleotides encoding the recombinant meditope enabled antibody or antigen binding fragment thereof and the sequence of nucleotides encoding the free meditope are separated by an internal ribosome entry site (IRES), a sequence of

nucleotides encoding a self-cleaving peptide, or a sequence of nucleotides encoding a peptide that causes ribosome skipping, optionally a T2A peptide. In some embodiments, the sequence of nucleotides encoding the recombinant meditope enabled antibody or antigen binding fragment thereof is operatively linked to a first promoter and the sequence of
5 nucleotides encoding the free meditope is operatively linked to a second promoter, wherein the first and second promoter can be the same or different.

[0045] In some embodiments, at least one of the one or more promoters is a conditional promoter. In some embodiments, the conditional promoter is an inducible promoter. In some
10 embodiments, the conditional promoter includes a Lac operator sequence, a tetracycline operator sequence, a galactose operator sequence or a doxycycline operator sequence, or is an analog thereof. In some embodiments, the conditional promoter is a repressible promoter. In some embodiments, the conditional promoter includes a Lac repressor or a tetracycline repressor, or is an analog thereof. In some embodiments, at least one of the one or more
15 promoters is selected from the group consisting of CMV, RSV, PGK, EF1 α , NSE, SV40, UBC, CAGG, synapsin, β -actin, and GFAP.

[0046] In some embodiments, provided herein is a vector including any of the nucleic acid molecules provided herein. In some embodiments, the vector is a pCEP4 vector, a viral vector, a retroviral vector, a lentiviral vector, or a gamma retroviral vector.

[0047] In some embodiments, provided herein is a cell including any of the nucleic acid
20 molecules or vectors provided herein. In some embodiments, provided herein is a cell including a first nucleic acid or vector including a sequence of nucleotides encoding any of the recombinant meditope enabled antibodies or antigen binding fragments thereof provided herein and a second nucleic acid or vector including a sequence of nucleotides encoding a free meditope.

[0048] In some embodiments, the free meditope includes a peptide having the formula:
X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)
wherein:
X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;
X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

5 X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

10 X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

15 X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

[0049] In some embodiments, the free meditope includes an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24,
20 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom.

[0050] In some embodiments, the first vector further includes a first promoter operatively linked to control expression of the recombinant meditope enabled antibody or antigen binding fragment thereof and the second vector further includes a second promoter operatively linked
25 to control expression of the free meditope, wherein the first promoter and second promoter can be the same or different. In some embodiments, at least one of the first promoter or the second promoter is a conditional promoter.

[0051] In some embodiments, the cell is a eukaryotic cell. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a CHO cell, a HEK-293 cell, or a
30 293T cell.

[0052] In some embodiments, provided herein is a method of making a meditope-enabled self-crosslinking antibody or antigen binding fragment thereof, the method including culturing a host cell under conditions suitable for expression of the sequence of nucleotides encoding the recombinant meditope-enabled antibody or antigen binding fragment thereof; and isolating the antibody or antigen binding fragment thereof.

[0053] In some embodiments, provided herein is a method of making a meditope-enabled self-crosslinking antibody or antigen binding fragment thereof, the method including culturing a host cell under conditions suitable for expression of both the sequence of nucleotides encoding the recombinant meditope-enabled antibody or antigen binding fragment thereof and the sequence of nucleotides encoding the free meditope; and isolating the antibody or antigen binding fragment thereof and free meditope.

[0054] In some embodiments, the antigen binding fragment is a Fab, Fab', Fv, scFv, or F(ab')₂ fragment.

[0055] In some embodiments, the method further includes conjugating a drug to the antibody or antigen binding fragment thereof.

[0056] In some embodiments, provided herein is an antibody or antigen binding fragment thereof produced by any of the methods provided herein. In some embodiments, provided herein is an antibody drug conjugate produced by any of the methods provided herein.

[0057] In some embodiments, provided herein is a composition including a plurality of any of the recombinant meditope enabled antibodies or antigen binding fragments thereof provided herein, or encoded by any of the nucleic acids provided herein, or expressed by the any of the vectors provided herein, expressed by any of the cells provided herein, or produced by any of the methods provided herein.

[0058] In some embodiments, the composition further includes a plurality of free meditoes.

[0059] In some embodiments, the free meditope includes the free meditope encoded by any of the nucleic acids provided herein, expressed by any of the vectors provided herein, expressed by any of the cells provided herein, or produced by the any of the methods provided herein.

[0060] In some embodiments, the free meditope includes a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

5 X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

10 X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

15 X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

20 X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

[0061] In some embodiments, the free meditope includes an amino acid sequence

selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24,
25 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50,
51, 52, 53, 54, 55, 186, 187, 188, 189, and 207, or a cyclic peptide derived therefrom.

[0062] In some embodiments, the ratio of the recombinant meditope enabled antibody or antigen binding fragment thereof to the free meditope is between 1:1 and 1:1,000 including about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:10, 1:15, 1:20, 1:25, 1:50, 1:75, 1:100, 1:150, 1:200,
30 1:250, 1:300, 1:400, 1:500, and 1:750.

[0063] In some embodiments, the free meditope binds the meditope binding site of a recombinant meditope enabled antibody or antigen binding fragment thereof of the plurality

of recombinant meditope enabled antibodies with a dissociation constant of less than at or about 10 μ M, less than at or about 5 μ M, or less than at or about 2 μ M, less than at or about 1 μ M, less than at or about 500, 400, 300, 200, 100 nM, or 200 picomolar or less..

[0064] In some embodiments, the plurality of recombinant meditope enabled antibodies or antigen binding fragments thereof includes a first and second recombinant meditope enabled antibodies or antigen binding fragments thereof, and the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is greater than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof.

[0065] In some embodiments, the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is between 2X and 1,000,000X greater than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof.

[0066] In some embodiments, the plurality of recombinant meditope enabled antibodies or antigen binding fragments thereof includes a first and second recombinant meditope enabled antibodies or antigen binding fragments thereof; and the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is less than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof.

[0067] In some embodiments, the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is between 2X and 1,000,000X less than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof.

[0068] In some embodiments, the plurality of recombinant meditope enabled antibodies or antigen binding fragments thereof includes a first and second recombinant meditope enabled antibodies or antigen binding fragments thereof, and the cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof binds the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof with dissociation constant of less than at or about 10 μ M, less than at or about 5 μ M, or less than at or about 2 μ M, less than at or about 1 μ M, less than at or about 500, 400, 300, 200, 100 nM, 200 picomolar or less.

[0069] In some embodiments, the composition has a pH of between 1 and 7.35 or between 7.45 and 13. In some embodiments, the plurality of recombinant meditope enabled antibodies or antigen binding fragments thereof includes a first recombinant meditope enabled antibody or antigen binding fragment thereof and a second recombinant meditope enabled antibody or antigen binding fragment thereof, wherein the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof is higher at a physiological pH than it is at a non-physiological pH.

[0070] In some embodiments, the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is lower at a physiological pH than it is at a non-physiological pH. In some embodiments, the physiological pH is the pH at a cell or a tissue of a disease or a condition.

[0071] In some embodiments, provided herein is a pharmaceutical composition including a pharmaceutically acceptable carrier and any of the recombinant meditope enabled antibodies or antigen binding fragment thereof described herein, encoded by any of the nucleic acids or vectors described herein, expressed by any of the cells provided herein, produced by the any of the methods provided herein, or any of the compositions provided herein. In some embodiments, the pharmaceutical composition is in human unit dose form.

Brief Description of the Drawings

[0072] Fig. 1 shows a modified Arg8 residue that may be used to optimize meditope binding parameters, and may be used in accordance with the embodiments described herein

(R = alkyl, substituted alkyl, aromatic or NHR''', where R''' = alkyl, substituted alkyl, or aromatic).

[0073] Fig. 2 shows the chemical structure of a meditope according to some embodiments. The circles indicate positions that can be modified, e.g., to improve meditope affinity for the Fab. The boxes indicate cyclization strategies. 'Click' chemistry and olefin metathesis, top and bottom far right boxes, respectively, are additional routes to cyclize the meditope.

[0074] Fig. 3 shows a procedure for conjugation of a meditope variant with fluorescein for FACS analysis. The figure illustrates the synthesis of dimeric and trimeric meditopes according to some embodiments, for meditopes containing lactam linkages. Sequence legend: (GQFDLSTRRLKG) SEQ ID NO:173; (GKLRRTSLDFQG) SEQ ID NO:174.

[0075] Fig. 4A shows meditope peptides binding to framework loops of cetuximab. The complex of cetuximab Fab (light chain is denoted by VL and CL; heavy chain is denoted by VH and CH) and cyclic CQFDLSTRRLKC (depicted within the shaded area and labeled with the word "meditope") (SEQ ID NO: 1) indicates that the meditope binds to an interface of the Fab framework, which is distinct from the CDR loops of cetuximab.

[0076] Fig. 4B (top) shows the stick representation of the cQFD meditope and (bottom) the stick representation of the cQYN meditope. The N- and C- terminal cysteines are solvent exposed and display high thermal factors.

[0077] Fig. 5 illustrate that the cQFD and cQYN meditopes do not bind to the CDRs of cetuximab, as was previously hypothesized. The figure shows an overlay of two crystal structures, one of a cetuximab Fab and its epitope, EGFR domain III, the other showing the cQFD meditope and cetuximab Fab, in which the cQFD meditope binds to the central cavity of the cetuximab Fab. The antigen, EGFR domain III, binds at the complementarity determining regions at a significant distance from the meditope binding site.

[0078] Fig. 6 shows an scFv-meditope linker. scFvs are created by fusing the light chain variable domain to the heavy chain variable domain (or vice versa) through a 12-20 amino acid linker (typically {GGGS}3-5). In this example, a portion of the flexible linker sequence can be replaced with the meditope sequence.

[0079] Fig. 7A shows CD-33 expressing cells stained for fluorescence microscopy with pHrodo™-labeled SnAP-body variant 1, SnAP-body variant 2, or control antibody to determine receptor-mediated antibody endocytosis rates.

[0080] Fig. 7B shows the average amount antibody internalization as calculated by the amount of fluorescence detected in each cell stained with pHrodo™-labeled SnAP-body variant 1, SnAP-body variant 2, or control antibody and imaged using a confocal microscope. Higher values indicate increased receptor-mediated antibody endocytosis rates.

[0081] Fig. 8 shows histogram plots of CD33 expressing cells stained with pHrodo™-labeled SnAP-body variant 1, SnAP-body variant 2, or control antibody. Higher values and peaks indicate increased receptor-mediated antibody endocytosis rates.

[0082] Figs. 9A-9D show size exclusion chromatographs of self-crosslinking antibody monomers, dimers, and trimers. Fig. 9A shows results for the antibody control. Fig. 9B shows results for SnAP-body variant 1. Fig. 9C shows results for SnAP-body variant 2. Fig. 9D shows results for SnAP-body variant 3.

[0083] Fig. 10 shows self-crosslinking antibody monomers, dimers, trimers, and tetramers as depicted in a silver-stained native electrophoresis gel. A control antibody, SnAP-body variant 1, and SnAP-body variant 2 were run at both 100nM and 1nM concentrations.

[0084] Fig. 11 shows self-crosslinking antibody monomers, dimers, trimers, and tetramers as depicted in a silver-stained native electrophoresis gel. A control antibody, SnAP-body variant 1, SnAP-body variant 2, and SnAP-body variant 3 were run at both 100nM with and without the addition of 1μM cQFD meditope peptide (SEQ ID NO: 1). The results show that self-crosslinking can be modulated by meditope peptide.

[0085] Fig. 12 shows tumor growth reduction in a SK-OV-3-Luc ovarian xenograft mice model treated with SnAP-bodies.

[0086] Fig. 13 shows that no adverse effects were observed for the tested agents including the SnAP-bodies.

DETAILED DESCRIPTION

[0087] Provided herein are self-crosslinking recombinant meditope enabled antibodies or antigen binding fragments thereof comprising a linker and a meditope. The linkers of the invention are attached to the meditope and to the antibody or antigen binding fragment at an position on the antibody or antigen binding fragment thereof that permits the meditope-linker to facilitate the interaction or cross-linking of meditope enabled antibodies or antigen binding fragments thereof while not allowing for the meditope to bind to a meditope binding site present in the antibody to which the meditope-linker is attached. Self cross-linking antibodies or fragments thereof can form complexes with other meditope enabled antibodies via the linkers and meditoes. In one embodiment, the meditope enabled antibodies or antigen binding fragments thereof bind to one or more epitopes present on the surface of a cell. The ability of the described self-crosslinking antibodies or antigen binding fragments thereof to form complexes permits these antibodies or antigen binding fragments to alter the distribution of a cell surface antigen to which the plurality of antibodies or antigen binding fragments thereof bind. Complex formation through the interaction of the self-crosslinking antibodies and their cognate epitopes on the target antigen can increase or promote clustering or co-localization of a cell surface antigen on a cell, which can increase or promote internalization of the complex. In turn, the increased internalization can be used to clear or reduce the concentration of a cell surface antigen from the surface of a target cell and to increase the rate of internalization of the complex into the target cell. Increasing internalization rates can increase the efficacy of certain therapies, or reduce the amount of drug necessary to achieve a particular therapeutic effect. Methods of increasing or promoting clustering of a cell surface antigen can include administering to the cell one or more self-crosslinking antibodies that specifically bind to a cell-surface antigen, thereby promoting clustering of the cell-surface antigen on the surface of the target cell. In certain embodiments, the self-crosslinking antibodies are conjugated to one or more agents.

I. SELF-CROSSLINKING ANTIBODIES

[0088] Self-crosslinking meditope enabled antibodies or antigen binding fragments thereof comprise a linker, a meditope, and a meditope enabled antibody or antigen binding fragment thereof. The linker comprises a rigid segment and a flexible segment and is adapted to bind to a meditope.

[0089] The linkers described herein are designed such that the mediotopes attached thereto generally do not bind to a mediotope binding site contained within the same antibody, but bind preferentially to mediotope binding sites on other mediotope enabled antibodies or antigen binding fragments thereof. Typically the linkers are constructed repeating units, such as amino acids, that when assembled permit the linker to contain different structural features. For example, in some embodiments, the linker comprises a rigid segment with a limited or reduced range of motion. In some embodiments, this rigidity can prevent or reduce a mediotope fused to the mediotope-enabled antibody from binding to a mediotope binding site on the same antibody or antigen binding fragment thereof.

[0090] In some embodiments, the linker comprises a flexible and/or unstructured segment. In some embodiments, the flexible and/or unstructured segment allows the linker to bend and/or rotate, thus allowing the mediotope to bind to the mediotope binding site of another antibody.

[0091] In some embodiments, when the linker is a peptide, the rigid segment typically comprises an amino acid sequence that produces a peptide with sufficient rigidity to limit the ability of the region to bend and/or rotate. In one embodiment, the rigid segment comprises an amino acid sequence that produces a peptide with an alpha helical structure. In another embodiment, the flexible and/or unstructured segment comprises an amino acid sequence that produces a peptide with sufficient flexibility to allow the flexible region to bend and/or rotate to allow the mediotope sufficient flexibility to bind to mediotope binding site.

A. Linkers

[0092] Provided herein are linkers as a component of the disclosed self-crosslinking mediotope enabled antibodies or antigen binding fragments. The term “linker” as used herein refers to a structure by which a mediotope is linked or connected to an antibody or antigen binding fragment thereof, including mediotope enabled antibodies or antigen binding fragments thereof. The linker may be any structure suitable to link and separate the mediotope from the antibody. Exemplary linkers may include one or more natural or unnatural amino acids which may be used to form a peptide, in some embodiments having a modified peptide backbone, a small chemical scaffold, a biotin-streptavidin, an organic or inorganic nanoparticle, a polynucleotide sequence, peptide-nucleic acids, or an organic polymer.

[0093] The linker may be attached to any portion of mediotope enabled antibody or antigen binding fragment thereof. In one embodiment, the linker is attached to the amino terminus of the heavy chain or light chain of a mediotope enabled antibody or antigen binding fragment thereof. In some embodiments, a linker with a mediotope is attached to each heavy chain or each light chain of the self-crosslinking antibody or fragment. In some embodiments, a linker with a mediotope is attached to one or more or all of the heavy chains and light chains of the self-crosslinking antibody. The linker can be attached to the antibody via a covalent and/or noncovalent bond.

1. Linker Structure

[0094] The linker can include various sequences or other structural features that provide various functions or properties. For example, it may be advantageous in some embodiments to reduce or inhibit the ability of a mediotope at one end of the linker to bind a mediotope binding site on the same mediotope enabled antibody or antigen binding fragment thereof. In some embodiments, the linker may comprise one or more segments that are rigid, structured, ordered, or relatively rigid, structured, or ordered in some embodiments. As an exemplary advantage, a rigid segment can reduce the ability of the linker to bend or move, thereby reducing the ability of the linker to curve, turn, or fold in a manner that allows the mediotope at one end of the linker to contact a mediotope binding site on the same or different mediotope enabled antibody or antigen binding fragment thereof.

[0095] In a preferred embodiment, the linker has sufficient rigidity to prevent mediotope binding to the mediotope binding site on the same side (e.g. ipsilateral) or the opposite side (e.g. contralateral) of the mediotope enabled antibody or antigen binding fragment thereof. This reduction in mediotope self-binding can enhance the self-crosslinking antibody's ability to bind other mediotope enabled antibodies, for example by freeing up its mediotope binding sites to bind mediotopes linked to other mediotope enabled antibodies or antigen binding fragments thereof.

[0096] The rigid, structured segment of the linker can comprise any peptide sequence or compound that reduces the ability of the linker to curve, turn, or fold in a manner that allows the mediotope at one end of the linker to contact a mediotope binding site on the same or other Fab region of the antibody. In some embodiments, the rigid, structured segment comprises a peptide. In some embodiments, the linker can contain one or more structural elements that comprise a rigid, alpha helical segment, region, domain, or peptide, which can include a

sequence of amino acid residues which is prone to forming an alpha helix. In some embodiments, these sequences can include Met, Ala, Leu, Lys, Gln, Arg, Glu, Ser, and Pro amino acids, which may play a role in promoting alpha helical structures.

[0097] In some embodiments, hydrophobic residues can increase the interactions between different segments or domains of a protein. Hydrophobic residues include Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, and Trp. Thus, in some embodiments, a rigid segment of the linker does not include, or includes a reduced number of, hydrophobic residues in order to reduce the interactions between the linker segments and/or between the linker and the mediotope or antibody. In some embodiments, it may be advantageous for a rigid segment of the linker to include hydrophobic residues in order to increase the interactions between a plurality of alpha helices that comprise a rigid segment of a linker. Examples of rigid segments comprising a plurality of alpha helices include the four helix bundle 1FHA (SEQ ID NO: 272) and myoglobin 3RGK (SEQ ID NO: 273).

[0098] In some embodiments, the rigid, structured segment comprises a plurality of alpha helical segments, regions, domains, or peptides, including two, three, four, five, six, seven, eight, or more alpha helical segments. In some embodiments, the plurality of alpha helical segments are connected via turns, loops, and/or hairpins. Exemplary turns include one or more α -turns, β -turns, γ -turns, δ -turns, and π -turns. Hairpins include beta hairpins. Such turns, loops, and hairpins may allow folding between the plurality of rigid alpha helical segments. Folding can allow for the interaction between the alpha helical domains, and such interaction can enhance the rigidity of the rigid segment. In some embodiments, a rigid, structured segment comprises a 3_{10} -helix or a π -helix, including, for example, at the carboxy or amino terminus of an alpha helix.

[0099] It may be advantageous in some embodiments to increase the ability of a mediotope connected to an antibody via the linker to bind a mediotope binding site of another mediotope enabled antibody. Thus, in some embodiments, the linker includes structural features that enhance such binding. For example, in some embodiments, the linker optionally includes one or more segments that are unstructured, flexible, disordered, or relatively unstructured, flexible, or disordered. As an exemplary advantage, a flexible or disordered segment can increase the ability of the linker or a portion of the linker to bend or move, thereby increasing the ability of the linker to curve, turn, or fold in a manner that allows the mediotope at one end

of the linker to contact and/or remain bound to a mediotope binding site on another mediotope enabled antibody.

[0100] In some aspects, flexible segments of the linker can be designed to behave like a denatured peptide sequence under physiological conditions, such as having a large conformational freedom of the peptide backbone. In some examples, these segments are essentially devoid of secondary structure, e.g., at physiological conditions or in aqueous solutions. In some embodiments, a flexible segment can comprise one or more glycine residues, including one or more consecutive glycine residues. Glycine residues can disrupt protein structure, including alpha helices. This disruption can be in part because of glycine's minimal side chain, which can allow for increased flexibility. Thus, in some embodiments, a flexible segment of the linker includes 1, 2, 3, 4, 5, 6, or more glycine residues, including 1, 2, 3, 4, 5, 6, or more consecutive glycine residues. In some embodiments, a flexible segment can comprise one or more glycine residues and one or more proline residues. In some embodiments, a flexible segment of the linker comprises the amino acid sequence of SEQ ID NO: 265.

[0101] In some aspects, the linker has one or more of the following properties: unstructured conformation, conformational flexibility, enhanced aqueous solubility, high degree of protease resistance, low immunogenicity, low binding to mammalian receptors, a defined degree of charge, and increased hydrodynamic (or Stokes) radii. In some embodiments, the linker is systematically or randomly designed to prevent or cause steric hindrance of antibody/epitope interactions, antibody/antibody interactions, or antibody/mediotop interactions. Example modifications include amino acid substitutions, additions, deletions, or modifications. In some embodiments, steric hindrance can prevent receptors from clustering, signaling, or from undergoing receptor-mediated endocytosis. In some embodiments, preventing steric hindrance can cause receptors to cluster, signal, or undergo receptor-mediated endocytosis.

[0102] Flexible segments can be used alone or can be combined with one or more rigid segments as described herein. For example, in some embodiments the linker is a compound having one or more chains (e.g., a polypeptide chain) having the formula:



where L^{1A} is a rigid, structured segment and L^{2A} is a flexible, unstructured segment of the linker.

[0103] In some embodiments the linker is a compound having one or more chains (e.g., a polypeptide chain) having the formula:



where L^{2A} is a flexible, unstructured segment and L^{1A} is a rigid, structured segment of the linker.

[0104] In some embodiments, the linker can include more than one flexible, unstructured segment. For example, in some embodiments the linker is a compound having one or more chains (e.g., a polypeptide chain) having the formula:



where L^{1A} is a rigid, structured segment and L^{2A} and L^{2B} are flexible, unstructured segments of the linker.

[0105] In some embodiments the linker is a compound having one or more chains (e.g., a polypeptide chain) having the formula:



where L^{1A} and L^{1B} are rigid, structured segments and L^{2A} is a flexible, unstructured segment of the linker. Exemplary rigid linker segments include, but are not limited to, the peptide sequences encoded by SEQ ID NOS: 266-274.

2. Linker and Segment Length

[0106] The length of the rigid and flexible segments of the linker should be of a sufficient length that is optimally long enough to allow the meditope attached to the linker to bind a meditope binding site on another antibody. It may also be advantageous to use a linker that is short enough to prevent or reduce the binding of the meditope to a meditope binding site on the same meditope enabled antibody or antigen binding fragment thereof. In some embodiments the length of the linker can be at least 10 Å. In some embodiments the length of the linker is at least 10 Å and preferable less than 80 Å.

[0107] The distance between the amino terminus of the heavy chain of one Fab region and the meditope binding site of the contralateral fab region in the same antibody in some embodiments is ~80 Å. This distance can vary depending on the sequence, structure, and flexibility of the antibody. In some embodiments, the carboxy terminus of the linker and the meditope are separated by a distance of between 10-80, 10-70, 15-60, 20-50, or 25-40 Å. In some embodiments, the carboxy terminus of the linker and an end of the meditope are

separated by a distance of between 10-80, 10-70, 15-60, 20-50, or 25-40 Å. In some embodiments, the length of a linker or linker segment can be varied by selecting an appropriate peptide sequence.

[0108] In some embodiments, the length of the linker can be determined by the number of amino acids that comprise the linker or linker segment. Alpha helical segments, described below, comprise a series of turns. Each turn of the helix can have a pitch of about 5.4 Å and comprises about 3.6 amino acid residues. Thus, the length of the linker can be adjusted by adding or removing amino acids. In some embodiments, the length of a linker or linker segment can be determined by the secondary or tertiary structure of the linker. As will be described below, in some embodiments the linker or segment comprises a peptide sequence that includes a plurality of folded alpha helices. In some embodiments, the length of the linker can be adjusted by modifying the secondary or tertiary structure of such peptides.

[0109] Controlling the position of the mediotope and its ability to bind to mediotope binding sites on other mediotope enabled antibodies can also be enhanced in some embodiments by varying the length of the linker, or by varying the distance between one end of the linker and another end of the linker. For example, in some embodiments, a length of the linker is less than the distance between the amino terminus of the antibody chain to which the linker is connected and the mediotope binding site on the same side of the mediotope enabled antibody or antigen binding fragment thereof to which the linker is bound. In some embodiments, a length of the linker is less than a distance between the amino terminus of the antibody chain to which the linker is connected and the mediotope binding site on the other side of the mediotope enabled antibody or antigen binding fragment thereof to which the linker is bound.

[0110] Controlling the position of the mediotope can also be enhanced in some embodiments by varying the length of the segments and composition of the linker. For example, in some embodiments, the length of the one or more rigid segments is longer than the length of the one or more flexible segments. This can reduce the likelihood that the mediotope will bind to a mediotope binding site on the same antibody by extending the mediotope away from the antibody Fab regions with a longer rigid region than flexible region.

[0111] The length of the linker can also alter the geometry of the clustering. For instance, it may be advantageous to bring two receptors in close proximity, potentially

leading to higher activity of the intracellular signaling molecules. Here, the linker between the antibody and mediotope can be approximately 10 Å or more. Alternatively, it may be advantageous to keep receptors at a distance. Here, rigid linkers and/or longer linkers between the antibody and mediotope can be used to “push” apart specific receptors.

5 **[0112]** In some aspects, the linker is designed to have a length that is the same or approximately the same as the distance between two receptors on a cell surface to be targeted. In some embodiments, the receptors can be the same or different. For example, the two receptors can comprise different amino acid sequences and/or different epitopes. In some contexts, two mAbs that recognize different epitopes on a single antigen act synergistically
10 (see Kamat, V. et al., *Cancer Biol Ther* 7, 726-733 (2008)). In some examples, self-crosslinking antibodies have the flexibility of being able to pair up with any mediotope enabled antibody. In some aspects, self-crosslinking antibody variants (e.g., generated by altering linker geometry) further enhance specificity and synergistic effects. Thus, in some examples, the length of the linker is designed to mimic or approximate the distance between a
15 self-crosslinking antibody bound to a cell surface antigen and the mediotope binding site of another antibody bound to a cell surface antigen.

[0113] A variety of methods have been established in the art to discern the presence or absence of secondary and tertiary structures in a given polypeptide. In particular, secondary structure can be measured spectrophotometrically, e.g., by circular dichroism spectroscopy in
20 the "far-UV" spectral region (190-250 nm). Secondary structure elements, such as alpha-helix and beta-sheet, each give rise to a characteristic shape and magnitude of CD spectra. Secondary structure can also be predicted for a polypeptide sequence via certain computer programs or algorithms, such as the well-known Chou-Fasman algorithm (Chou, P. Y., et al. (1974) *Biochemistry*, 13:222-45) and the Garnier-Osguthorpe-Robson ("GOR") algorithm
25 (Garnier J, Gibrat J F, Robson B. (1996), GOR method for predicting protein secondary structure from amino acid sequence. *Methods Enzymol* 266:540-553), as described in US Patent Application Publication No. 20030228309A1. For a given sequence, the algorithms can predict whether there exists some or no secondary structure at all, expressed as the total and/or percentage of residues of the sequence that form, for example, alpha-helices or beta-
30 sheets or the percentage of residues of the sequence predicted to result in random coil formation (which lacks secondary structure).

[0114] In one embodiment, the linker has an alpha-helix percentage ranging from 50% to more than about 95% as determined by the Chou-Fasman algorithm. In another embodiment, the linker has a beta-sheet percentage ranging from 0% to less than about 5% as determined by the Chou-Fasman algorithm. In some embodiments, the linker has an alpha-helix percentage ranging from 50% to more than about 95% and a beta-sheet percentage ranging from 0% to less than about 5% as determined by the Chou-Fasman algorithm. In some embodiments, the linker has an alpha helix percentage more than about 60%, more than about 65%, more than about 70%, more than about 75%, more than about 80%, more than about 85%, more than about 90%, or more than about 95% as determined by the Chou-Fasman algorithm. In some aspects, the linker is designed to avoid the presence of certain protease cleavage sites, such as sites for cleavage by serum protease(s) and/or to avoid immunogenicity.

[0115] Among the provided linkers are those having the amino acid sequence set forth as SEQ ID NO: 262, 263, and 264, or a modified variant thereof wherein any one, two, three, or four of the residues is optionally substituted with a conjugated amino acid, such as in place of a lysine residue.

3. Modifications

[0116] The linker can include various sequences or other structural features that provide various functions or properties to allow the linker to be derivatized. Exemplary structural elements include the presence or absence of a protease cleavage site, an immunogenic sequence, and residues, sites or tags including, for example aldehyde tags compatible with formylglycine-generating enzyme (FGE), lysines, tyrosines, glutamic acids, aspartic acids and unnatural amino acids, which can be used, for example in the conjugation of therapeutic or diagnostic agents.

[0117] In some aspects, the linkers of the provided compounds, such as a cleavage site for a protease present in the lysosomal compartment, e.g., MMP cleavage sites, ADAM cleavage sites, and/or cathepsin cleavage sites.

[0118] In some aspects, it contains no three contiguous amino acids that are identical unless the amino acids are serine or glycine or, has a subsequence score of less than 10, 9, 8, 7, 6, 5, 4, 3, or 2, or contains at least one residue other than glycine and serine. In some aspects, the linker does not contain a cleavage site for (or is not cleaved by) any serum

protease, or for one or more or any of: proteins of the blood coagulation pathway family, Factors XIIIa, XIIa, XIa, Xa, IXa, and VIIa, thrombin, plasma kallikrein, activated PC, Prothrombinase, hK1, PSA/hK3, hK10, hK15, activated protein C (APC), Hageman factor (Coagulation factor XII), Factor Xa, ADAMTS13, von Willebrand factor-cleaving protease (VWFCP),
5 protease nexin 2, Plasmin, Trypsin, α -chymotrypsin, matrix metalloproteinase-2, matrix metalloproteinase-9, Elastase, MASP-1 (mannose-binding lectin -associated serine protease-1), MASP-2, MASP-3, Cathepsin K, Cathepsin B, Streptokinase, Plasma Procarboxypeptidase B, Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), plasminogen activator family (such as tissue plasminogen activator, urinary plasminogen activator (uPA)),
10 Urokinase, complement convertase family proteins, Factor C1r, C1s, Factor D, and C3 convertases, such as C4b2a, C3bBb, and C3bBbC3b.

[0119] In some embodiments, the linkers are designed to avoid or reduce potential immunogenicity, such as by minimizing the likelihood of T cell epitope(s). The ability of a peptide to bind a given MHC Class II molecule for presentation on the surface of an antigen
15 presenting cell (APC) is dependent on a number of factors, including the primary sequence of the peptide. In one aspect, a peptide or linker of the present disclosure has a low degree of immunogenicity due to its sequence being resistant to antigen processing in APCs. In another aspect, a peptide or linker of the present disclosure has a sequence that substantially does not bind an MHC receptor, or does not bind an MHC receptor in a degree sufficient to
20 elicit an immune response. The present disclosure provides linkers and peptides comprising the linkers, wherein the linkers and peptides are substantially non-repetitive in the primary sequence and are designed to reduce binding with MHC II receptors. In other aspects, the peptides and linkers of the present disclosure do not form epitopes for T-cell receptor or antibody binding, resulting in a low degree of immunogenicity. In one aspect, avoidance of
25 immunogenicity can attribute to, at least in part, a result of the conformational flexibility of the linker sequences; *i.e.*, the lack of secondary structure due to the selection and order of amino acid residues. For example, sequences having a tendency to adapt compactly folded conformations in an aqueous solution or under a physiologic condition are more likely to result in conformational epitopes, than sequences having a relatively lower tendency to adapt
30 compactly folded conformations in the aqueous solution or under the physiologic condition. The administration of fusion proteins comprising a linker of the present disclosure, using conventional therapeutic practices and dosing, would generally not result in the formation of neutralizing antibodies to the linker sequence. In one aspect, a linker sequence of low

immunogenicity reduces the immunogenicity of the fusion partner, for example, when the linker is fused to linked to a mediotope.

[0120] In one embodiment, the linker may contain or may be substantially free of epitopes recognized by human T cells. The elimination of such epitopes for the purpose of generating less immunogenic proteins has been disclosed previously; see for example WO 98/52976, WO 02/079232, and WO 00/3317 which are incorporated by reference herein. The same principles, e.g. the identification of epitopes, can be used to introduce such epitopes into the linker. Assays for human T cell epitopes have been described (Stickler, M., et al. (2003) *J Immunol Methods*, 281: 95-108). Of particular interest are peptide sequences that can be oligomerized with or without generating T cell epitopes or non-human sequences. This is achieved by testing direct repeats of these sequences for the presence of T-cell epitopes and for the occurrence of 6 to 15-mer and, in particular, 9-mer sequences that are not human, and then altering the design of the linker sequence to include or to eliminate or disrupt the epitope sequence. In some embodiments, the linker sequences are substantially non-immunogenic by the restriction of the numbers of epitopes of the linker predicted to bind MHC receptors. With a reduction in the numbers of epitopes capable of binding to MHC receptors, there is a concomitant reduction in the potential for T cell activation as well as T cell helper function, reduced B cell activation or up-regulation and reduced antibody production. The low degree of predicted T-cell epitopes can be determined by epitope prediction algorithms such as, e.g., TEPITOPE (Sturniolo, T., et al. (1999) *Nat Biotechnol*, 17: 555-61). The TEPITOPE score of a given peptide frame within a protein is the log of the K_d (dissociation constant, affinity) of the binding of that peptide frame to multiple of the most common human MHC alleles, as disclosed in Sturniolo, T. et al. (1999) *Nature Biotechnology* 17:555). The score ranges over at least 20 logs, from about 10 to about -10 (corresponding to binding constraints of $10e^{10} K_d$ to $10e^{-10} K_d$), and can be reduced by avoiding hydrophobic amino acids that serve as anchor residues during peptide display on MHC, such as M, I, L, V, F. In some embodiments, a linker sequence does not have a predicted T-cell epitope at a TEPITOPE threshold score of about -5 , or -6 , or -7 , or -8 , or -9 , or at a TEPITOPE score of -10 . As used herein, a score of “ -9 ” is a more stringent TEPITOPE threshold than a score of -5 .

[0121] TEPITOPE scores of 9-mer peptide sequence can be calculated by adding pocket potentials as described by Sturniolo [Sturniolo, T., et al. (1999) *Nat Biotechnol*, 17: 555]. TEPITOPE scores calculated by this method range from approximately -10 to $+10$.

However, 9-mer peptides that lack a hydrophobic amino acid (FKLMVWY)(SEQ ID NO: 240) in P1 position have calculated TEPITOPE scores in the range of -1009 to -989. This value is biologically meaningless and reflects the fact that a hydrophobic amino acid serves as an anchor residue for HLA binding and peptides lacking a hydrophobic residue in P1 are considered non binders to HLA.

[0122] In some embodiments, the linker is or is not predicted to contain any MHC Class II epitope, for example, as predicted by an epitope-identification program or algorithm. In one embodiment, a linker of the present disclosure has or is predicted to have 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 MHC Class II epitopes. In another embodiment, a linker disclosed herein has or is predicted to have no more than about 2, no more than about 3, no more than about 4, no more than about 5, no more than about 6, no more than about 7, no more than about 8, no more than about 9, no more than about 10, no more than about 11, no more than about 12, no more than about 13, no more than about 14, no more than about 15, no more than about 16, no more than about 17, no more than about 18, no more than about 19, no more than about 20, no more than about 21, no more than about 22, no more than about 23, no more than about 24, no more than about 25, no more than about 26, no more than about 27, no more than about 28, no more than about 29, or no more than about 30 MHC Class II epitopes.

[0123] In some embodiments, the linker may or may not contain any predicted MHC Class II epitope as predicted by the ProPred tool, which is described in Singh, H. and Raghava, G.P.S. (2001), ProPred: Prediction of HLA-DR binding sites, *Bioinformatics*, 17(12):1236-37. ProPred is a graphical web tool for predicting MHC Class II binding regions in antigenic protein sequences. In one aspect, prediction of MHC Class II epitope using the ProPred tool utilizes quantitative matrices derived from Sturniolo, T., et al. (1999), *Nat Biotechnol*, 17: 555.

[0124] Additionally, the non-repetitive sequence and corresponding lack of epitopes in a linker sequence limit or enhance the ability of B cells to bind to or be activated by the linker. A repetitive sequence is recognized and can form multivalent contacts with even a few B cells and, as a consequence of the cross-linking of multiple T-cell independent receptors, can stimulate B cell proliferation and antibody production. In contrast, while a linker can make contacts with many different B cells over its extended sequence, each individual B cell may only make one or a small number of contacts with an individual linker due to the lack of

repetitiveness of the sequence. In one embodiment, a linker of the present disclosure typically has a much lower tendency to stimulate proliferation of B cells and thus an immune response. In one embodiment, a mediotope fused to a linker has reduced immunogenicity as compared to the corresponding mediotope that is not fused to a linker.

5 **[0125]** In one embodiment, a non-repetitive linker typically forms weaker contacts with an antibody than a linker with a high degree of repetitiveness. Antibodies are multivalent molecules, for example, IgGs have two identical binding sites and IgMs contain 10 identical binding sites. Thus antibodies against repetitive sequences can form multivalent contacts with such repetitive sequences with high avidity, which can affect the potency and/or
10 elimination of such repetitive sequences. In contrast, antibodies against non-repetitive linkers likely yield only monovalent interactions, resulting in less likelihood of immune clearance such that a peptide comprising a non-repetitive linker can remain in circulation for an increased period of time.

[0126] A linker sequence can be evaluated to identify candidate MHC Class I epitopes,
15 e.g. using an algorithm for the prediction of an MHC Class I epitope. Many different predictive programs are available for the identification of potential MHC Class I epitopes, i.e., epitopes that are capable of being displayed on an MHC Class I molecule, in a given polypeptide. A number of exemplary algorithms are described in WO 2009/051555, the disclosure of which is incorporated herein by reference for all purposes. Examples of
20 epitope-identification programs can be found at the websites of the following organizations and facilities: Institute of Microbial Technology (India), ProPred-I tool as described in Singh, H. and Raghava, G. P. S. *Bioinformatics* 22;19(8):1009-14 (2003). SYFPEITHI, as described in Hans-Georg Rammensee, et al., *Immunogenetics* (1999) 50: 213-219. Immune Epitope Database. See e.g. Kim Y, Sidney J, Pinilla C, Sette A, Peters B., *BMC*
25 *Bioinformatics* 10:394 (2009). Max-Planck-Institute for Infection Biology. See e.g. J. Hakenberg, A. Nussbaum, H. Schild, H.-G. Rammensee, C. Kuttler, H.-G. Holzhütter, P.-M. Kloetzel, S.H.E. Kaufmann, H.-J. Mollenkopf (2003) MAPPP - MHC-I Antigenic Peptide Processing Prediction. *Applied Bioinformatics* 2(3):155-158. Technical University of Denmark, NetChop Server, as described in Nielsen M, Lundegaard C, Lund O, Kesmir C.
30 *Immunogenetics*.57(1-2): 33-41, 2005.

[0127] The algorithms used within these prediction web sites can be found at the same sites. The following is a non-exhaustive list of references describing suitable prediction

algorithms: Parker et al. (1994) Scheme for ranking potential HLA-A2 binding peptides based on independent binding of individual peptide side-chains, *J. Immunol.*, 152, 163-175; Hans-Georg Rammensee et al. (1999) SYFPEITHI: database for MHC ligands and peptide motifs, *Immunogenetics* 50: 213-219; Reche et al. (2002) Prediction of MHC Class I binding peptides using profile motifs. *Hum Immunol.* 63 (9):701-9; Greenbaum et al. (2007) *Journal of Molecular Recognition* 20 (2):75-82.

[0128] In one embodiment, a linker of the present disclosure does not contain any epitope for an MHC receptor. In one embodiment, a linker of the present disclosure does not contain any MHC Class I or Class II epitope. In another embodiment, a linker disclosed herein does not contain any predicted MHC Class I epitope, for example, as predicted by an epitope-identification program or algorithm. In one embodiment, a linker of the present disclosure has or is predicted to have 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 MHC Class I epitopes. In another embodiment, a linker disclosed herein has or is predicted to have no more than about 2, no more than about 3, no more than about 4, no more than about 5, no more than about 6, no more than about 7, no more than about 8, no more than about 9, no more than about 10, no more than about 11, no more than about 12, no more than about 13, no more than about 14, no more than about 15, no more than about 16, no more than about 17, no more than about 18, no more than about 19, no more than about 20, no more than about 21, no more than about 22, no more than about 23, no more than about 24, no more than about 25, no more than about 26, no more than about 27, no more than about 28, no more than about 29, or no more than about 30 MHC Class I epitopes.

[0129] In some embodiments, the linker contains a reactive functionality, which can be used for derivatization, e.g., conjugation of the mediotope, e.g., via the scaffold or linker, to an agent, such as a diagnostic, e.g., imaging agent or therapeutic agent. In some embodiments, the linker comprises one or more conjugation sites, including, for example, lysines, tyrosines, glutamic acids, aspartic acids, FGE sequences, or an unnatural amino acids useful in conjugating scaffolds, linkers, or agents. In some embodiments, the number and location of conjugation sites can be controlled by adding or removing conjugation sites, thereby controlling the amount or location of the subsequently conjugated agent. In some embodiments, a linker comprising a PASylation sequence, a sortase sequence, or an intein sequence further comprises one or more conjugation sites. For example, in some

embodiments, the meditope comprises one or more PASylation sequences, including, for example, in the linker. PASylation sequences can comprise prolines, alanines, and serines in a defined or random sequence. PASylation sequences can therefore include peptides comprising neutral and hydrophobic amino acids. SEQ ID NO: 231 discloses an exemplary trivalent meditope. The sequence comprising PASylation is described in Morath, et al. *Mol Pharm* 2015 May 4;12(5):1431-42. PASylation may improve drug delivery and prolong plasma half-life. For example PASylation may increase the hydrodynamic volume of a protein, thus prolonging circulation and/or boosting bioactivity before kidney filtration.

[0130] In some embodiments, thiol functionalities can be introduced in any suitable position on the linker and can be selectively modified using a number of external reagents containing diagnostic or therapeutic agents, such as imaging agents, other proteins and peptides, metal chelators, siRNAs, nanoparticles, cytotoxic agents, and the like.

[0131] For example, in some embodiments, the meditope, a modified variant thereof, or the linker comprises a sequence wherein any one, two, three, or four of the residues is optionally substituted with a conjugated amino acid, such as at a lysine. The chain in some embodiments is a conjugated peptidyl moiety, comprising a metal chelator bound to a metal ion, a small molecule, a chemotherapeutic agent, a therapeutic antibody or a functional fragment thereof, a toxin, a radioisotope, an enzyme, a nuclease, a hormone, an immunomodulator, an oligonucleotide, an organic or inorganic nanoparticle, an RNAi molecule, an siRNA, a chelator, a boron compound, a photoactive agent, a dye, a fluorescent or luminescent substance, an enzyme, an enhancing agent, a radioactive substance, or a chelator.

B. Meditopes

[0132] Provided herein are meditopes for use with the disclosed methods of altering the distribution of cell surface antigens, as well as vectors, cells, libraries, and other systems containing the same.

[0133] The term “meditope,” as used herein, refers to a peptide or peptides that binds to a central cavity, such as a meditope-binding site of a meditope-enabled antibody or antigen binding fragment thereof, which antibody or antigen binding fragment thereof has a threonine at position 40, an asparagine at position 41, and an aspartate at position 85 of its light chain, according to Kabat numbering, or contains a meditope binding site containing residues that

correspond to those within the meditope-binding site of cetuximab, meditope-enabled trastuzumab, or meditope-enabled M5A, disclosed herein. In some embodiments, meditoypes can be fused to an antibody via a linker, as previously described. In some embodiments, the meditope is a free meditope. Exemplary meditoypes include, but are not limited to, the cQFD (SEQ ID NO: 1) and cQYN (SEQ ID NO: 2) peptides and variants thereof (“meditope variants” or “variant meditoypes”). Other molecules may also bind to meditope binding sites of meditope-enabled antibodies, with functional characteristics similar to those of a meditope. Such molecules, defined as “meditope analogs,” may include, but are not limited to, small molecules, aptamers, nucleic acid molecules, peptibodies and any other substance able to bind to the same meditope binding site as a meditope. In some embodiments, the meditope sequence is cyclized as disclosed herein (e.g. the terminal (or near terminal) cysteine residues form a disulfide bond).

[0134] Among the provided meditoypes are meditope variants (also called variant meditoypes), having one or more modifications, e.g., structural modifications, as compared to meditope 1 or 2 (meditope of SEQ ID NO: 1 or 2), and methods for producing the same. In some embodiments, cQFD and cQYN meditoypes are used as starting points in the design of meditope variants. In some aspects, the meditope variants are designed to have altered properties, such as increased or altered affinity, altered pH dependence, or different affinities under different physiological conditions for one or more of the provided meditope-enabled antibodies, including cetuximab and other antibodies described herein, e.g., as compared to the unmodified meditoypes, cQFD and cQYN. Meditope variants are designed and produced using various chemical and biophysical methods.

[0135] Meditope variants include, but are not limited to, variants incorporating modifications to meditoypes, e.g., cQFD and cQYN and others described herein. Suitable modifications include, but are not limited to, any peptide modification known in the art, such as, but not limited to, modifications to the manner and/or position of peptide cyclization, modifications to one or more amino acid components of the cyclic peptide, or adding or deleting one or more amino acid from the cyclic peptide. In a particular example, cQFD may be altered with one or more of the following modifications: a modification of Arg8, a modification of Phe3, a modification of Leu5, a modification of Leu10, change to the mode of peptide cyclization, and/or an incorporation of hydratable carbonyl functionality at one or more positions, and one or more amino acid deletions or additions. In the case of cQYN,

suitable modifications may include one or more of the following: a modification of Arg8, a modification of Leu5, a modification of Leu10, change to the mode of peptide cyclization, and/or an incorporation of hydratable carbonyl functionality at one or more positions, and one or more deletions or additions. Certain amino acid positions within the mediotope may be deleted or replaced with a different natural amino acid or an unnatural amino acid, or the mediotope may be chemically conjugated with a fragment, for example by using “click chemistry”. It is shown herein that a mediotope in which Arg9 of SEQ ID NO: 1 has been mutated to citrulline binds to cetuximab. In addition, the amino and carboxy termini can be extended with further amino acids beyond (i.e., in addition to) the cyclic portion of the mediotope variant in order to make additional contact to the Fab. For example, Protein L has been added to the C-terminus of the cQFD mediotope and preliminary data shows that this binds with much higher affinity.

[0136] Also provided are self-crosslinking antibodies comprising mediotopes with specific affinities for a mediotope binding site of a mediotope enabled antibody. In some embodiments, the self-crosslinking antibody comprises a mediotope or variant with a low or reduced binding affinity for a mediotope binding site, for example as compared to SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, a self-crosslinking antibody comprising a mediotope or variant with a low or reduced binding affinity can reduce or eliminate self-crosslinking under certain conditions. For example, it may be possible to use or store self-crosslinking antibodies with reduced self-crosslinking abilities at higher concentrations and/or without the need for additional free mediotope. Such antibodies may be less likely to form large aggregates or precipitate out of solution during production or storage, yet still enhance antibody or antigen internalization where the concentration of antigen is high enough to promote antibody-antibody self-crosslinking interactions.

[0137] In some embodiments, the self-crosslinking antibody comprises a mediotope or variant thereof with a high or increased binding affinity for a mediotope binding site, for example as compared to SEQ ID NO:1 or SEQ ID NO:2. In some embodiments, a self-crosslinking antibody comprising a mediotope or variant with a high or increased binding affinity can increase self-crosslinking under certain conditions. This may be advantageous, for example, for increasing antibody or antigen internalization when the concentration of an antigen is low or reduced on a particular cell surface. This may also be advantageous when administrations of lower amounts or concentrations of self-crosslinking antibody are desired.

[0138] In some embodiments, the mediotopes include those listed in Tables 1 and 2, as well as such mediotopes with additional amino acids, such as those up to 16 amino acids in length. For example, in some aspects, the mediotope is one of mediotopes 1, 2, or 15-55, further including a serine before the first residues, i.e., at position zero. The mediotopes listed in Table 1 employ a disulfide linkage to connect the C and N termini, except that certain mediotopes contain an additional sequence, such as a tail or a leader, such that the linkage is not between the two terminal residues. Exemplary tail and leader sequences are those having between 1 and 50 amino acids in length, such as between 1 and 40, 1 and 30, 1 and 25, 1 and 20, 1 and 15, 1 and 10, 9, 8, 7, 6, 5, 4, 3, or 2 amino acids in length, such as the tails set forth as R5A and R5B, herein. Exemplary tails and leader sequences contain any one or more G, S, P, K, and/or D residue(s). Exemplary tails and leaders include GGGSK, G, GPGGSDPG, and GPGGSDPG. For example, the mediotope having SEQ ID NO: 31 contained an additional tail, meaning that the disulfide linkage is not between the two terminal residues. Likewise, certain other mediotopes in the table (SEQ ID NOS: 187-190, 207) contain tails and/or leaders, resulting in linkage between residues other than the terminal residues. For the peptides in Table 2, a lactam bridge, a linkage other than disulfide (such as [3+2] cycloaddition), or no linkage is used (e.g., an acyclic or linear variant). Additional mediotopes that may be used according to the embodiments described herein include any mediotope as defined herein that binds to an antibody framework binding interface (i.e., between the Fab light and heavy chains) of cetuximab or any other therapeutic antibody. For example, in addition to the cyclic peptides cQFD and cQYN, some embodiments include one or more variants of cQFD and cQYN.

Table 1

SEQ ID NO	Mediotope Number	Sequence	Modification	Linkage method
1	1	C-QFDLSTRRLK-C	original	Disulfide 1-Cys : 12-Cys
2	2	C-QYNLSSRALK-C	original	Disulfide 1-Cys : 12-Cys
15	15	C-qFDLSTRRLK-C	q = D-glutamine	Disulfide 1-Cys : 12-Cys
16	16	C-QYDLSTRRLK-C	Y = tyrosine	Disulfide 1-Cys : 12-Cys
17	17	C-QXDLSTRRLK-C	X = β - β' -di-phenyl-Ala	Disulfide 1-Cys : 12-Cys
18	18	C-QFDXSTRRLK-C	X = β - β' -di-phenyl-Ala	Disulfide 1-Cys : 12-Cys
19	19	C-QFDESTRX $\underline{\text{L}}$ K-C	F = phenylalanine, X = citrulline	Disulfide 1-Cys : 12-Cys
20	20	C-QFDESTRRLK-C	F = phenylalanine	Disulfide 1-Cys : 12-Cys
21	21	C-QFDESTRRLK-C	E = glutamic acid	Disulfide 1-Cys : 12-Cys
22	22	C-QFDYSTRRLK-C	Y = tyrosine	Disulfide 1-Cys : 12-Cys
23	23	C-QFDLSTRQK-C	Q = glutamine	Disulfide 1-Cys : 12-Cys
24	24	C-QFDLSTRQLK-C	Q = glutamine	Disulfide 1-Cys : 12-Cys
25	25	C-QYNLSTARLK-C	Y = tyrosine; N = asparagine; A = alanine	Disulfide 1-Cys : 12-Cys
26	26	C-QADLSTRRLK-C	A = alanine	Disulfide 1-Cys : 12-Cys
27	27	C-QFDASTRRLK-C	A = alanine	Disulfide 1-Cys : 12-Cys
28	28	C-QFDLSTARLK-C	A = alanine	Disulfide 1-Cys : 12-Cys
29	29	C-QFDLSTRRAK-C	A = alanine	Disulfide 1-Cys : 12-Cys

30	30	C-QFDLSTRREK-C	E = glutamic acid	Disulfide 1-Cys : 12-Cys
31	31	AcC-QFDLSTRRLR-CGGGSK	AcC-N-acetylcysteine R = arginine	Disulfide 1-AcCys : 12-Cys
186		C-QFDLSTRRLR-C	R = arginine	Disulfide 1-Cys : 12-Cys
187		GC-QFDLSTRRLR-C	R = arginine	Disulfide 2-Cys : 13-Cys
188		GPGGSDPGC-QFDLSTRRLR-C	R = arginine	Disulfide 9-Cys : 20-Cys
189		C-QFDLSTRRLR-CG	R = arginine	Disulfide 1-Cys : 12-Cys
190		GPGGSDPGC-QFDLSTRRLR-CG	R = arginine	Disulfide 9-Cys : 20-Cys
207		GC-QFDLSTRRLR-CG	R = arginine	Disulfide 2-Cys : 13-Cys

Table 2

SEQ ID NO		Sequence	Modification	Linkage method
32	32	G-QFDLSTRRLK-G	G = glycine	Lactam 1-Gly : 12-Gly
33	33	G-QHDLSTRRLK-G	H = histidine	Lactam 1-Gly : 12-Gly
34	34	G-QNDLSTRRLK-G	N = asparagine	Lactam 1-Gly : 12-Gly
35	35	G-QQDLSTRRLK-G	Q = glutamine	Lactam 1-Gly : 12-Gly
36	36	G-QXDLSTRRLK-G	X = 2-bromo-L-phenylalanine	Lactam 1-Gly : 12-Gly
37	37	G-QXDLSTRRLK-G	X = 3-bromo-L-phenylalanine	Lactam 1-Gly : 12-Gly
38	38	G-QXDLSTRRLK-G	X = 4-bromo-L-phenylalanine	Lactam 1-Gly : 12-Gly
39	39	G-QFDLSTRXLK-G	X = citrulline	Lactam 1-Gly : 12-Gly
40	40	G-QFDLSTXXLK-G	X = citrulline	Lactam 1-Gly : 12-Gly
41	41	G-QFDLSTXRLK-G	X = citrulline	Lactam 1-Gly : 12-Gly
42	42	Q-FDLSTRRLK-X	X = 7-aminoheptanoic acid	Lactam 1-Gln : 11-X
43	43	X-QFDLSTRRLK-X	X = β -alanine	Lactam 1-X : 12-X
44	44	X-QFDLSTRRLK-X'	X = diaminopropionic acid; X' = iso-aspartic acid	Lactam 1-X : 12-X'
45	45	X-QFDLSTRRLK-X'	X = β -alanine; X' = iso-aspartic acid	Lactam 1-X : 12-X'
46	46	X-QFDLSTRRLK-X'	X = diaminopropionic acid; X' = β -alanine	Lactam 1-X : 12-X'
47	47	F-DLSTRRL-K		Lactam 1-Phe : 9-Lys
48	48	C-QFDLSTRRLK-C		Disulfide 1-Cys : 12-Cys; Lactam 4-Asp to 11-Lys
49	49	Q-YDLSTRRLK-X	Y = tyrosine, X = 7-aminoheptanoic acid	Lactam 1-Gln : 11-X
50	50	X-QFDLSTRRLK-X'	X = β -azidoalanine, X' = propargylglycine	[3+2] cycloaddition Azide-1-X: alkyne-12-X'
51	51	Q-XDLSTRRLK-X'	X = β - β' -di-phenyl-Ala, X' = 7-aminoheptanoic acid	Lactam 1-Gln : 11-X'
52	52	qFDLSTRRLK-X	q = D-glutamine, X = 7-aminoheptanoic acid	Lactam 1-Gln : 11-X
53	53	Q-XDXSTRRLK-X'	X = β - β' -di-phenyl-Ala, X' = 7-aminoheptanoic acid	Lactam 1-Gln : 11-X'
54	54	Q-FDLSTXRLK-X'	X = n-butyl-arginine, X' = 7-aminoheptanoic acid	Lactam 1-Gln : 11-X'
55	55	SQFDLSTRRLKS		No linkage

[0139] The mediotpe variants typically have an amino acid sequence length of between 5 and 16 amino acids, e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 amino acids in length, such as between 8 and 13 amino acids in length, e.g., between 9 and 12 amino acids in length. The mediotpe can additionally be conjugated to or associated with (e.g., as part of a fusion protein or peptide) with another molecule, such as another peptide, including a linker or agent. Thus, in this case, the compound containing the mediotpe may contain additional amino acid residues beyond the lengths described in this paragraph, where the mediotpe portion contains

between 5 and 16 amino acids and the complex or compound contains additional amino acids. Examples are described herein, e.g., SEQ ID NO: 31 above.

[0140] In some embodiments, the variant mediotopes are cyclic peptides. In other embodiments, they are linear or acyclic peptides.

- 5 **[0141]** The mediotopes can include peptides, or cyclic peptides derived from such peptides, for example, where the peptides have the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (Formula V),

for example, where:

X1 = Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

10 X2 = Gln or null;

X3 = Phe, Tyr, β - β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, or 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X4 = Asp or Asn;

15 X5 = Leu; β - β' -diphenyl-Ala; Phe; Trp; Tyr; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 = Ser;

X7 = Thr or Ser;

20 X8 = Arg, Ser, a modified Arg, or a hydratable carbonyl or boronic acid-containing residue;

X9 = Arg, Ala;

X10 = Leu, Gln, Glu, β - β' -diphenyl-Ala; Phe; Trp; Tyr; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a

25 boronic acid-containing residue;

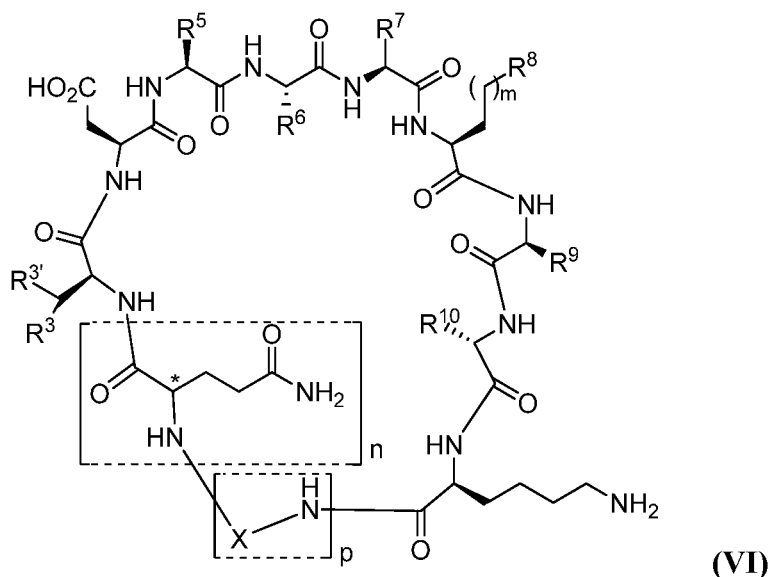
X11 = Lys; and

X12 = Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

[0142] In some aspects, the modified Arg has a structure of the formula shown in Figure

- 30 1. In some aspects, the modified Phe is a Phe with one or more halogen incorporated into the phenyl ring. In some aspects, formula V is not SEQ ID NO: 1 or SEQ ID NO: 2.

[0143] In some embodiments, the mediotopes are peptides having the structure of Formula (VI):



wherein:

5 the center marked with “*” is in the “R” or “S” configuration;

R^3 and $R^{3'}$ are independently H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4} alkyl, -OH, fluoro, chloro, bromo, and iodo; R^5 is:

(A) C_{1-8} alkyl, optionally substituted with one or more substituents selected from oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$ alkyl, $-CH=CH-CHO$, $-CH=CH-C(O)C_{1-4}$ alkyl, $-CH=CH-CO_2C_{1-4}$ alkyl, $-CO_2H$, and $-CONH_2$; or

(B) C_{1-4} alkyl substituted with:

a) one or two phenyl, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) naphthyl, imidazole, or indole;

R^6 is $-C_{1-4}$ alkylene-OH or $-C_{1-4}$ alkylene-SH;

R^7 is $-C_{1-4}$ alkylene-OH or $-C_{1-4}$ alkylene-SH;

20 m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, -B(OH)₂, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C₁₋₄alkyl, -CH=CH-CO₂C₁₋₄alkyl, -CO₂H, and -CO₂C₁₋₄alkyl;

R^c is H, C₁₋₈alkyl, C₃₋₈cycloalkyl, branched alkyl, or aryl;

R^d is H or a C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl, C₃₋₈cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of -N₃, -NH₂, -OH, -SH, halogen, oxo, acetal, ketal, -B(OH)₂, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C₁₋₄alkyl, -CH=CH-CO₂C₁₋₄alkyl, -CO₂H, and -CO₂C₁₋₄alkyl group;

R^e is H, -NHR^d, or a C₁₋₁₂alkyl, C₃₋₈cycloalkyl, C₂₋₁₂alkenyl, C₂₋₈alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of -N₃, -NH₂, -OH, -SH, oxo, C₂₋₄acetal, C₂₋₄ketal, -B(OH)₂, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C₁₋₄alkyl, -CH=CH-CO₂C₁₋₄alkyl, and -CO₂C₁₋₄alkyl; or

(b) C₁₋₁₂ alkyl substituted with an oxo, acetal, ketal, -B(OH)₂, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C₁₋₄alkyl, -CH=CH-CO₂C₁₋₄alkyl, or -CO₂C₁₋₄alkyl;

R⁹ is C₁₋₄alkyl or -C₁₋₂alkylene-R^x;

wherein R^x is -CO₂H, -CONH₂, -CH₂NHC(O)NH₂, or -CH₂NHC(=NH)NH₂;

R¹⁰ is:

(1) C₁₋₈alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, -B(OH)₂, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C₁₋₄alkyl, -CH=CH-CO₂C₁₋₄alkyl, -CO₂C₁₋₄alkyl, -CO₂H, and -CONH₂; or

(2) C₁₋₄alkyl substituted with one or two phenyl, or one naphthyl, imidazole, or indole, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C₁₋₈alkylene or C₂₋₈alkenylene, each carbon thereof optionally substituted with oxo, -C(O)-, -NHC(O)-, -CO₂H, -NH₂, or -NHC(O)R^y;

wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$ alkyl, $-\text{CH}(R^z)\text{C}(\text{O})-$ or $-\text{CH}(R^z)\text{CO}_2\text{H}$;

R^z is $-\text{H}$ or $-C_{1-4}$ alkyl optionally substituted with $-\text{OH}$, $-\text{SH}$, or $-\text{NH}_2$;

5 or a pharmaceutically acceptable salt thereof.

[0144] In some cases X is C_{1-8} alkylene or C_{2-8} alkenylene, each carbon thereof optionally substituted with oxo, $-\text{CO}_2\text{H}$, $-\text{NH}_2$, or $-\text{NHC}(\text{O})R^y$; wherein one carbon of said alkylene is optionally replaced with $-\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})-$, a 5-membered heteroaryl ring, or -S-S-; one carbon of said alkenylene is optionally replaced with $-\text{NHC}(\text{O})-$; and R^y is $-C_{1-4}$ alkyl, $-\text{CH}(R^z)\text{C}(\text{O})-$ or $-\text{CH}(R^z)\text{CO}_2\text{H}$; R^z is $-\text{H}$ or $-C_{1-4}$ alkyl optionally substituted with $-\text{OH}$, $-\text{SH}$, or $-\text{NH}_2$; or a pharmaceutically acceptable salt thereof.

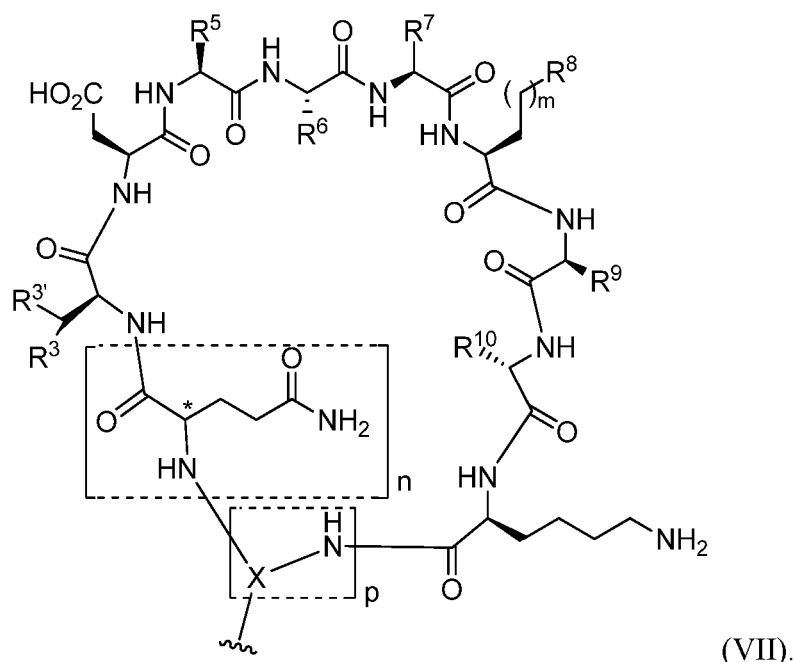
[0145] In some cases X is C_{1-8} alkylene or C_{2-8} alkenylene, each of which is optionally substituted with $-\text{CO}_2\text{H}$, $-\text{NH}_2$, or $-\text{NHC}(\text{O})R^y$; wherein one carbon of said alkylene is optionally replaced with $-\text{C}(\text{O})\text{NH}-$, a 5-membered heteroaryl ring, or -S-S-; and R^y is $-C_{1-4}$ alkyl or $-\text{CH}(R^z)\text{CO}_2\text{H}$; wherein R^z is $-\text{H}$ or $-C_{1-4}$ alkyl optionally substituted with $-\text{OH}$, $-\text{SH}$, or $-\text{NH}_2$; or a pharmaceutically acceptable salt thereof.

[0146] In some cases, such mediotopes are not SEQ ID NO: 1 or 2, or are not cyclic peptides derived from such sequences, and/or are not mediotope 1 or 2.

[0147] In some embodiments of the mediotope of Formula (VI), m is 0, 1, or 2. In other embodiments, R^3 is H or phenyl and $R^{3'}$ is phenyl, 2-bromophenyl, 3-bromophenyl, or 4-bromophenyl. In further embodiments, R^5 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl, each optionally substituted with an oxo, $-\text{B}(\text{OH})_2$, $-\text{CO}_2\text{H}$, or $-\text{CONH}_2$ group, or with one or two phenyl groups each optionally substituted with a bromo or chloro substituent. In further embodiments, R^8 is $-\text{OH}$, $-\text{NH}_2$, $-\text{N}(R^c)\text{C}(\text{O})R^e$, or $-\text{N}(R^c)\text{C}(=\text{NR}^d)R^e$. In still further embodiments, R^c is H or methyl, R^d is H or C_{1-4} alkyl, and R^e is C_{1-4} alkyl, or $-\text{NH}(C_{1-4}\text{alkyl})$. In other embodiments, R^9 is methyl or ethyl, optionally substituted with $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{CH}_2\text{NHC}(\text{O})\text{NH}_2$, or $-\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$. In still other embodiments, R^{10} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl, each optionally substituted with an oxo, $-\text{B}(\text{OH})_2$, $-\text{CO}_2\text{H}$, or $-\text{CONH}_2$ group. In still other embodiments, $-\text{X-NH}-$ is $-\text{Cys-Cys}-$, $-\text{Gly-Gly}-$, $-\text{C}(\text{O})(\text{CH}_2)_6\text{-NH}-$, $-\beta\text{-Ala-}\beta\text{-Ala-}$, $-\text{C}(\text{O})\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}(\text{CO}_2\text{H})\text{-NH-}$,

-C(O)CH(NH₂)CH₂NHC(O)CH₂CH(CO₂H)-NH-, -β-Ala-C(O)CH₂CH(CO₂H)-NH-, or -C(O)CH(NH₂)CH₂-triazinyl-CH₂-CH(CO₂H)-NH-.

[0148] In some embodiments, the mediotopes are peptides having the structure of Formula (VII):



[0149] The center marked with “*” is in the “R” or “S” configuration. The symbol $\sim$ denotes the point of attachment of R^{1A} to L^{1A}.

[0150] R³ and R^{3'} are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C₁₋₄alkyl, -OH, fluoro, chloro, bromo, and iodo.

[0151] R⁵ is: (A) C₁₋₈alkyl, optionally substituted with one or more substituents selected from oxo, acetal, ketal, -B(OH)₂, boronic ester, phosphonate ester, ortho ester, -CO₂C₁₋₄alkyl, -CH=CH-CHO, -CH=CH-C(O)C₁₋₄alkyl, -CH=CH-CO₂C₁₋₄alkyl, -CO₂H, and -CONH₂; or (B) C₁₋₄alkyl substituted with: a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or b) a naphthyl, imidazole, or indole group.

[0152] R⁶ is -C₁₋₄alkylene-OH or -C₁₋₄alkylene-SH. R⁷ is -C₁₋₄alkylene-OH or -C₁₋₄alkylene-SH. The symbol m is 0, 1, 2, 3, 4, or 5.

[0153] R^8 is -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$. R^a is H. R^b is H or C_{1-8} alkyl optionally substituted with one or more substituents selected from oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, $-CH=CH-CHO$, $-CH=CH-C(O)C_{1-4}$ alkyl, $-CH=CH-CO_2C_{1-4}$ alkyl, $-CO_2H$, or $-CO_2C_{1-4}$ alkyl. R^c is H, C_{1-8} alkyl, C_{3-8} cycloalkyl, branched alkyl, or aryl. R^d is H or a C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, branched alkyl, or aryl, each optionally substituted with one or more substituents selected from $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CH=CH-CHO$, $-CH=CH-C(O)C_{1-4}$ alkyl, $-CH=CH-CO_2C_{1-4}$ alkyl, $-CO_2H$, and $-CO_2C_{1-4}$ alkyl group. R^e is H; $-NHR^d$; or a C_{1-12} alkyl, C_{3-8} cycloalkyl, C_{2-12} alkenyl, C_{2-8} alkynyl, or aryl group, each optionally substituted with one or more substituents selected from $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4} acetal, C_{2-4} ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CH=CH-CHO$, $-CH=CH-C(O)C_{1-4}$ alkyl, $-CH=CH-CO_2C_{1-4}$ alkyl, and $-CO_2C_{1-4}$ alkyl. Alternatively, R^8 is a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, $-CH=CH-CHO$, $-CH=CH-C(O)C_{1-4}$ alkyl, $-CH=CH-CO_2C_{1-4}$ alkyl, or $-CO_2C_{1-4}$ alkyl.

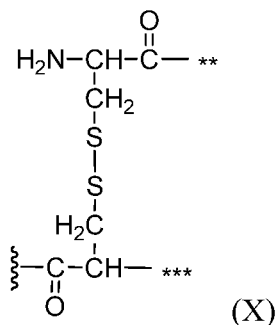
[0154] R^9 is C_{1-4} alkyl or $-C_{1-2}$ alkylene- R^x . R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$.

[0155] R^{10} is: (1) C_{1-8} alkyl optionally substituted with one or more substituents selected from oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CH=CH-CHO$, $-CH=CH-C(O)C_{1-4}$ alkyl, $-CH=CH-CO_2C_{1-4}$ alkyl, $-CO_2C_{1-4}$ alkyl, $-CO_2H$, and $-CONH_2$; or (2) C_{1-4} alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

[0156] The symbol n is 0 or 1. The symbol p is 0 or 1.

[0157] X is (1) a linker resulting from any of the mediotope cyclization strategies discussed herein; (2) substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene or substituted heteroarylene or (3) C_{1-8} alkylene or C_{2-8} alkenylene, each carbon thereof optionally substituted with oxo, $-C(O)-$, $-NH_2$, $-NHC(O)-$ or $-NHC(O)R^y$. One carbon of the X C_{1-8} alkylene is optionally replaced with $-C(O)NH-$, a 5-membered heteroaryl ring, or $-S-S-$. R^y is $-C_{1-4}$ alkyl or $-CH(R^z)C(O)-$ or $-CH(R^z)CO_2H$. R^z is $-H$ or $-C_{1-4}$ alkyl optionally

substituted with $-\text{OH}$, $-\text{SH}$, or $-\text{NH}_2$. Formula VII includes all appropriate pharmaceutically acceptable salts. In (1), X is considered a substituted linker due to its chemical trivalency and because X may optionally include further substituents as set forth above (e.g. $-\text{NH}_2$ and oxo). In some embodiments, X is:



where ** represents the point of attachment to the glutamine attached to X in Formula VII and *** represents the point of attachment to the nitrogen attached to X and lysine in Formula VII. The symbol --- denotes the point of attachment of X to the remainder of the molecule.

- 10 **[0158]** In some embodiments of the mediotope of Formula VII, m is 0, 1, or 2. In other
embodiments, R^3 is H or phenyl and $\text{R}^{3'}$ is phenyl, 2-bromophenyl, 3-bromophenyl, or 4-
bromophenyl. In further embodiments, R^5 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl,
sec-butyl, or tert-butyl, each optionally substituted with an oxo, $-\text{B}(\text{OH})_2$, $-\text{CO}_2\text{H}$, or
15 $-\text{CONH}_2$ group, or with one or two phenyl groups each optionally substituted with a bromo
or chloro substituent. In further embodiments, R^8 is $-\text{OH}$, $-\text{NH}_2$, $-\text{N}(\text{R}^c)\text{C}(\text{O})\text{R}^e$, or
 $-\text{N}(\text{R}^c)\text{C}(=\text{NR}^d)\text{R}^e$. In still further embodiments, R^c is H or methyl, R^d is H or C_{1-4} alkyl, and
 R^e is C_{1-4} alkyl, or $-\text{NH}(\text{C}_{1-4}\text{alkyl})$. In other embodiments, R^9 is methyl or ethyl, optionally
substituted with $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{CH}_2\text{NHC}(\text{O})\text{NH}_2$, or $-\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$. In still other
embodiments, R^{10} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl,
20 each optionally substituted with an oxo, $-\text{B}(\text{OH})_2$, $-\text{CO}_2\text{H}$, or $-\text{CONH}_2$ group. In still other
embodiments, $-\text{X}-\text{NH}-$ is $-\text{Cys}-\text{Cys}-$ (e.g. bound through a disulfide bridge), $-\text{Gly}-\text{Gly}-$,
 $-\text{C}(\text{O})(\text{CH}_2)_6-\text{NH}-$, $-\beta\text{-Ala}-\beta\text{-Ala}-$, $-\text{C}(\text{O})\text{CH}(\text{NH}_2)\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}(\text{CO}_2\text{H})-\text{NH}-$,
 $-\text{C}(\text{O})\text{CH}(\text{NH}_2)\text{CH}_2\text{NHC}(\text{O})\text{CH}_2\text{CH}(\text{CO}_2\text{H})-\text{NH}-$, $-\beta\text{-Ala}-\text{C}(\text{O})\text{CH}_2\text{CH}(\text{CO}_2\text{H})-\text{NH}-$, or
 $-\text{C}(\text{O})\text{CH}(\text{NH}_2)\text{CH}_2\text{-triazinyl-CH}_2\text{-CH}(\text{CO}_2\text{H})-\text{NH}-$.

1. *Modifications*

[0159] Based on the structural and thermodynamic data, multiple positions within the mediotopes 1 and 2 described herein have been identified as target sites for modification, e.g., with different natural or non-natural amino acids, to enhance the overall binding affinity and/or to alter another property as described herein. Such modifications include, but are not limited to, modification of cQFD or cQYN to generate a head-to-tail cyclic lactam peptide, modification of Arg8, modification of position 3 (e.g., Phe3 of cQFD or variant thereof), modification of Leu5, modification of Leu10, and/or incorporation of hydratable carbonyl functionality (see Figure 2). As demonstrated herein, mutation of each of Phe3, Leu5, and Arg8 to alanine in the original mediotope of cQFD reduced the affinity of the resulting compounds for the mediotope-enabled antibody binding interface by 10–140-fold. In some aspects, the variant mediotopes include those having modifications at one or more of position 1, 3, 5, 8, 10, and 12 of the mediotope of SEQ ID NO: 1 or 2, or other mediotope listed in Table 1 or 2.

a. Position 8

[0160] In some embodiments, the mediotope variants contain a modification in the position corresponding to position 8 (Arg8) of mediotope 1 or 2. In the unmodified mediotope (cQFD; SEQ ID NO: 1), Arg8 is extended, making a hydrogen bond with the heavy chain carbonyl of Q105 of the mediotope-enabled antibody heavy chain. The immediate area about this residue is hydrophobic yet solvent exposed. In some aspects, the mediotopes contain a modified residue at this position (e.g., modified Arg8). In some examples, the modified residue maintains the iminium functionality of the Arg8 residue useful for mediotope-enabled antibody H-bonding, and introduces a substituted or unsubstituted hydrophobic arm to fill the cavity. Such modifications result in significant gains in binding, due to entropic increases, as supported by ligand docking calculations. Such modifications may be incorporated by using an N-alkyl guanidinium group, or an alkyl-amidine functionality. In either case, the substituted group of the terminal N-atom can be alkyl or aryl, wherein each position of the alkyl or aryl group may be optionally substituted with additional functionalities within the group including the terminal position. In one example, a modified Arginine (modified Arg8), having a structure as shown in Figure 1, is substituted for Arg8 of the mediotope, e.g., of SEQ ID NO: 1 or 2 with the butyl group on the NH₂ (shown in Figure 1 as NHR). In some

aspects, the variant meditope contains an n-butyl-arginine or butylamidine modification at position 8.

b. Position 3

[0161] In some embodiments, the meditope variants contain a modification in the position corresponding to position 3, such as Phe3 of meditope 1. The hydroxyl group of the meditope variant Phe3Tyr cQYN (SEQ ID NO: 2) has an alteration in the extended conformation of the Arg8 side chain as compared to cQFD (SEQ ID NO: 1). Data herein suggest the formation of a favorable hydrogen bond network, with water bound to the Fab. Enthalpy-driven optimization has proven successful in many small-molecule approaches in drug design and there are opportunities in the provided meditope designs for engineering increases in entropy. In some embodiments, approaches resulting in enthalpic and/or entropic gains in meditope designs are used to generate the variant meditope designs, e.g., to optimize binding.

[0162] For example, when bound to a meditope-enabled antibody, the hydrophobic phenyl ring of Phe3 is surrounded by a fairly polar array of side chain residues of the meditope-enabled antibody Fab. In some embodiments, one or more halogens is introduced on the phenyl ring of this residue, to allow for a halogen bonding interaction with the polar side chain residues. A halogen bond is a relatively strong non-covalent bond, similar to a hydrogen bond but involving the interaction of a halogen such as bromine or chlorine (or other halogen), with an oxygen atom. In some aspects, the residue at this position is modified to incorporate a halogen substituent. In some aspects, Phe3 is replaced with 2-bromo-, 3-bromo-, or 4-bromophenylalanine, in order to place a bromine atom in a position suitable for halogen bonding with a meditope-enabled antibody, e.g., at positions Tyr87 (light chain), Gln38, and/or Tyr91 (heavy chain) of a meditope-enabled antibody, respectively. Such phenylalanine derivatives are commercially available and in some aspects are incorporated into the cyclic peptide meditope variant by solid phase peptide synthesis (SPPS). Exemplary variant meditope designs include those containing 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, or 4-bromo-L-phenylalanine in the position corresponding to Phe3 of meditope 1.

[0163] In another example, the meditope incorporates an additional phenyl group at this position, for example, by replacing Phe3 with β,β' -diphenylalanine.

c. Positions 5 and 10 (e.g., Leu5, Leu10 of mediotopes 1 or 2)

[0164] In some embodiments, the mediotope variants contain a modification in the position corresponding to position 5 or 10 (Leu5 or Leu10) of mediotopes 1 or 2. As shown herein, the side chains of Leu5 and Leu10 of mediotope 1 make hydrophobic contacts to the mediotope-enabled Fab,. In certain embodiments, one or more properties of the mediotopes, e.g., affinity, are altered by incorporating a different natural amino acid, or a non-natural amino acid at one or both of these positions, e.g., thereby changing the amount of surface area that can be extended. In one embodiment, natural amino acids (Phe/Tyr/Trp) and non-natural analogs (e.g., β,β' -diphenyl-L-alanine, or amino acids incorporating side chains that include branched alkyl, extended aromatics such as naphthyl, or other hydrophobic groups) are systematically introduced via SPPS at one or both positions.

2. Conjugation

[0165] In certain embodiments, the mediotope is conjugated to an agent, such as a therapeutic agent, a diagnostic agent, or a detectable agent. The peptide can be conjugated to the agent via any suitable means, such as via a chemical linker. In certain embodiments, the chemical linker is a covalent linker. In embodiments, the chemical linker comprises a substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene and/or substituted or unsubstituted heteroarylene.

[0166] In certain embodiments, the chemical linker comprises a PEG linker. In certain embodiments, the chemical linker comprises a peptide linker (e.g., one or more natural or unnatural amino acids, such as glycine, lysine, tyrosine, glutamic acid, aspartic acid, etc.).

[0167] The chemical linker can be bonded to the mediotope at any suitable location, such as the N-terminus, the C-terminus, and/or off a side chain. In certain embodiments, the chemical linker is bonded to the N-terminus. In another embodiment, the chemical linker is bonded to the C-terminus. In still another embodiment, the mediotope comprises more than one chemical linker, where the chemical linkers are bonded to the N-terminus and the C-terminus. In some embodiments, the chemical linker comprises the amino acid sequence – GGGK.

[0168] In certain embodiments disclosed herein, the chemical linker may further comprise a commercially available linker known in the art for forming antibody-drug

conjugates. Accordingly, in certain embodiments, the chemical linker may comprise a linker selected from the group consisting of Ala-Ala-Asn-PAB, ALD-BZ-OSu, ALD-di-EG-OPFP, ALD-di-EG-OSu, ALD-mono-EG-OPFP, ALD-mono-EG-OSu, ALD-tetra-EG-OPFP, ALD-tetra-EG-OSu, ALD-tri-EG-OPFP, ALD-tri-EG-OSu, BCOT-di-EG-OPFP, BCOT-di-EG-OSu, BCOT-tetra-EG-OPFP, BCOT-tetra-EG-OSu, BCOT-tri-EG-OPFP, BCOT-tri-EG-OSu, Boc-NMe-DAE, BrAH, Br-di-EG-OSu, Br-tetra-EG-OSu, Br-tri-EG-OSu, COT-acetic acid, COT-di-EG-OPFP, COT-di-EG-OSu, COT-tetra-EG-OPFP, COT-tetra-EG-OSu, COT-tri-EG-OPFP, COT-tri-EG-OSu, DHA, DHH, Fmoc-Ala-Ala-Asn-PAB-PNP, Fmoc-Phe-Lys(Trt)-PAB-PNP, Fmoc-Val-Cit-PAB, Fmoc-Val-Cit-PAB-PNP, HAC, MAH, MAL-di-EG-OPFP, MAL-di-EG-OSu, MAL-HA-OSu, MAL-tetra-EG-OPFP, MAL-tetra-EG-OSu, MAL-tri-EG-OPFP, MAL-tri-EG-OSu, MBA, MC-Val-Cit-PAB-PNP, MDB, MEL-di-EG-OPFP, MEL-di-EG-OSu, MEL-tetra-EG-OPFP, MEL-tetra-EG-OSu, MEL-tri-EG-OPFP, MEL-tri-EG-OSu, MMC, N3BA, N3-di-EG-OPFP, N3-di-EG-OSu, N3-tetra-EG-OPFP, N3-tetra-EG-OSu, N3-tri-EG-OPFP, N3-tri-EG-OSu, PAB, PHA-di-EG-OPFP, PHA-di-EG-OSu, PHA-tetra-EG-OPFP, PHA-tetra-EG-OSu, PHA-tri-EG-OPFP, PHA-tri-EG-OSu, Phe-Lys(Fmoc)-PAB, Phe-Lys(Trt)-PAB, Py-ds-But-OPFP, Py-ds-But-OSu, Py-ds-dmBut-OPFP, Py-ds-dmBut-OSu, Py-ds-Prp-OPFP, Py-ds-Prp-OSu, and Val-Cit-PAB (ALB Materials Inc, Nevada, U.S.).

[0169] Non-limiting examples of conjugated mediotope peptides are shown in the table below.

NAME	Description
DM1-MCC-cQFD (048-004)	Ac-CQFDLSTRRLRCGGGK-OH (SEQ ID NO: 307); C:C=disulfide-DM1
MMAD-PAB-cv-Glu-cQFD (048-002)	Ac-CQFDLSTRRLRCGGGK-OH (SEQ ID NO: 307); C:C=disulfide-MMAD
DM1-MCC-cQFD-Di-Ph-Ala (048-003)	Ac-CQFDXSTRRLRCGGGK (SEQ ID NO: 308); C:C=Disulfide; X= β,β -diphenyl-Ala -DM1
MMAD-PAB-cv-Glu-cQFD-Di-Ph-Ala (048-001)	Ac-CQFDXSTRRLRCGGGK (SEQ ID NO: 308); C:C=Disulfide; X= β,β -diphenyl-Ala-MMAD
MMAD-PAB-cv-Glu-MB-002-203	MMAD conjugated photoactivatable long cQFD photo-Met 10; 1505048089
MMAD-PAB-cv-Glu-MB-002-204	MMAD conjugated photoactivatable long cQFD photo-Met 9; 1505048087
MMAD-PAB-cv-Glu-MB-002-205	MMAD conjugated photoactivatable long cQFD photo-Met 8; 1505048088
MMAD-cv-PAB-MB-002-206	MMAD conjugated photoactivatable long cQFD azido-Phe 6; 1509048150
MMAD-cv-PAB-MB-002-208	MMAD conjugated photoactivatable long cQFD azido-Phe 3;

MMAD-cv-PAB-MB-002-209	MMAD conjugated photoactivatable long cQFD azido-Phe 10;
MMAD-cv-PAB-MB-002-210	MMAD conjugated photoactivatable long cQFD benzoyl-Phe 3;
MMAD-cv-PAB-MB-002-211	MMAD conjugated photoactivatable long cQFD benzoyl-Phe 10;
Ac-CQFDLSTRXRCCGGGK-MCC-DM1	DM1 conjugated photoactivatable long cQFD photo-Met 10
Ac-CQFDLSTRXRCCGGGK-PEG4-vc-PAB-duocarmycin SA	Duocarmycin SA conjugated photoactivatable long cQFD photo-Met 10
Ac-CQFDLSTRXRCCGGGK-Glu-Val-Ala-PAB-PBD	PBD conjugated photoactivatable long cQFD photo-Met 10
Ac-CQFDLSTRXRCCGGGK-linker-alpha-Amanitin	Amanitin conjugated photoactivatable long cQFD photo-Met 10

MMAD: Monomethyl auristatin D

3. Alternative cyclization strategies and replacement of disulfide bridge

[0170] In certain embodiments, the variant mediotopes include a disulfide bridge, as in cQFD and cQYN. Disulfide bridges may be formed by the reaction of the side chains of two cysteine residues. In certain embodiments, the disulfide bridge in a mediotope, e.g., mediotope 1 or 2, is replaced with an alternative linkage or is removed. Thus, among the variant mediotopes are those having alternative linkages or lacking the disulfide bridge of the original mediotopes.

[0171] In some aspects, the linkage is made between one or more unnatural amino acids within the amino acid chain. Examples of linkages that may be made with unnatural amino acids include linkages comprising (i) stable hydrazone or oxime-based linkages made by reaction of a residue comprising an aldehyde or ketone with a residue comprising an amine group, where the amine nitrogen is substituted with -NH₂ or alkyloxy group (e.g., reaction of a p-acetylphenylalanine, m-acetylphenylalanine, or p-(3-oxobutanoyl)-L-phenylalanine residue with a p-(2-amino-3-hydroxyethyl)-phenylalanine residue), (ii) thiol reactive by incorporating phenylselenidylalanine, (iii) a UV crosslinker containing benzophenone by incorporating p-benzoyl-L-phenylalanine, (iv) amine reactive by incorporating p-isopropylthiocarbonyl-phenylalanine or p-ethylthiocarbonyl-phenylalanine, (v) heterocyclic linkages, such as a triazine, thiazole, thiazolidine, or oxazole linkage, made, for example, by reaction of a residue containing an azide group with a residue containing an alkyne group via Huisgen cycloaddition (e.g., reaction of a p-propargyloxyphenylalanine residue with a p-azidophenylalanine residue); (v) an amide bond made by reaction of an acid group in one residue with an amine group in another residue; (vi) an ester bond made by reaction of an

acid group in one residue with an alcohol in another residue, such as a serine; (vii) a double bond, made by reaction of two residues each containing a terminal olefin, e.g., by olefin metathesis (e.g., reaction of two allylglycine residues or two N-allyl substituted amino acids), or (viii) by reaction of any other pair of suitable residues known in the art. For a review, see, 5 for example, Davies, J.S., "The Cyclization of Peptides and Depsipeptides," *J. Peptide Sci.* 2003, 9, 471-501. In one embodiment, the mediotope may direct a reactive group to an unnatural amino acid incorporated into the Fab, such as p-acetylphenylalanine.

[0172] Various methods for cyclization of a mediotope may be used, e.g., to address *in vivo* stability and to enable chemoselective control for subsequent conjugation chemistry. In 10 some embodiments, the cyclization strategy is a lactam cyclization strategy, including head-to-tail (head-tail) lactam cyclization (between the terminal residues of the acyclic peptide) and/or lactam linkage between other residues. Lactam formation may also be effected by incorporating residues such as glycine, β -Ala, 7-aminoheptanoic acid, and the like, into the acyclic mediotope cyclization precursors to produce different lactam ring sizes and modes of 15 connectivity. Additional cyclization strategies such as "click" chemistry and olefin metathesis also can be used (see Figure 2, right boxes). Such methods of peptide and peptidomimetic cyclization are well known in the art.

[0173] In some embodiments, the mediotopes containing lactam linkages are more stable, *in vivo*, e.g., have a linkage that is more stable *in vivo* compared to mediotopes with other 20 linkages.

[0174] In some embodiments, the terminal residues of an acyclic peptide are reacted to form a cyclic mediotope, e.g., cyclic mediotope variant. In other embodiments, other positions are amenable to cyclization, including between residues 3 and 11 and 4 and 11. Thus, in some aspects, the mediotopes contain a linkage formed between residues other than the N- 25 terminal and C-terminal residues, such as between residues 3 and 11 and/or 4 and 11, e.g., of a 12-amino acid peptide.

[0175] In some embodiments, the mediotopes, e.g., variant mediotopes, contain a reactive amine functionality (e.g., Lys11), which can be used for subsequent conjugation of the mediotope variant, e.g., to a scaffold or linker or to an agent, such as a diagnostic, e.g., 30 imaging, agent or therapeutic agent as described herein. For example, Figure 3 shows a procedure for conjugation of a mediotope variant with fluorescein for FACS analysis; this

strategy can be applied to other imaging and other agents, including DOTA for *in vivo* PET imaging.

C. Meditope Enabled Antibodies

[0176] Provided are mediotope-enabled antibodies and antigen binding fragments thereof that are capable of binding to one or more mediotopes via mediotope-binding sites. In some cases, the mediotope-enabled antibody binds to a cyclic peptide of SEQ ID NO: 1 or 2 (mediotopes 1 or 2) and/or to one or more variants thereof, such as mediotopes 1, 2, 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, or 55 (mediotopes based on peptides having the sequences set forth in SEQ ID NOS: 1, 2, 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, or 55), or in some cases, any of mediotopes 1, 2, or 15-55 and/or mediotopes of any of SEQ ID NOS: 186-190 and 207. Among the provided mediotope-enabled antibodies are those that bind to a mediotope or mediotopes with an affinity similar to that of cetuximab. For example, in certain aspects, the antibodies bind to the mediotope(s) with a dissociation constant of less than at or about 10 μ M, less than at or about 5 μ M, or less than at or about 2 μ M, less than at or about 1 μ M, less than at or about 500, 400, 300, 200, 100 nM, or less, such as at or about 200 picomolar or less. In some cases, the dissociation constant, such as any of those listed herein, is that measured using a particular technique, such as surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), fluorescence, fluorescence polarization, NMR, IR, calorimetry titrations; kinetic exclusion; circular dichroism, differential scanning calorimetry, or other known method. For example, in some cases, the analog or mediotope exhibits a binding constant of less than at or about 10 μ M, less than at or about 5 μ M, or less than at or about 2 μ M, less than at or about 1 μ M, less than at or about 500, 400, 300, 200, 100 nm, or less, as measured by SPR or as measured by ITC or as measured by any of these methods.

[0177] In some examples, the mediotope-binding site is a structural feature of the monoclonal antibody cetuximab. Thus, in some cases, the mediotope-binding site contains residues corresponding to those within the mediotope binding site of cetuximab. X-ray crystallographic analysis has revealed that the peptides of SEQ ID NO: 1 binds to a mediotope-binding site within the central cavity of the cetuximab Fab fragment, defined by various residues of the heavy and light chains (see Figures 4A and 5), with a binding constant of $\sim$ 700 nM.

[0178] In certain embodiments, the unique interactions between the mediotopes and the mediotope binding site are exploited to generate additional mediotope-enabled antibodies. In some embodiments, the mediotope-enabled antibodies are generated by modifying cetuximab or an antibody other than cetuximab (sometimes referred to as the template antibody), such as an antibody having one or more CDRs distinct from those of cetuximab, to confer the ability to bind to one or more of the provided mediotopes, such as a mediotope of SEQ ID NO: 1 or 2, or variant thereof.

[0179] The template antibody can be a human or humanized antibody or a mouse antibody. In one aspect, the modifications include substituting residues within the central cavity of the Fab fragment, typically within the framework regions (FRs) of the heavy and light chain variable regions and/or the constant regions to render the template antibody mediotope-enabled. For example, where the template antibody is a human or humanized antibody, the modifications generally include substitutions at residues within the heavy and light chain variable region FRs. In some embodiments, such residues are replaced with the corresponding residue present in cetuximab, or comparable amino acid. Thus, in certain embodiments, residues within the FRs of a human or humanized antibody are replaced with corresponding murine residues; in certain embodiments, they are replaced by other residues, such as those having similar functional groups or moieties for interacting with the mediotopes. Typically, the residues replaced by corresponding murine (or other) residues are found within the central Fab cavity, and thus are not exposed to the immune system. As such, in some embodiments, introducing these amino acid substitutions in a human or humanized antibody do not increase or do not substantially increase the antigenicity of the modified template antibody, in the context of delivery to a human subject. In addition, antigenicity prediction algorithms may be further used to indicate that the human sequence with the point mutations should not be antigenic.

[0180] In some embodiments one or more residues that are replaced in a mediotope binding site are selected to give a self-crosslinking antibody a specific binding affinity for a specific mediotope, which can be a free mediotope, a mediotope bound to an antibody via a linker, or both. For example, some embodiments of a self-crosslinking antibody comprise mediotope binding sites that exhibit high or increased affinity for a first mediotope and low or reduced affinity for a second mediotope. In some embodiments, the first mediotope is a free mediotope and the second mediotope is attached to a self-crosslinking antibody via a linker, as

described herein. Such embodiments can be advantageous, for example, when free meditope is used to control or modulate antibody self-crosslinking, as described herein. In other embodiments, the first meditope is attached to a self-crosslinking antibody via a linker, and the second meditope is a free meditope. Such embodiments can be advantageous, for example, when high concentrations of free meditope are used and/or when antigen levels or concentrations are low or reduced.

[0181] In some embodiments, the one or more residues that are replaced, are selected from light chain framework residues 10, 39-43, 45, 83, 85, 100 and/or 104, according to Kabat numbering (see Kabat E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition. NIH Publication No. 91-3242, incorporated herein by reference in its entirety), and/or heavy chain framework residue numbers 40, 89 and/or 105, according to Kabat numbering. In general, unless otherwise specified, amino acid positions in the heavy or light chain of an antibody refer to Kabat numbering. Also encompassed within the present disclosure are residues in other antibodies corresponding to the residues of cetuximab described herein, such as those within the cetuximab meditope-binding site. In some embodiments, residues in the template antibody corresponding to light chain residues 9, 10, 39, 40, 41, 42, 43, 45, 83, 85, 100, and/or 104, and/or heavy chain residues 40, 89, and/or 105, are replaced, for example, with amino acids present at those positions within cetuximab. In some embodiments, the meditope-enabled antibody contains, within its light chain framework regions (or within one or more such FRs, e.g., FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of the template antibody; and/or contains, within its heavy chain framework regions (or within one or more such FRs, e.g., FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H(s)) of the template antibody; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of the template antibody; and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL regions of the template antibody. In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, compared to

the template antibody. In some aspects, the antibody contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications within the light chain (e.g., FR-Ls) compared to the template antibody and/or contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications within the heavy chain (e.g., FR-Hs) compared to the template antibody.

[0182] In one embodiment, the one or more residues replaced are light chain framework residues including, but not limited to, 10, 40, 41, 83 and 85, according to Kabat numbering. In one embodiment, light chain residue 40 is replaced with threonine; light chain residue 41 is replaced with asparagine, light chain residue 83 is replaced with isoleucine or valine, and/or light chain residue 85 is replaced with aspartate. In one embodiment, light chain residue 40 is replaced with threonine; light chain residue 41 is replaced with asparagine, light chain residue 83 is replaced with glutamate, and/or light chain residue 85 is replaced with aspartate. In a particular example, light chain framework Pro40 is replaced with Thr (P40T) or Ser (P40S), light chain framework Gly41 is replaced with Asn (G41N), light chain framework residue Phe83 is replaced with Ile (F83I) or Val (F83V) or glutamate (F83E) and light chain framework residue Thr85 is replaced with Asp (T85D) or Asn (T85N). In some embodiments, including, for example, cetuximab, light chain framework residue Ile83 is replaced with glutamate (I83E).

[0183] Thus, among the provided mediotope-enabled antibodies are antibodies having one or more modifications, typically amino acid substitutions, at residues that correspond to positions within the mediotope binding site of cetuximab or other mediotope-enabled antibody, such as those described herein, including mediotope-enabled trastuzumab and mediotope-enabled M5A. Among the antibodies are those having a VL region with a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, and an aspartate or asparagine at position 85, according to Kabat numbering, for example, an antibody with a VL region having a threonine at position 40, an asparagine at position 41, and an aspartate at position 85. In some embodiments, the antibody has a VH region with a serine at position 40 and an isoleucine at position 89 and/or a VH region with a serine or proline at position 40 and an isoleucine, tyrosine, methionine, phenylalanine, or tryptophan at position 89, according to Kabat numbering. In some embodiments, the VL region has an isoleucine or leucine at position 10, and/or an isoleucine at position 83 or a glutamate at position 83. In some

embodiments, the VL region has a valine or isoleucine at position 9 and/or a residue other than glutamine at position 100.

[0184] In some examples, the VL region has a valine or isoleucine at position 9, an isoleucine or leucine at position 10, an arginine at position 39, a threonine at position 40, an asparagine at position 41, a glycine at position 42, a serine at position 43, an isoleucine or glutamate at position 83, an aspartate at position 85, and an alanine at position 100; and the VH region has a serine at position 40 and an isoleucine at position 89, according to Kabat numbering. In some examples, the VL region does not contain a proline at position 40, a glycine at position 41, or a threonine at position 85, according to Kabat numbering, and/or the VH region does not contain an asparagine or alanine at position 40 or a valine at position 89, according to Kabat numbering. In some examples, the VL region does not contain an serine at position 10, a proline at position 40, a glycine at position 41, an phenylalanine at position 83, or a threonine at position 85, according to Kabat numbering, and/or the VH region does not contain an asparagine or alanine at position 40 or a valine at position 89, according to Kabat numbering.

[0185] In some aspects, the antibody has a light chain having P8 , V9 or I9, I10 or L10, Q38, R39, T40, N41 G42, S43, P44, R45, D82, I83, A84, D85, Y86, Y87, G99, A100, G101, T102, K103, L104, E105, R142, S162, V163, T164, E165, Q166, D167, S168, and Y173, according to Kabat numbering, and/or a heavy chain having Q6, P9, R38, Q39, S40, P41, G42, K43, G44, L45, S84, D86, T87, A88, I89, Y90, Y91, W103, G104, Q105, G106, T107, L108, V109, T110, V111, Y147, E150, P151, V152, T173, F174, P175, A176, V177, Y185, S186, and L187, according to Kabat numbering.

[0186] In some aspects, the antibody has a light chain having P8 , V9 or I9, I10 or L10, Q38, R39, T40, N41 G42, S43, P44, R45, D82, E83, A84, D85, Y86, Y87, G99, A100, G101, T102, K103, L104, E105, R142, S162, V163, T164, E165, Q166, D167, S168, and Y173, according to Kabat numbering, and/or a heavy chain having Q6, P9, R38, Q39, S40, P41, G42, K43, G44, L45, S84, D86, T87, A88, I89, Y90, Y91, W103, G104, Q105, G106, T107, L108, V109, T110, V111, Y147, E150, P151, V152, T173, F174, P175, A176, V177, Y185, S186, and L187, according to Kabat numbering.

[0187] In some embodiments, the mediotope-enabled antibody is generated by mutating 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 residues in the light chain of an antibody, such as a human or

humanized antibody, e.g., trastuzumab, for example, to resemble the corresponding positions in cetuximab (based on Kabat numbering). In some aspects, such an antibody contains mutated residues at positions 9, 10, 39, 40, 41, 42, 43, 45, 83, 85, and 100 of the light chain, based on Kabat numbering, compared to the human or humanized sequence. In one aspect, the light chain of the mediotope-enabled antibody contains: V9 or I9, I10 or L10, R39, T40, N41 G42, S43, R45, I83 or E83, D85, and A100, e.g.: V9, I10, R39, T40, N41, G42, S43, R45, I83, D85, and A100, based on Kabat numbering. In some embodiments, the antibody is otherwise human or humanized.

[0188] In some embodiments, the mediotope-enabled antibody is generated by mutating 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 residues such as 1 or 2 residues in the heavy chain of an antibody, such as a human or humanized antibody, e.g., trastuzumab, for example, to resemble the corresponding positions in cetuximab. In some aspects, such an antibody contains mutated residues at positions 40 and 89 in the heavy chain, based on Kabat numbering, compared to the human or humanized sequence. In one aspect, the heavy chain contains S40 and I89, based on Kabat numbering. In some embodiments, the antibody is otherwise human or humanized.

[0189] In some embodiments the mediotope-enabled antibody contains 13 mutations, e.g., compared to the humanized or human sequence. In one aspect, the mediotope-enabled antibody contains a light chain having 11 mutations and a heavy chain having two mutations, compared to the humanized or human sequence. In some aspects, the antibody contains V9 or I9, I10 or L10, R39, T40, N41 G42, S43, R45, I83, D85, and A100 in the light chain and S40 and I89 in the heavy chain, based on Kabat numbering. In some aspects, the antibody contains V9 or I9, I10 or L10, R39, T40, N41 G42, S43, R45, E83, D85, and A100 in the light chain and S40 and I89 in the heavy chain, based on Kabat numbering. In some aspects, the antibody contains V9, I10, R39, T40, N41 G42, S43, R45, I83, D85, and A100 in the light chain and S40 and I89 in the heavy chain, based on Kabat numbering. In some aspects, the antibody contains V9, I10, R39, T40, N41 G42, S43, R45, E83, D85, and A100 in the light chain and S40 and I89 in the heavy chain, based on Kabat numbering. In some embodiments, the antibody and/or the framework regions thereof is or are otherwise human or humanized.

[0190] In other embodiments, the mediotope-enabled antibodies are generated via CDR grafting, typically by modifying one or more complementarity determining region (CDR) (e.g., one or more of CDRs 1-3) of the heavy and/or light chain of a mediotope-enabled

antibody, such as any of the mediotope-enabled antibodies described herein, to replace them with other CDRs, such as CDRs of existing or new antibodies. CDR grafting is standard practice for producing humanized monoclonal antibodies, e.g., by grafting CDRs of an antibody generated in a non-human species, such as mouse, onto a human antibody

5 framework. See U.S. Patent Nos. 5,558,864 and 8,133,982; Kettleborough et al., "Humanization of a mouse monoclonal antibody by CDR-grafting: the importance of framework residues on loop conformation," *Protein Eng.*, 4:773-783 (1991). Thus, in certain embodiments, the antigen specificity of a mediotope-enabled antibody is altered by grafting the CDRs of preexisting or newly-generated antibodies of interest. Also among the provided
10 mediotope-enabled antibodies are such CDR-grafted mediotope-enabled antibodies.

[0191] In some embodiments, the mediotope-enabled antibodies are generated, using one of the antibodies disclosed herein (e.g., cetuximab, mediotope-enabled trastuzumab, or mediotope-enabled M5A (anti-CEA) antibody) as a template sequence, and carrying out one or more known antibody engineering methods to alter it, for example, to alter its antigen-
15 binding characteristics, producing a mediotope-enabled antibody with distinct characteristics. Known antibody engineering methods typically employed to alter antigen binding and other properties include various in vitro randomization, affinity maturation, and selection methods, including error-prone PCR, spiked PCR, site-directed mutagenesis, phage display and other selection methods. Also provided are constructs, libraries, and expression systems, including
20 GPI-linked expression systems, for carrying out such methods. Thus, in certain embodiments, the provided mediotope-enabled antibody has a light chain and/or heavy chain variable region with the framework region or regions (FRs) of a mediotope-enabled antibody, such as cetuximab, a mediotope-enabled trastuzumab, or a mediotope-enabled M5A (or FR(s) with at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the
25 FR(s) of such an antibody). In some aspects, such an antibody has one or more CDRs that are distinct from the CDRs of that mediotope-enabled antibody.

[0192] For example, in some embodiments, the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and/or an FR-L4 of the light chain sequence set forth in SEQ ID NO: 71 (or an FR-L1, FR-L2, FR-L3,
30 and/or FR-L4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-L1, FR-L2, FR-L3, and/or FR-L4 of SEQ ID NO: 71), and in some aspects at least one CDR that is distinct from the CDRs of the light chain sequence set forth

in SEQ ID NO: 71; and/or a VH region with an amino acid sequence having a heavy chain FR1 (FR-H1), an FR-H2, an FR-H3, and/or an FR-H4, of the heavy chain sequence set forth in SEQ ID NO: 72 (or an FR-H1, FR-H2, FR-H3, and/or FR-H4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-H1, FR-H2, FR-H3, and/or FR-H4 of SEQ ID NO: 72), and in some aspects at least one CDR that is distinct from the CDRs of the heavy chain sequence set forth in SEQ ID NO: 72.

[0193] In some embodiments, the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and/or an FR-L4 of the light chain sequence set forth in SEQ ID NO: 9 (or an FR-L1, FR-L2, FR-L3, and/or FR-L4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-L1, FR-L2, FR-L3, and/or FR-L4 of SEQ ID NO: 9), and in some aspects at least one CDR that is distinct from the CDRs of the light chain sequence set forth in SEQ ID NO: 9; and/or a VH region with an amino acid sequence having a heavy chain FR1 (FR-H1), an FR-H2, an FR-H3, and/or an FR-H4, of the heavy chain sequence set forth in SEQ ID NO: 6 (or an FR-H1, FR-H2, FR-H3, and/or FR-H4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-H1, FR-H2, FR-H3, and/or FR-H4 of SEQ ID NO: 6), and in some aspects at least one CDR that is distinct from the CDRs of the heavy chain sequence set forth in SEQ ID NO: 6.

[0194] In some embodiments, the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and/or an FR-L4 of the light chain sequence set forth in SEQ ID NO: 68 (or an FR-L1, FR-L2, FR-L3, and/or FR-L4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-L1, FR-L2, FR-L3, and/or FR-L4 of SEQ ID NO: 68), and in some aspects at least one CDR distinct from CDRs of the light chain sequence set forth in SEQ ID NO: 68; and/or a VH region with an amino acid sequence having a heavy chain FR1 (FR-H1), an FR-H2, an FR-H3, and/or an FR-H4, of the heavy chain sequence set forth in SEQ ID NO: 70 (or an FR-H1, FR-H2, FR-H3, and/or FR-H4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-H1, FR-H2, FR-H3, and/or FR-H4 of SEQ ID NO: 70), and in some aspects at least one CDR distinct from CDRs of the heavy chain sequence set forth in SEQ ID NO: 70.

[0195] In some embodiments, the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and/or an FR-L4 of the

light chain sequence set forth in SEQ ID NO: 61 (or an FR-L1, FR-L2, FR-L3, and/or FR-L4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-L1, FR-L2, FR-L3, and/or FR-L4 of SEQ ID NO: 61), and in some aspects at least one CDR that is distinct from the CDRs of the light chain sequence set forth in SEQ ID NO: 61; and/or a VH region with an amino acid sequence having a heavy chain FR1 (FR-H1), an FR-H2, an FR-H3, and/or an FR-H4, of the heavy chain sequence set forth in SEQ ID NO: 63 (or an FR-H1, FR-H2, FR-H3, and/or FR-H4 that is at least at or about 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identical to the FR-H1, FR-H2, FR-H3, and/or FR-H4 of SEQ ID NO: 63), and in some aspects at least one CDR that is distinct from the CDRs of the heavy chain sequence set forth in SEQ ID NO: 63. In some embodiments, the mediotope-enabled antibody has one or more CDRs distinct from the CDRs set forth in SEQ ID NO: 6, 7, 9, 10, 12, 14, 61, 63, 68, 69, 70, 71, and/or 72.

[0196] In some embodiments, the mediotope is an antibody other than cetuximab, does not specifically bind to an EGFR, binds to an antigen other than EGFR, and/or does not specifically bind to the epitope on EGFR that is specifically bound by cetuximab.

[0197] In some examples, the mediotope-enabled antibody is generated based on a template antibody that is selected from among abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, Fbta05, fontolizumab, gemtuzumab, lintuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, Trbs07, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab, anrukinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab, mavrilimumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, the antibody produced by the hybridoma 10B5, B6H12.2, and urelumab, fragments thereof, antibodies having the CDRs and/or antigen-binding regions thereof, and/or antibodies that compete for binding

with such antibodies; and/or antibodies having a sequence set forth in any of SEQ ID NOs: 78-124, and/or 125-170, fragments thereof antibodies having the CDRs and/or antigen-binding regions thereof, and/or antibodies that compete for binding with such antibodies.

Table 3 lists CAS® Registry Numbers for certain antibodies.

5 **Table 3**

Antibody	CAS Registry number
abagovomab	792921-10-9
abciximab	143653-53-6
adalimumab	331731-18-1
adecatumumab	503605-66-1
alemtuzumab	216503-57-0
indium (111In) altumomab pentetate	156586-92-4
arcitumomab	154361-48-5
arcitumumab	154361-48-5
atlizumab	375823-41-9
basiliximab	152923-56-3
bectumomab	158318-63-9
belimumab	356547-88-1
benralizumab	1044511-01-4
bevacizumab	216974-75-3
brentuximab	914088-09-8
canakinumab	914613-48-2
capromab pendetide	145464-28-4
capromab	151763-64-3
catumaxomab	509077-98-9
certolizumab	428863-50-7
certolizumab	428863-50-7
cetuximab	205923-56-4
clivatuzumab tetraxetan	943976-23-6
daclizumab	152923-56-3
denosumab	615258-40-7
eculizumab	219685-50-4
edrecolomab	156586-89-9
efalizumab	214745-43-4
etaracizumab	892553-42-3
etrumaxomab	509077-99-0
fanolesomab	225239-31-6
FBTA05	Lymphomun/FBTA05
fontolizumab	326859-36-3
gemtuzumab	220578-59-6
lintuzumab	166089-32-3
girentuximab	916138-87-9
golimumab	476181-74-5

ibritumomab	174722-31-7
igovomab	171656-50-1
Infliximab	170277-31-3
ipilimumab	477202-00-9
labetuzumab	219649-07-7
mepolizumab	196078-29-2
muromonab-CD3	140608-64-6
natalizumab	189261-10-7
nimotuzumab	828933-61-3
ofatumumab	679818-59-8
omalizumab	242138-07-4
oregovomab	213327-37-8
palivizumab	188039-54-5
panitumumab	339177-26-3
ranibizumab	347396-82-1
rituximab	174722-31-7
satumomab	138955-26-7
sulesomab	167747-19-5
tiuxetan (ibritumomab)	174722-31-7
tocilizumab	375823-41-9
tositumomab	192391-48-3
trastuzumab	180288-69-1
ustekinumab	815610-63-0
votumumab	148189-70-2
zalutumumab	667901-13-5
brodalumab	1174395-19-7
anrukinzumab	910649-32-0
bapineuzumab	648895-38-9
dalotuzumab	1005389-60-5
demcizumab (OMP-21M18)	1292853-12-3
ganitumab	905703-97-1
inotuzumab	635715-01-4
mavrilimumab	1085337-57-0
moxetumomab	1020748-57-5
moxetumomab pasudotox	1020748-57-5
rilotumumab	872514-65-3
sifalimumab	1143503-67-6
tanezumab	880266-57-9
tralokinumab	1044515-88-9
tremelimumab	745013-59-6
urelumab	934823-49-1
necitumumab	906805-06-9

[0198] In other examples, the template antibody is selected from among: abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate,

- anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab,
- 5 fanolesomab, Fbta05, fontolizumab, gemtuzumab, lintuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, Trbs07,
- 10 ustekinumab, visilizumab, votumumab, zalutumumab, the antibody produced by the hybridoma 10B5, and brodalumab, or tiuzetan. In some such examples, the one or more CDRs are CDRs present in these template antibodies, and/or the antibodies specifically bind to the same antigen or epitope as such antibodies, and/or compete for binding with such antibodies to their antigens.
- 15 **[0199]** Thus, in some cases, the meditope-enabled antibodies (including fragments thereof) specifically binds to an antigen selected from the group consisting of: CA-125, glycoprotein (GP) IIb/IIIa receptor, TNF-alpha, CD52, TAG-72, Carcinoembryonic antigen (CEA), interleukin-6 receptor (IL-6R), IL-2, interleukin-2 receptor a-chain (CD25), CD22, CD23 (also known as CD23A, Fc epsilon RII, FcεRII, FCE2, CLEC4J, C-Type Lectin
- 20 Domain Family 4 Member J, Immunoglobulin E-Binding Factor, Lymphocyte IgE Receptor, BLAST-2, or IGEBF), CD37 (also known as tetraspanin-26, TSPAN26, tspan-26, or GP52-40), Mucin-1, Prolactin Receptor (also known as PRL-R), SDC-1 (also known as CD138, Syndecan Proteoglycan 1, Syndecan 1, or Heparan Sulfate Proteoglycan Fibroblast Growth Factor Receptor), B-cell activating factor, interleukin-5 receptor (CD125), VEGF, VEGF-A,
- 25 CD30, IL-1beta, prostate specific membrane antigen (PSMA), CD3, EpCAM, EGF receptor (EGFR), MUC1, human interleukin-2 receptor, Tac, RANK ligand, a complement protein, e.g., C5, EpCAM, CD11a, e.g., human CD11a, an integrin, e.g., alpha-v beta-3 integrin, vitronectin receptor alpha v beta 3 integrin, HER2, neu, CD3, CD15, CD20 (small and/or large loops), Interferon gamma, CD33, CA-IX, TNF alpha, , CTLA-4, carcinoembryonic
- 30 antigen, IL-5, CD3 epsilon, CAM, Alpha-4-integrin, IgE, e.g., IgE Fc region, an RSV antigen, e.g., fusion protein of respiratory syncytial virus (RSV), TAG-72, NCA-90 (granulocyte cell antigen), IL-6, GD2, GD3, IL-12, IL-23, IL-17, CTAA16.88, IL13, interleukin-1 beta, beta-amyloid, IGF-1 receptor (IGF-1R), delta-like ligand 4 (DLL4), alpha

subunit of granulocyte macrophage colony stimulating factor receptor, hepatocyte growth factor, IFN-alpha, nerve growth factor, IL-13, PD-L1, CD326, CD47, and CD137. In some examples, the meditope-enabled antigen binds to another antigen identified as a target in a disease or condition of interest, such as cancer or other disease.

5

1. *CD19*

[0200] In one embodiment, the template antibody is an anti-CD19 antibody, for example, a human or humanized antibody or a mouse antibody for CD19, such as MOR208, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof. In some embodiments, the meditope-enabled antibody specifically binds to

10 CD19. CD19 (or cluster of differentiation-19) is, for example, identified by NCBI Accession No. NP_001171569 or UniProt Identifier P15391. In one aspect, CD19 is found on the surface of B cells from earliest recognizable B-lineage cells during development to B-cell blasts but is lost on maturation to plasma cells. In certain aspects, CD19 is a regulatory molecule that decreases the threshold for antigen receptor-dependent stimulation.

15

[0201] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 226 and/or of SEQ ID NO: 227 (with or without a leader sequence), which set forth light chain and heavy chain amino acid sequences, respectively, of MOR208 (XmAb@5574) (a monoclonal antibody that specifically binds to CD19, e.g., CD19 of immature, mature and malignant B cells), and/or comprises the amino acid sequence of SEQ

20 ID NO: 245 and/or 246 (with or without a leader sequence), which set forth VL and VH amino acid sequences of MOR208, respectively.

[0202] In some aspects, the meditope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the light chain sequence set forth in SEQ ID NO: 226, or of the light chain or VL of MOR208, and/or a CDR (i.e., one or more CDR,

25 e.g., CDR1, CDR2, and/or CDR3) of the heavy chain set forth in SEQ ID NO: 227, or of the heavy chain or VH of MOR208.

[0203] In some aspects, the VL region of the meditope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications,

30 compared to the amino acid sequence set forth as SEQ ID NO: 245, with or without the leader sequence, and/or the VH region of the meditope-enabled antibody contains one or

more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of the VH region of the amino acid sequence set forth as SEQ ID NO: 246, with or without the leader sequence.

5 **[0204]** In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of MOR208, or of SEQ ID NO: 226; and/or
 10 contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of MOR208, or SEQ ID NO: 227; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83,
 15 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of MOR208 or SEQ ID NO: 246; and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of MOR208 or SEQ ID NO: 245. In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all,
 20 of the CDRs within the heavy and/or light chain, as compared to MOR208 (e.g., as compared to the CDR(s) of SEQ ID NO: 226 or 227).

[0205] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD19 that is specifically bound by MOR208, but does specifically bind CD19, or does not contain the CDRs of MOR208, and/or does not compete for antigen binding with
 25 MOR208, but does specifically bind to CD19.

[0206] In some embodiments, the mediotope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 305 and/or has a heavy chain comprising the amino acid sequence of SEQ ID NO: 306. In some embodiments, the mediotope-enabled antibody or fragment comprises the cQFD mediotope, the variant 3 linker,
 30 and/or is fused to the heavy chain of a mediotope enabled anti-CD19 antibody (e.g., SEQ ID NO: 306).

2. CD22

[0207] In some embodiments, the template antibody is an anti-CD22 antibody, for example, a human or humanized antibody or a mouse antibody for CD22, such as epratuzumab, or moxetumomab, or an antibody having a heavy chain, light chain, V_H, or V_L, of such an antibody, or a functional fragment thereof. In some embodiments, the mediotope-enabled antibody specifically binds to CD22. CD22 (or cluster of differentiation-22) is a molecule belonging to the SIGLEC family of lectins, for example, as identified by NCBI Accession No. NP_001762 or UniProt Identifier P20273. In one aspect, CD22 is found on the surface of mature B cells and to a lesser extent on some immature B cells. In certain aspects, CD22 is a regulatory molecule that prevents the over-activation of the immune system and the development of autoimmune diseases. In one embodiment, a template antibody for CD22 specifically binds to one or more epitopes on a polypeptide or protein having the amino acid sequence of SEQ ID NO: 175, or a polypeptide or protein having the amino acid sequence encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 176.

[0208] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 177 and/or of SEQ ID NO: 178 (with or without the leader sequence, which in each sequence is identified by amino acid positions within the sequence), which set forth light chain and heavy chain amino acid sequences, respectively, of epratuzumab (a humanized monoclonal antibody that specifically binds to CD22, e.g., CD22 of mature and malignant B cells), and/or comprises the amino acid sequence of SEQ ID NO: 179 and/or 183 (with or without the leader sequence, which in each sequence is identified by amino acid positions within the sequence), which set forth V_L and V_H amino acid sequences of epratuzumab, respectively.

[0209] The epratuzumab light chain sequence is set forth in SEQ ID NO: 177, which comprises the leader sequence set forth in amino acid positions 1-20 in SEQ ID NO: 177. The epratuzumab heavy chain sequence is set forth in SEQ ID NO: 178, which comprises the leader sequence set forth in amino acid positions 1-19 in SEQ ID NO: 178. The epratuzumab light chain variable (V_L) region sequence is set forth in SEQ ID NO: 179, which comprises the leader sequence set forth in amino acid positions 1-20 in SEQ ID NO: 179. The epratuzumab heavy chain variable (V_H) region sequence is set forth in SEQ ID NO: 183,

which comprises the leader sequence set forth in amino acid positions 1-19 in SEQ ID NO: 183.

[0210] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the light chain or VL sequence set forth in SEQ ID NO: 177 or SEQ ID NO: 179, or of the light chain or VL of epratuzumab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the heavy chain or VH sequence set forth in SEQ ID NO: 178 or 183, or of the heavy chain or VH of epratuzumab.

[0211] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 179, with or without the leader sequence, and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 183, with or without the leader sequence.

[0212] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of epratuzumab, or of SEQ ID NO: 177 or of 179; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of epratuzumab, of SEQ ID NO: 178 or of 183; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of epratuzumab (e.g., to the amino acid sequence of SEQ ID NO: 183); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of epratuzumab (e.g., to the amino acid sequence of SEQ ID NO: 179). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to

epratuzumab (e.g., as compared to the CDR(s) of SEQ ID NO: 177 or 179 or SEQ ID NO: 178 or 183).

[0213] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD22 that is specifically bound by epratuzumab, but does specifically bind CD22, or does not contain the CDRs of epratuzumab, and/or does not compete for antigen binding with epratuzumab, but does specifically bind to CD22.

[0214] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 65 and/or of SEQ ID NO: 67 (with or without the leader sequence/residue, which is the N-terminal methionine of SEQ ID NO: 67), which set forth V_L and V_H amino acid sequences, respectively, of moxetumomab (an anti-CD22 mouse monoclonal antibody), and/or comprises the amino acid sequence of SEQ ID NO: 66 (with or without the leader sequence, which is the N-terminal methionine of SEQ ID NO: 66), which sets forth a heavy chain amino acid sequence of moxetumomab.

[0215] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 65, or of the light chain or VL of moxetumomab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the heavy chain or VH sequence set forth in SEQ ID NO: 66 or 67, or of the heavy chain or VH of moxetumomab.

[0216] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 65 with or without the leader sequence, or VL of moxetumomab and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 67, with or without the leader sequence, or VH of moxetumomab.

[0217] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework

- regions (or respective one or more FR-L(s)) of moxetumomab, or of SEQ ID NO: 65; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of moxetumomab, of SEQ ID NO: 66 or 67; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of moxetumomab (e.g., to the amino acid sequence of SEQ ID NO: 67); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of moxetumomab (e.g., to the amino acid sequence of SEQ ID NO: 65). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to moxetumomab (e.g., as compared to the CDR(s) of SEQ ID NO: 65 or 66 or 67).
- 15 **[0218]** In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD22 that is specifically bound by moxetumomab, but does specifically bind CD22, or does not contain the CDRs of moxetumomab, and/or does not compete for antigen binding with moxetumomab, but does specifically bind to CD22.

3. CD23

- 20 **[0219]** In one embodiment, the template antibody is an anti-CD23 antibody, for example, a human or humanized antibody or a mouse antibody for CD23, such as lumiliximab, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof.
- [0220]** In some embodiments, the mediotope-enabled antibody specifically binds to CD23. CD23 is also known as Fc epsilon RII, or FcεRII, is the “low-affinity” receptor for IgE, an antibody isotype involved in allergy and resistance to parasites, and is important in regulation of IgE levels. CD23 is a C-type lectin, for example, as identified by NCBI Accession No. NP_001193948.2 or UniProt Identifier P06734. CD23 antigen is a 45-kDa type II transmembrane glycoprotein that is expressed on several hematopoietic cell types. In some aspects, CD23 is expressed on mature B cells, activated macrophages, eosinophils, follicular dendritic cells, and platelets. CD23 is the only FcR that does not belong to the immunoglobulin gene superfamily. The functions of CD23 include modulation of IgE
- 25
- 30

production by B cells and promoting the survival of germinal center-derived B cells. The expression of CD23 is highly upregulated in normally activated follicular B cells and in CLL cells.

[0221] In one embodiment, a template antibody for CD23 specifically binds to one or more epitopes on a polypeptide or protein having the amino acid sequence of SEQ ID NO: 172, or a polypeptide or protein having the amino acid sequence encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 184.

[0222] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 185 and/or of SEQ ID NO: 190 (with or without the leader sequence/residue, which where applicable corresponds to amino acids 1-22 of SEQ ID NO: 185 and amino acids 1-19 of SEQ ID NO: 190), which set forth VL and VH amino acid sequences, respectively, of lumiliximab.

[0223] Lumiliximab (also known as IDEC-152, P5E8, gomiliximab; Biogen Idec) is a primatized anti-CD23 mAb that contains cynomolgus macaque variable regions and human constant regions (IgG1- κ). It was originally developed to inhibit the production of IgE by activated human peripheral blood B cells; however, later on it gained an appreciation as a potent anti-CD23 mAb. Preclinical data suggest that lumiliximab mediates its antitumor effect on CLL cells and CD23-expressing B cells predominantly by the intrinsic pathway of apoptosis (i.e., inducing downregulation of anti-apoptotic proteins Bcl-2, Bcl-XL and XIAP, activation of Bax and release of mitochondrial cytochrome c). Synergistic cytotoxicity has also been demonstrated on CD23-expressing B-cell lines and primary CLL cells when lumiliximab was combined with rituximab or fludarabine in xenograft models. In a Phase I clinical trial of 46 heavily pretreated CLL patients, lumiliximab showed modest clinical activity as a single agent. Although no objective Complete Responses (CRs) or Partial Responses (PRs) were observed, lumiliximab did reduce enlarged lymph node size in 52% of patients and decreased peripheral blood lymphocyte counts in 91% of patients. The safety profile of lumiliximab demonstrated that the majority of adverse events (AEs) are limited to grade 1/2. Lumiliximab was not immunosuppressive and the MTD (maximum tolerated dose) was not reached.

[0224] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID

NO: 185, or of the light chain or VL of lumiliximab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 190, or of the heavy chain or VH of lumiliximab.

[0225] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 185 with or without the leader sequence, or VL of lumiliximab and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 190, with or without the leader sequence, or VH of lumiliximab.

[0226] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of lumiliximab, or of SEQ ID NO: 185; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of lumiliximab, of SEQ ID NO: 190; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of lumiliximab (e.g., to the amino acid sequence of SEQ ID NO: 190); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of lumiliximab (e.g., to the amino acid sequence of SEQ ID NO: 185). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to lumiliximab (e.g., as compared to the CDR(s) of SEQ ID NO: 185 or 190).

[0227] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD23 that is specifically bound by lumiliximab, but does specifically bind

CD23, or does not contain the CDRs of lumiliximab, and/or does not compete for antigen binding with lumiliximab, but does specifically bind to CD23.

4. CD33

[0228] In one embodiment, the template antibody is an anti-CD33 antibody, for example, a human or humanized antibody or a mouse antibody for CD33, such as gemtuzumab, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof. In some embodiments, the meditope-enabled antibody specifically binds to CD33. CD33 (or cluster of differentiation-33) is, for example, identified by UniProt Identifier P20138. In one aspect, CD33 is found on the surface of myeloid cells.

[0229] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 224 and/or of SEQ ID NO: 225 (with or without a leader sequence), which set forth light chain and heavy chain amino acid sequences, respectively, of gemtuzumab (Mylotarg) (a monoclonal antibody that specifically binds to CD33, e.g., CD33 of immature, mature and malignant B cells), and/or comprises the amino acid sequence of SEQ ID NO: 243 and/or 245 (with or without a leader sequence), which set forth VL and VH amino acid sequences of gemtuzumab, respectively.

[0230] In some embodiments, the meditope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 293 and/or has a heavy chain comprising the amino acid sequence of SEQ ID NO: 294. In some embodiments, the meditope-enabled antibody or fragment comprises the cQFD meditope, the variant 1 linker, and/or is fused to the heavy chain of a meditope enabled gemtuzumab (e.g., SEQ ID NO: 294).

[0231] In some embodiments, the meditope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 295 and/or has a heavy chain comprising the amino acid sequence of SEQ ID NO: 296. In some embodiments, the meditope-enabled antibody or fragment comprises the cQFD meditope, the variant 2 linker, and/or is fused to the heavy chain of a meditope enabled gemtuzumab (e.g., SEQ ID NO: 296).

[0232] In some embodiments, the meditope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 297 and/or has a heavy chain

comprising the amino acid sequence of SEQ ID NO: 298. In some embodiments, the mediotope-enabled antibody or fragment comprises the cQFD mediotope, the variant 3 linker, and/or is fused to the heavy chain of a mediotope enabled gemtuzumab (e.g., SEQ ID NO: 298).

- 5 **[0233]** In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the light chain sequence set forth in SEQ ID NO: 224, or of the light chain or VL of gemtuzumab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the heavy chain set forth in SEQ ID NO: 225, or of the heavy chain or VH of gemtuzumab.
- 10 **[0234]** In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 243, with or without the leader sequence, and/or the VH region of the mediotope-enabled antibody contains one or
15 more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of the VH region of the amino acid sequence set forth as SEQ ID NO: 244, with or without the leader sequence.
- 20 **[0235]** In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of gemtuzumab, or of SEQ ID NO: 224; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g.,
25 within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of gemtuzumab, or SEQ ID NO: 225; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region
30 of gemtuzumab or SEQ ID NO: 244; and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of gemtuzumab or SEQ ID NO: 243. In some

embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to gemtuzumab (e.g., as compared to the CDR(s) of SEQ ID NO: 224 or 225).

5 [0236] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD33 that is specifically bound by gemtuzumab, but does specifically bind CD33, or does not contain the CDRs of gemtuzumab, and/or does not compete for antigen binding with gemtuzumab, but does specifically bind to CD33.

10 [0237] In one embodiment, the present disclosure provides a mediotope-enabled lintuzumab. In one embodiment, the mediotope-enabled lintuzumab comprises a heavy chain of SEQ ID NO: 289, 290, 291 or 292. In one embodiment, the mediotope-enabled lintuzumab comprises a light chain of SEQ ID NO: 285, 286, 287 or 288. The original amino acid sequences of lintuzumab are provided in SEQ ID NO: 284 (heavy chain) and 283 (light chain) as references.

15 [0238] In one embodiment, the template antibody is an anti-CD33 antibody, for example, a human or humanized antibody or a mouse antibody for CD33, such as lintuzumab, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof. In some embodiments, the mediotope-enabled antibody specifically binds to CD33. CD33 (or cluster of differentiation-33) is, for example, identified by UniProt Identifier P20138. In one aspect, CD33 is found on the surface of myeloid cells.

20 [0239] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 285-288 and/or of SEQ ID NO: 289-292 (with or without a leader sequence shown as underlined residues), which set forth light chain and heavy chain amino acid sequences, respectively, of lintuzumab (a monoclonal antibody that specifically binds to CD33, e.g., CD33 of immature, mature and malignant B cells).

25 [0240] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the light chain sequence set forth in SEQ ID NO: 284, or of the light chain or VL of lintuzumab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the heavy chain set forth in SEQ ID NO: 283, or of the heavy chain or VH of lintuzumab.

[0241] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications).

[0242] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of lintuzumab, or of SEQ ID NO: 285-288; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of lintuzumab, or SEQ ID NO: 289-292; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of lintuzumab or SEQ ID NO: 289-292; and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of lintuzumab or SEQ ID NO: 285-288. In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to lintuzumab (e.g., as compared to the CDR(s) of SEQ ID NO: 285-288 or 289-292).

[0243] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD33 that is specifically bound by lintuzumab, but does specifically bind CD33, or does not contain the CDRs of lintuzumab, and/or does not compete for antigen binding with lintuzumab, but does specifically bind to CD33.

5. CD37

[0244] In one embodiment, the template antibody is an anti-CD37 antibody, for example, a human or humanized antibody or a mouse antibody for CD37, such as otlertuzumab, or an

antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof.

[0245] In some embodiments, the meditope-enabled antibody specifically binds to CD37. CD37, also known as GP52-40 or TSPAN26, is a member of the transmembrane 4
5 superfamily, also known as the tetraspanin family. WO 2011112978 discloses CD37-binding molecules and immunoconjugates thereof, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

[0246] In one embodiment, a template antibody for CD37 specifically binds to one or more epitopes on a polypeptide or protein having the amino acid sequence of SEQ ID NO:
10 191, or a polypeptide or protein having the amino acid sequence encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 192.

[0247] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 193 and/or of SEQ ID NO: 194, which set forth VL and VH amino acid sequences, respectively, of otlertuzumab. Otlertuzumab (also known as Betalutin or
15 IMGN529) targets CD37, which has an expression profile similar to that of CD20 on NHL subtypes.

[0248] In some aspects, the meditope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 193, or of the light chain or VL of otlertuzumab, and/or a CDR (i.e., one or more CDR,
20 e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 194, or of the heavy chain or VH of otlertuzumab.

[0249] In some aspects, the VL region of the meditope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications,
25 compared to the amino acid sequence set forth as SEQ ID NO: 193, or VL of otlertuzumab and/or the VH region of the meditope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 194, or VH of otlertuzumab.

[0250] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of otlertuzumab, or of SEQ ID NO: 193; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of otlertuzumab, of SEQ ID NO: 194; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of otlertuzumab (e.g., to the amino acid sequence of SEQ ID NO: 194); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of otlertuzumab (e.g., to the amino acid sequence of SEQ ID NO: 193). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to otlertuzumab (e.g., as compared to the CDR(s) of SEQ ID NO: 193 or 194).

[0251] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a CD37 that is specifically bound by otlertuzumab, but does specifically bind CD37, or does not contain the CDRs of otlertuzumab, and/or does not compete for antigen binding with otlertuzumab, but does specifically bind to CD37.

6. *Mucin-1*

[0252] In one embodiment, the template antibody is an anti- Mucin-1 antibody, for example, a human or humanized antibody or a mouse antibody for Mucin-1, such as hPAM4-Cide (also known as clivatuzumab tetraxetan), or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof.

[0253] In some embodiments, the mediotope-enabled antibody specifically binds to Mucin 1. Mucin-1 is also known as Mucin 1, cell surface associated (MUC1), or polymorphic epithelial mucin (PEM)) and is a mucin encoded by the MUC1 gene in humans, of example, as identified by NCBI Accession No. NP_001018021 or UniProt Identifier P15941. In one embodiment, a template antibody for Mucin-1 specifically binds to one or more epitopes on a

polypeptide or protein having the amino acid sequence of SEQ ID NO: 195, or a polypeptide or protein having the amino acid sequence encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 196.

[0254] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 197 and/or of SEQ ID NO: 198, which set forth VL and VH amino acid sequences, respectively, of hPAM4-Cide (also known as clivatuzumab tetraxetan), respectively. WO 2010042562 discloses additional Mucin-1 antibodies, the disclosure of which is incorporated herein by reference for all purposes.

[0255] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 197, or of the light chain or VL of hPAM4-Cide, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 198, or of the heavy chain or VH of hPAM4-Cide.

[0256] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 197 with or without the leader sequence, or VL of hPAM4-Cide and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 198, with or without the leader sequence, or VH of hPAM4-Cide.

[0257] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of hPAM4-Cide, or of SEQ ID NO: 197; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of hPAM4-Cide, of SEQ ID NO:

198; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of hPAM4-Cide (e.g., to the amino acid sequence of SEQ ID NO: 198); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of hPAM4-Cide (e.g., to the amino acid sequence of SEQ ID NO: 197). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to hPAM4-Cide (e.g., as compared to the CDR(s) of SEQ ID NO: 197 or 198). SEQ ID NO:197 shows an hPAM4-Cide light chain variable (VL) region sequence and SEQ ID NO:198 shows an hPAM4-Cide heavy chain variable (HL) region sequence.

[0258] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a Mucin1 that is specifically bound by hPAM4-Cide, but does specifically bind Mucin1, or does not contain the CDRs of hPAM4-Cide, and/or does not compete for antigen binding with hPAM4-Cide, but does specifically bind to Mucin1.

7. *Prolactin Receptor*

[0259] In one embodiment, the template antibody is an anti- prolactin receptor (PRLR) antibody, for example, a human or humanized antibody or a mouse antibody for prolactin receptor, such as LFA-102 or 002-H08, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof.

[0260] In some embodiments, the mediotope-enabled antibody specifically binds to prolactin receptor. In one aspect, the prolactin receptor is encoded by a gene on Chromosome 5p13-14, and interacts with the prolactin molecule as a transmembrane receptor. The prolactin receptor contains an extracellular region that binds prolactin, a transmembrane region, and a cytoplasmic region.

[0261] In some embodiments, the template antibody comprises the amino acid sequence of a VL and/or VH amino acid sequence of LFA-102, which is a humanized monoclonal antibody of the IgG1 kappa subtype, and binds to the putative dimerization region of PRLR in a non-ligand competitive manner and inhibits PRL-induced signaling.

[0262] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL of LFA-102, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH of LFA-102.

[0263] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the VL of LFA-102 and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the VH of LFA-102.

[0264] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of LFA-102; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of LFA-102; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of LFA-102; and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of LFA-102. In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to LFA-102.

[0265] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a prolactin receptor that is specifically bound by LFA-102, but does specifically bind prolactin receptor, or does not contain the CDRs of LFA-102, and/or does not compete for antigen binding with LFA-102, but does specifically bind to prolactin receptor.

[0266] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 208 and/or of SEQ ID NO: 209, which set forth VL and VH amino acid

sequences, respectively, of 002-H08. Application Publication No. US 20120315276 discloses prolactin receptor antibodies including 002-H08, the disclosure of which is incorporated herein by reference for all purposes.

[0267] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 208, or of the light chain or VL of 002-H08, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 209, or of the heavy chain or VH of 002-H08.

[0268] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 208, or VL of 002-H08 and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 209, or VH of 002-H08.

[0269] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of 002-H08, or of SEQ ID NO: 208; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of 002-H08, or of SEQ ID NO: 209; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of 002-H08 (e.g., to the amino acid sequence of SEQ ID NO: 209); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of 002-H08 (e.g., to the amino acid sequence of SEQ ID NO: 208). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the

heavy and/or light chain, as compared to 002-H08 (e.g., as compared to the CDR(s) of SEQ ID NO: 208 or 209).

[0270] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a prolactin receptor that is specifically bound by 002-H08, but does specifically
5 bind prolactin receptor, or does not contain the CDRs of 002-H08, and/or does not compete for antigen binding with 002-H08, but does specifically bind to prolactin receptor.

8. *SDC-1*

[0271] In one embodiment, the template antibody is an anti-SDC-1 antibody, for example, a human or humanized antibody or a mouse antibody for SDC-1 (also known as
10 Syndecan 1, or CD138), such as indatuximab ravtansine, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof.

[0272] In some embodiments, the mediotope-enabled antibody specifically binds to SDC-1. In one aspect, SDC-1 is a transmembrane (type I) heparan sulfate proteoglycan and is a member of the syndecan proteoglycan family. The syndecans mediate cell binding, cell
15 signaling, and cytoskeletal organization and syndecan receptors are required for internalization of the HIV-1 tat protein. The syndecan-1 protein functions as an integral membrane protein and participates in cell proliferation, cell migration and cell-matrix interactions via its receptor for extracellular matrix proteins. Altered syndecan-1 expression has been detected in several different tumor types. While several transcript variants may
20 exist for this gene, the full-length nature of only two have been described to date. These two represent the major variants of this gene and encode the same protein. In one embodiment, a template antibody for SDC-1 specifically binds to one or more epitopes on a polypeptide or protein having the amino acid sequence of SEQ ID NO: 210.

[0273] In some embodiments, the template antibody comprises the amino acid sequence
25 of SEQ ID NO: 211 and/or of SEQ ID NO: 212, which set forth VL and VH amino acid sequences, respectively, of indatuximab ravtansine. Indatuximab ravtansine (also known as BT-062, BT062, or B-B4) is a SDC-1 antibody.

[0274] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID
30 NO: 211, or of the light chain or VL of indatuximab ravtansine, and/or a CDR (i.e., one or

more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 212, or of the heavy chain or VH of indatuximab ravtansine.

[0275] In some aspects, the VL region of the meditope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 211, or VL of indatuximab ravtansine and/or the VH region of the meditope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 212, with or without the leader sequence, or VH of indatuximab ravtansine.

[0276] In some embodiments, the meditope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of indatuximab ravtansine, or of SEQ ID NO: 211; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of indatuximab ravtansine, of SEQ ID NO: 212; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of indatuximab ravtansine (e.g., to the amino acid sequence of SEQ ID NO: 212); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of indatuximab ravtansine (e.g., to the amino acid sequence of SEQ ID NO: 211). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to indatuximab ravtansine (e.g., as compared to the CDR(s) of SEQ ID NO: 211 or 212).

[0277] In some aspects, the meditope-enabled antibody does not specifically bind to the epitope of a SDC-1 that is specifically bound by indatuximab ravtansine, but does specifically

bind SDC-1, or does not contain the CDRs of indatuximab ravtansine, and/or does not compete for antigen binding with indatuximab ravtansine, but does specifically bind to SDC-1.

9. HER-2

5 [0278] In one embodiment, the template antibody is an anti-HER-2 antibody, for example, a human or humanized antibody or a mouse antibody for HER-2 (also known as ERBB2), such as trastuzumab (Herceptin®), or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof.

[0279] In some embodiments, the mediotope-enabled antibody specifically binds to HER-
10 2. In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 303, or of the light chain or VL of trastuzumab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 304, or of the heavy chain or VH of trastuzumab.

15 [0280] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence of trastuzumab and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are
20 in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of trastuzumab.

[0281] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87,
25 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of trastuzumab; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87,
30 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of trastuzumab; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92,

93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of trastuzumab; and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of trastuzumab. In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to trastuzumab.

[0282] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a HER-2 that is specifically bound by trastuzumab, but does specifically bind HER-2, or does not contain the CDRs of trastuzumab, and/or does not compete for antigen binding with trastuzumab, but does specifically bind to HER-2.

[0283] In some embodiments, the mediotope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 303 and/or has a heavy chain comprising the amino acid sequence of SEQ ID NO: 304. In some embodiments, the mediotope-enabled antibody or fragment comprises the cQFD mediotope, the variant 3 linker, and/or is fused to the heavy chain of a mediotope enabled trastuzumab (e.g., SEQ ID NO: 304).

10. EGFR

[0284] In one embodiment, the template antibody is an anti-EGFR antibody, for example, a human or humanized antibody or a mouse antibody for EGFR, such as ABT-806, zatuximab, or an antibody having a heavy chain, light chain, VH, or VL, of such an antibody, or a functional fragment thereof. In some aspects, the anti-EGFR template antibody is not cetuximab, does not contain all or some CDRs of cetuximab, and/or does not compete for binding with cetuximab.

[0285] In one embodiment, a template antibody for EGFR specifically binds to one or more epitopes on a polypeptide or protein having the amino acid sequence of SEQ ID NO: 213, or a polypeptide or protein having the amino acid sequence encoded by a polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 214.

[0286] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 215 and/or of SEQ ID NO: 216, which set forth VL and VH amino acid sequences, respectively, of ABT-806 (also known as mAb806/414), which is an EGFR

antibody, and/or comprises the amino acid sequence of SEQ ID NO: 217 and SEQ ID NO: 218 which set forth light chain and heavy chain sequences of ABT-806, respectively.

[0287] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 215, or of the light chain or VL of ABT-806, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 216, or of the heavy chain or VH of ABT-806.

[0288] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 215, or VL of ABT-806 and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 216, or VH of ABT-806.

[0289] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of ABT-806, or of SEQ ID NO: 215; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of ABT-806, of SEQ ID NO: 216; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of ABT-806 (e.g., to the amino acid sequence of SEQ ID NO: 216); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of ABT-806 (e.g., to the amino acid sequence of SEQ ID NO: 215). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the

heavy and/or light chain, as compared to ABT-806 (e.g., as compared to the CDR(s) of SEQ ID NO: 215 or 216).

[0290] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a EGFR that is specifically bound by ABT-806, but does specifically bind EGFR, or does not contain the CDRs of ABT-806, and/or does not compete for antigen binding with ABT-806, but does specifically bind to EGFR.

[0291] In some embodiments, the template antibody comprises the amino acid sequence of SEQ ID NO: 219 and/or of SEQ ID NO: 220, which set forth VL and VH amino acid sequences, respectively, of zatuximab, and/or comprises the amino acid sequence of SEQ ID NO: 221 and/or 222, which set forth light and heavy chain sequences of zatuximab, an EGFR antibody.

[0292] In some aspects, the mediotope-enabled antibody or fragment has a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VL sequence set forth in SEQ ID NO: 219, or of the light chain or VL of zatuximab, and/or a CDR (i.e., one or more CDR, e.g., CDR1, CDR2, and/or CDR3) of the VH sequence set forth in SEQ ID NO: 220, or of the heavy chain or VH of zatuximab.

[0293] In some aspects, the VL region of the mediotope-enabled antibody contains one or more, generally a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications, compared to the amino acid sequence set forth as SEQ ID NO: 219, or VL of zatuximab and/or the VH region of the mediotope-enabled antibody contains one or more, e.g., a plurality of modifications (which generally are in the framework regions), such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 modifications) compared to the amino acid sequence of SEQ ID NO: 220, or VH of zatuximab.

[0294] In some embodiments, the mediotope-enabled antibody contains, within its light chain framework regions (or within one or more such regions, e.g., within FR-L1, FR-L2, FR-L3, and/or FR-L4), at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the light chain framework regions (or respective one or more FR-L(s)) of zatuximab, or of SEQ ID NO: 219; and/or contains, within its heavy chain framework regions (or within one or more such regions, e.g., within FR-H1, FR-H2, FR-H3, and/or FR-H4), at least at or about 75, 76, 77, 78, 79, 80, 81,

82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the heavy chain framework regions (or respective one or more FR-H) of zatuximab, of SEQ ID NO: 220; and/or contains, within its VH region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VH region of zatuximab (e.g., to the amino acid sequence of SEQ ID NO: 220); and/or contains, within its VL region, at least at or about 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99 % identity to the VL region of zatuximab (e.g., to the amino acid sequence of SEQ ID NO: 220). In some embodiments, the antibody contains all or at least 95, 96, 97, 98, or 99 % identity within one or more, e.g., all, of the CDRs within the heavy and/or light chain, as compared to zatuximab (e.g., as compared to the CDR(s) of SEQ ID NO: 219 or 220).

[0295] In some aspects, the mediotope-enabled antibody does not specifically bind to the epitope of a EGFR that is specifically bound by zatuximab, but does specifically bind EGFR, or does not contain the CDRs of zatuximab, and/or does not compete for antigen binding with zatuximab, but does specifically bind to EGFR.

[0296] In some embodiments, the mediotope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 299 and/or has a heavy chain comprising the amino acid sequence of SEQ ID NO: 300. In some embodiments, the mediotope-enabled antibody or fragment comprises the cQFD mediotope, the variant 1 linker, and/or is fused to cetuximab.

[0297] In some embodiments, the mediotope-enabled antibody or fragment has a light chain comprising the amino acid sequence of SEQ ID NO: 301 and/or has a heavy chain comprising the amino acid sequence of SEQ ID NO: 302. In some embodiments, the mediotope-enabled antibody or fragment comprises the cQFD mediotope, the variant 3 linker, and/or is fused to cetuximab substituted as I83E (Kabat numbering), e.g., SEQ ID NO: 302.

[0298] The mediotope-enabled antibodies generally further include a constant region, typically a heavy and light chain constant region, which generally are human or partially human constant regions. In some aspects, the heavy chain constant region includes a CH1, or a portion thereof. In some aspects, the light chain constant region includes a CL, or a portion thereof. In some embodiments, the portion of the constant region is sufficient to render the antibody capable of binding to the mediotope, e.g., with the requisite binding affinity. In some

aspects, the constant regions are the constant regions of cetuximab or trastuzumab. Thus, in some aspects, the heavy chain constant regions are one or more human IgG1 constant regions; in some aspects, the light chain constant regions are kappa constant chain regions. In other examples, the constant regions can include those of other isotypes, including human (or other organism, e.g., murine or chicken) IgG1, IgG2, IgG3, IgG4, IgEs, IgA1, IgA2, IgD, or IgM, and can include kappa or lambda constant regions. Thus, among the provided mediotope-enabled antibodies are those generated by mutation of residues in other IgGs, such as human, murine, or chicken, or other immunoglobulins. In other words, the mediotope-enabling methods provided herein may be used for any antibody, including IgA, IgE, IgD, and IgM and from any organism that produces antibodies including but not limited to chicken, murine, rat, bovine, rabbit, primates, and goat.

[0299] For example, the sequences of the first constant region (CH1) of a human IgG1, IgG2, IgG3, and IgG4 differ at residues that are not within the mediotope-binding region of cetuximab, confirming that the mediotope-enabling technology is applicable to isotypes other than the IgG1 of cetuximab. As another example, the sequence and structural alignment of an IgG1 and an IgE Fab domain indicates residues on the IgE near the mediotope binding site.

[0300] The provided methods for mediotope-site grafting of the Fab cavity within monoclonal antibodies can be used to create a unique handle for mediotope binding and used with the technology previously disclosed and for newly-generated antibodies. In certain embodiments, the mediotope binding site can be created on pre-existing and all future monoclonal antibodies.

[0301] Also provided are methods for modifying the mediotope-enabled antibodies, for example, to alter various properties of the mediotope-enabled antibodies, including aspects of the interaction with the mediotopes, including affinity, avidity, pH-dependence, as well as other aspects, including pharmacokinetics (PK) and pharmacodynamics (PD) of the antibodies. Thus, also among the provided mediotope-enabled antibodies are those modified antibodies generated according to those methods, e.g., by generating a pharmacophore binding model, including antibodies having any one or more of the modifications described in section F, below.

[0302] Also among the antibodies used as template antibodies to generate the mediotope-enabled antibodies are modified antibodies and portions thereof, such as a CovX-BodyTM.

Thus, among the provided meditope-enabled antibodies are CovX-bodies, modified to allow their binding to one or more of the provided meditoes, e.g., with an affinity as described herein.

[0303] Also provided are complexes containing one or more meditope bound to a meditope-enabled antibody, such as any of the antibodies described herein.

[0304] Also provided are nucleic acids, such as cDNA and RNA molecules, encoding the meditope-enabled antibodies, and vectors and libraries containing the same, as well as methods for their use, including selection and expression methods and methods for generating transgenic animals using such constructs.

[0305] The table below shows the sequences of additional linkers and meditope enabled antibodies which are referenced in the application.

#	SEQUENCE	ANNOTATION
254	QIVLTQSPAIMASASPGEKVTITCSASSSISYMHWFQ QRTNGSPRLWIYTTSNLASGVPARFSGSGSGTSYSL TISRMEAEDEADYCHQRSTYPLTFGAGTKLELKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKSTYSLSTLTLL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Anti-CD33 Light Chain
255	CQFDLSTRRLKCGGGAREEAAKAAEEAKKAAEEAAK AAQVQLQQSGAELAKPGASVKMSCKASGYTFTSYRM HWVKQSPGQGLEWIGYINPSTGYTEYNQKFKDKATL TADKSSSTAYMQLSSLTFEDSAIYYCARGGGVFDYW GQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTP PVLDSGDSFFLYSKLTVDKSRWQQGNVFSQSVMHEA LHNHYTQKSLSLSPGK	Anti-CD33 SnAP-body variant 1 heavy chain
256	CQFDLSTRRLKCGGGAAARAAAAAARAQVQLQQ SGAELAKPGASVKMSCKASGYTFTSYRMHWVKQSPG QGLEWIGYINPSTGYTEYNQKFKDKATLTADKSSST AYMQLSSLTFEDSAIYYCARGGGVFDYWGQGTTLTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSGDS	Anti-CD33 SnAP-body variant 2 heavy chain

	FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	
257	QVQLQQSGAELAKPGASVKMSCKASGYTFTSYRMHW VKQSPGGGLEWIGYINPSTGYTEYNQKFKDKATLTA DKSSSTAYMQLSSLTFEDSAIYYCARGGGVFDYWGQ GTTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK	Control anti-CD33 heavy chain
258	QIVLTQSPAIMASASPGEKVTITCSASSISYMHWFQ QKPGTSPKLWIYTTSNLASGVPARFSGSGSGTSYSL TISRMEAEDAATYYCHQRSTYPLTFGSGTKLELK	Meditope-enabled Gemtuzumab VL
259	DIQMTQSPSTLSASVGDRTITCRASQSINTWLAWY QQKPGKAPKLLMYKASSLESGVPSRFISGSGTEFT LTISLQPDFFATYYCQQYNDSKMFQGQTKVEVK	Meditope-enabled Gemtuzumab VL
260	QVQLQQSGAELAKPGASVKMSCKASGYTFTSYRMHW VKQRPQGGLWIGYINPSTGYTEYNQKFKDKATLTA DKSSSTAYMQLSSLTFEDSAVYYCARGGGVFDYWGQ GTTTLTVSS	Meditope-enabled gemtuzumab VH
261	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSRSAI IW VRQAPGGGLEWMGGIIVPMFGPPNYAQKFQGRVTITA DESTNTAYMELSSLRSEDTAFYFCAGGYGIYSPEEY NGGLVTVSS	Meditope-enabled gemtuzumab VH
262	GGGAREEAAKAAEEAKKAAEEAAKAA	Synthetic linker 1
263	GGGAAARAAAAAARA	Synthetic linker 2
264	GGGSKDEIDSAVK	Synthetic linker 3
265	GGG	Flexible linker portion 1
266	AREEAAKAAEEAKKAAEEAAKAA	Rigid linker portion 1
267	AAAAAARAAAAARA	Rigid linker portion 2
268	SKDEIDSAVK	Rigid linker portion 3
269	HSQGTFTSDYSKYLDSSRAQDFVQWLMNT	1GCN glucagon
270	CGGREGVLKKLRAVENELHYNKSLLEEVKDELQKMRQL	Leucine zipper 1C94:A
271	GGREGVLKKLRAVENELHYNKSLLEEVKDELQKMRQL	Leucine zipper 1C94:A
272	MTTASTSQVRQNYHQDSEAAINRQINLELYASYVYL SMSYYFDRDDVALKNFAKYFLHQSHREHAELMK LQNQRGGRIFLQDIQKPCDDWESGLNAMECALHLE KNVNQSLLELHKLATDKNDPHLCDFIETHYLNQVK AIKELGDHVTNLRKMGAPESGLAEYLFDKHTLGDS NES	Four helix bundle 1FHA

273	GLSDGEWQLVLNVWGKVEADIPGHGQEVLIIRLFKGH PETLEKFDRFKHLKSEDEMKASEDLKKHGATVLTAL GGILKKKGHHEAEIKPLAQSHATKHKIPVKYLEFIS EAI IQVLQSKHPGDFGADAQGAMNKALELFRKDMAS NYKELGFQG	Myoglobin 3RGK
274	YAEAAKAAEAAKAAEAAKAF	EK peptide
275	CQFDLSTRRLKCGGGAREEAAKAAEEAKKAAEEAAK AAQVQLQQSGAELAKPGASVKMSCKASGYTFTSYRM HWVKQSPGQGLEWIGYINPSTGYTEYNQKFKDKATL TADKSSSTAYMQLSSLTFEDSAIYYCARGGGVFDYW GQGTTLTVSS	SnAP-body Variant 1 VH
276	QIVLTQSPAIMASASPGEKVTITCSASSSISYMHWFQ QRTNGSPRLWIYTTSNLASGVPARFSGSGSGTSYSL TISRMEAEDEADYCHQRSTYPLTFGAGTKLELKRT VAAPSVFIFFPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of meditope enabled gentuzumab
277	CQFDLSTRRLKCGGGAREEAAKAAEEAKKAAEEAAKA AQVQLQQSGAELAKPGASVKMSCKASGYTFTSYRMHW VKQSPGQGLEWIGYINPSTGYTEYNQKFKDKATLTAD KSSSTAYMQLSSLTFEDSAIYYCARGGGVFDYWGQGT TLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT CPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYITLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	cQFD meditope, variant 1 linker, fused to the heavy chain of meditope enabled gentuzumab
278	CQFDLSTRRLKCGGGAARAAAAARAQVQLQQ SGAELAKPGASVKMSCKASGYTFTSYRMHWVKQSPG QGLEWIGYINPSTGYTEYNQKFKDKATLTADKSSST AYMQLSSLTFEDSAIYYCARGGGVFDYWGQGTTLTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYITLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	cQFD meditope, variant 2 linker, fused to the heavy chain of meditope enabled gentuzumab
279	CQFDLSTRRLKCGGGSKDEIDSAVKQVQLQQSGAEL AKPGASVKMSCKASGYTFTSYRMHWVKQSPGQGLEW IGYINPSTGYTEYNQKFKDKATLTADKSSSTAYMQL SSLTFEDSAIYYCARGGGVFDYWGQGTTLTVSSAST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS SLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT I	cQFD meditope, variant 3 linker, fused to the heavy chain of meditope enabled gentuzumab

	SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS PGK	
280	CQFDLSTRRLKCGGGAREEAAKAAEEAKKAAEEAAK AAQVQLKQSGPGLVQPSQSLSTCTVSGFSLTNYGV HWVRQSPGKGLEWLGVIWSSGNTDYNTPTTSRLSIN KDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEF AYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK DTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK	cQFD meditope, variant 1 linker, fused to the heavy chain of I83E cetuximab
281	DIQMTQSPSILSASVGDRTVITCRASQDVNTAVAWY QQRTNKAPRLLIYSASFLYSGVPSRFSRSGSDFT LTISLQPEDEADYQCQHYTTPPTFGAGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKSTYSLSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Meditope enabled trastuzumab light chain
282	CQFDLSTRRLKCGGGAREEAAKAAEEAKKAAEEAAK AAEVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYI HWVRQSPGKGLEWVARIYPTNGYTRYADSVKGRFTI SADTSKNTAYLQMNSLRAEDTAIYYCSRWGGDGFYA MDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	cQFD meditope, variant 1 linker, fused to the heavy chain of meditope enabled trastuzumab
283	DIQMTQSPSSLSASVGDRTVITCRASESVDNYGISF MNWFQQKPGKAPKLLIYAASNQSGVPSRFSGSGSG TDFTLTISLQPDDEFATYYCQQSKEVPWTFGQGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKSTYSL STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	Lintuzumab light chain
284	EVQLVQSGAEVKKPGSSVKVSKASGYTFTDYNMHW VRQAPGQGLEWIGYIYPYNGGTGYNQKFKSKATITA DESTNTAYMELSSLRSEDTAVYYCARGRPAMDYWGQ GTLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN	Lintuzumab heavy chain

	KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALH NHYTQKSLSLSPGK	
285	DIQMTQSPSILSASVGDRVTITCRASESVDNYGISF MNWFQQRNTKAPRLLIYAASNQSGVPSRFSGSGSG TDFTLTISSLQPDDEADYYCQQSKEVPWTFGAGTKL EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	Meditope-enabled lintuzumab light chain
286	DIQMTQSPSILSASVGDRVTITCRASESVDNYGISF MNWFQQRNTKAPRLLIYAASNQSGVPSRFSGSGSG TDFTLTISSLQPDDEADYYCQQSKEVPWTFGAGTKL EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	Meditope-enabled lintuzumab light chain, variant 1
287	DIQMTQSPSILSASVGDRVTITCRASESVDNYGISF MNWFQQRNTKAPRLLIYAASNQSGVPSRFSGSGSG TDFTLTISSLQPDDEADYYCQQSKEVPWTFGAGTKL EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	Meditope-enabled lintuzumab light chain, variant 2
288	DIQMTQSPSILSASVGDRVTITCRASESVDNYGISF MNWFQQRNTKAPRLLIYAASNQSGVPSRFSGSGSG TDFTLTISSLQPDDEADYYCQQSKEVPWTFGAGTKL EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG EC	Meditope-enabled lintuzumab light chain, variant 3
289	EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYNMHW VRQSPGQGLEWIGYIYPYNGGTGYNQKFKSKATITA DESTNTAYMELSSLRSEDTAIYYCARGRPAMDYWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKHTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSVSMHEALH NHYTQKSLSLSPGK	Meditope-enabled lintuzumab heavy chain
290	<u>CQFDLSTRRLKCGGGAREEAAKAAEEAKKAAEEAAKAA</u> EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYNMHW VRQSPGQGLEWIGYIYPYNGGTGYNQKFKSKATITA DESTNTAYMELSSLRSEDTAIYYCARGRPAMDYWGQ	Meditope-enabled lintuzumab heavy chain, variant 1

	GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALH NHYTQKSLSLSPGK	
291	<u>CQFDLSTRRLKCGGGAAARAAAAAARA</u> EVQLVQSGAEVKKPGSSVKVSKASGYTFTDYNMHW VRQSPGQGLEWIGYIYPYNGGTGYNQKFKSKATITA DESTNTAYMELSSLRSEDTAIYYCARGRPAMDYWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALH NHYTQKSLSLSPGK	Meditope-enabled lintuzumab heavy chain, variant 2
292	<u>CQFDLSTRRLKCGGGSKDEIDSAVK</u> EVQLVQSGAEVKKPGSSVKVSKASGYTFTDYNMHW VRQSPGQGLEWIGYIYPYNGGTGYNQKFKSKATITA DESTNTAYMELSSLRSEDTAIYYCARGRPAMDYWGQ GTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALH NHYTQKSLSLSPGK	Meditope-enabled lintuzumab heavy chain, variant 3
293	QIVLTQSPAIMASASPGEKVTITCSASSISYMHWFQ QRTNGSPRLWIYTTSNLASGVPARFSGSGSTSYSL TISRMEAEDEADYCHQRSTYPLTFGAGTKLELKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYLSLSSTLT LTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of CD33- SnAPbody MB-005-101
294	<u>CQFDLSTRRLK</u> CG GAREEAAKAAEEAKKAAEEAAKAA QVQLQQSGAELAKPGASVKMSCKASGYTFTSYRM HWVKQSPGQGLEWIGYINPSTGYTEYNQKFKDKATL TADKSSSTAYMQLSSLT FEDSAIYYCARGGGVFYDW GQGTTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKV	Heavy chain of CD33- SnAPbody MB-005-101. The cQFD meditope (<i>italic and underlined</i>) and variant 1 linker (bold) are fused to the heavy chain of meditope enabled gemtuzumab

	EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
295	QIVLTQSPAIMASASPGEKVTITCSASSSISYMHWFQQRRTNGSPRLWIYTTSNLASGVPARFSGSGSGTSYSLTISRMEAEDEADYYCHQRSTYPLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of CD33-SnAPbody MB-005-102
296	<u><i>CQFDLSTRRLKC</i></u> GGGAAARAAAAAARA QVQLQQ SGAELAKPGASVKMSCKASGYTFTSYRMHWVKQSPGQGLEWIGYINPSTGYTEYNQKFKDKATLTADKSSSTAYMQLSSSLTFEDSAIYYCARGGGVFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	Heavy chain of CD33-SnAPbody MB-005-102. The cQFD meditope (<i>italic and underlined</i>) and variant 2 linker (bold) are fused to the heavy chain of meditope enabled gemtuzumab
297	QIVLTQSPAIMASASPGEKVTITCSASSSISYMHWFQQRRTNGSPRLWIYTTSNLASGVPARFSGSGSGTSYSLTISRMEAEDEADYYCHQRSTYPLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of CD33-SnAPbody MB-005-103
298	<u><i>CQFDLSTRRLKC</i></u> GGGSKDEIDSAVK QVQLQQSGAEL AKPGASVKMSCKASGYTFTSYRMHWVKQSPGQGLEWIGYINPSTGYTEYNQKFKDKATLTADKSSSTAYMQLSSSLTFEDSAIYYCARGGGVFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	Heavy chain of CD33-SnAPbody MB-005-103. The cQFD meditope (<i>italic and underlined</i>) and variant 3 linker (bold) are fused to the heavy chain of meditope enabled gemtuzumab

299	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWY QQRNGSPRLLIKYASESISGIPSRFSGSGSGTDFT LSINSVESEDIADYYCQNNNNWPTTFGAGTKLELKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of EGFR-SnAPbody MB005-104
300	<u><i>CQFDLSTRRLKC</i></u> GGGAREEEAAKAAEEAKKAAEEAAKAA QVQLKQSGPGLVQPSQSLITCTVSGFSLTNYGV HWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSIN KDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEF AYWGQGLTVTSAASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKHTCPCPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGK	Heavy chain of EGFR-SnAPbody MB005-104. The cQFD meditope (<i>italic and underlined</i>) and variant 1 linker (bold) are fused to the heavy chain of cetuximab
301	DILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWY QQRNGSPRLLIKYASESISGIPSRFSGSGSGTDFT LSINSVESEDEADYYCQNNNNWPTTFGAGTKLELKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of EGFR-SnAPbody MB005-105
302	<u><i>CQFDLSTRRLKC</i></u> GGGAREEEAAKAAEEAKKAAEEAAKAA QVQLKQSGPGLVQPSQSLITCTVSGFSLTNYGV HWVRQSPGKGLEWLGVIWSGGNTDYNTPFTSRLSIN KDNSKSQVFFKMNSLQSNDAIYYCARALTYDYEF AYWGQGLTVTSAASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKHTCPCPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGK	Heavy chain of EGFR-SnAPbody MB005-105. The cQFD meditope (<i>italic and underlined</i>) and variant 3 linker (bold) are fused to the heavy chain of I83E cetuximab
303	DIQMTQSPSILSASVGDRTTITCRASQDVNTAVAWY QQRNKAAPRLLIYSASFLYSGVPSRFSGSRSGTDFT LTISLQPEDEADYYCQQHYYTTPPTFGAGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of HER2-SnAPbody MB005-106
304	<u><i>CQFDLSTRRLKC</i></u> GGGAREEEAAKAAEEAKKAAEEAAKAAEV	Heavy chain of HER2-SnAPbody MB005-106. The

	QLVESGGGLVQPGGSLRLSCAASGFNIKDTYI HWVRQSPGKGLEWVARIYPTNGYTRYADSVKGRFTI SADTSKNTAYLQMNSLRAEDTAIYYCSRWGGDGFYA MDYWGQGTLLTVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG	cQFD meditope (<i>italic and underlined</i>) and variant 3 linker (bold) are fused to the heavy chain of meditope enabled trastuzumab
305	EIVLTQSPVILSASPGERVTTITCSASSGVNYMHWYQ QRTNGSPKRWIYDTSKLASGVPARFSGSGSGTDYSL TISSMEPEDEADYCHQRGSYTFGGGTGLEIKRTVA APSVFI FPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSK ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Light chain of CD19-SnAPbody MB005-107
306	<u><i>CQFDLSTRRLKC</i></u> GGGAREEAAKAAEEAKKAAEEAAKAA QVQLVQPGAEVVKPGASVKLSCKTSGYTFTSNWM HWVKQSPGQGLEWIGEIDPSDSYTNYNQNFQGKAKL TVDKSTSTAYMEVSSLRSDDTAIYYCARGSNPYYYA MDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK	Heavy chain of CD19-SnAPbody MB005-107. The cQFD meditope (<i>italic and underlined</i>) and variant 3 linker (bold) are fused to the heavy chain of meditope enabled anti CD19 antibody

II. COMPOSITIONS AND METHODS FOR GENERATING SELF-CROSSLINKING ANTIBODIES

A. Nucleic Acids, Vectors, and Cells Comprising the Same

- 5 **[0306]** Also provided are isolated nucleic acids encoding any of the antibodies described herein. In some embodiments, the nucleic acid further comprises a vector suitable for expression of the nucleic acid encoding any of the previously described self-crosslinking antibodies. In a still further specific aspect, the vector is in a host cell suitable for expression of the nucleic acid. In a still further specific aspect, the host cell is a eukaryotic cell or a

prokaryotic cell. In a still further specific aspect, the eukaryotic cell is a mammalian cell, such as Chinese Hamster Ovary (CHO) or HEK-293 and variants thereof.

[0307] In some embodiments, the nucleic acid further comprises a sequence of nucleotides encoding a free meditope. In some embodiments, a first nucleic acid comprises the sequence of nucleotides encoding the self-crosslinking antibody and a second nucleic acid comprises a sequence of nucleotides encoding the free meditope. The free meditope can comprise any of the cyclic peptides described herein, including, for example any of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom. In some embodiments, the free meditope is capable of binding a meditope binding site on the self-crosslinking antibody encoded by the nucleic acid.

[0308] The antibody or antigen binding fragment thereof, may be made using methods known in the art, for example, by a process comprising culturing a host cell containing nucleic acid encoding any of the previously described self-crosslinking antibodies or antigen-binding fragments in a form suitable for expression, under conditions suitable to produce such antibody or fragment, and recovering the antibody or fragment.

[0309] In some embodiments, self-crosslinking antibodies can be produced using recombinant methods. For recombinant production of an anti-antigen antibody, a nucleic acid encoding the antibody can be isolated and inserted into a replicable vector for further cloning (amplification of the DNA) or for expression. DNA encoding the antibody may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody). Many vectors are available, including, for example the pCEP4 vector, a viral vector, a retroviral vector, a lentiviral vector, or a gamma retroviral vector. The vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence.

1. Polycistronic Expression Vectors

[0310] In some embodiments, the expression vector is a bicistronic, tricistronic, or polycistronic vector (also called a multicistronic vector) capable of co-expressing both the

self-crosslinking antibody and the free mediotope. In some embodiments, the sequence of nucleotides encoding the free mediotope and the sequence of nucleotides encoding the self-crosslinking antibody are operatively linked or separated by a sequence of nucleotides encoding a self-cleaving peptide. In some embodiments, they are separated by a sequence of
5 nucleotides encoding a peptide that causes ribosome skipping, such as a picornavirus 2A ribosomal skip peptide or T2A peptide.

[0311] In some embodiments, the series of nucleic acids encoding the free mediotope and the series of nucleic acids encoding the self-crosslinking antibody are operatively linked or separated by an internal ribosome entry site (IRES). In some embodiments, the gene before
10 the IRES sequence is expressed at higher levels than the gene after the IRES sequence. It may be advantageous in some embodiments to place the sequence of nucleotides encoding the free mediotope before the IRES sequence and the sequence of nucleotides encoding the self-crosslinking antibody after the IRES sequence. This arrangement can allow for the expression of an excess of free-mediotope peptide compared to self-crosslinking antibody,
15 thereby reducing or preventing the antibodies from self-crosslinking during production, isolation, and/or during storage.

2. *Signal Sequence Component*

[0312] In some embodiments, a self-crosslinking antibody may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous
20 polypeptide, which can be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. The heterologous signal sequence selected preferably is one that is recognized and processed (*e.g.*, cleaved by a signal peptidase) by the host cell. For prokaryotic host cells that do not recognize and process a native antibody signal sequence, the signal sequence is substituted by a prokaryotic signal
25 sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion, the native signal sequence may be substituted by, *e.g.*, the yeast invertase leader, a factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders), or acid phosphatase leader, the *C. albicans* glucoamylase leader, or the signal described in WO 90/13646. In mammalian cell
30 expression, mammalian signal sequences as well as viral secretory leaders, for example, the herpes simplex gD signal, are available.

3. *Origin of Replication*

[0313] Both expression and cloning vectors generally contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. In cloning vectors this sequence can be one that enables the vector to replicate independently of the host

5 chromosomal DNA, and can include origins of replication or autonomously replicating sequences. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells. Generally, the
10 origin of replication component is not needed for mammalian expression vectors, although the SV40 origin may be used because it contains the early promoter.

4. *Selection Component*

[0314] Expression and cloning vectors may contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to
15 antibiotics or other toxins, *e.g.*, ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, *e.g.*, the gene encoding D-alanine racemase for *Bacilli*.

[0315] One example of a selection scheme utilizes a drug to arrest growth of a host cell. Those cells that are successfully transformed with a heterologous gene produce a protein
20 conferring drug resistance and thus survive the selection regimen. Examples of such dominant selection use the drugs neomycin, mycophenolic acid and hygromycin.

[0316] Another example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up antibody-encoding nucleic acid, such as DHFR, glutamine synthetase (GS), thymidine kinase, metallothionein-I and -II, preferably
25 primate metallothionein genes, adenosine deaminase, ornithine decarboxylase, *etc.*

[0317] For example, cells transformed with the DHFR gene are identified by culturing the transformants in a culture medium containing methotrexate (Mtx), a competitive antagonist of DHFR. Under these conditions, the DHFR gene is amplified along with any other co-transformed nucleic acid. A Chinese hamster ovary (CHO) cell line deficient in
30 endogenous DHFR activity (*e.g.*, ATCC CRL-9096) may be used.

[0318] Alternatively, cells transformed with the GS gene are identified by culturing the transformants in a culture medium containing L-methionine sulfoximine (Msx), an inhibitor of GS. Under these conditions, the GS gene is amplified along with any other co-transformed nucleic acid. The GS selection/amplification system may be used in combination with the DHFR selection/amplification system described above.

[0319] Alternatively, host cells (particularly wild-type hosts that contain endogenous DHFR) transformed or co-transformed with DNA sequences encoding an antibody of interest, wild-type DHFR gene, and another selectable marker such as aminoglycoside 3'-phosphotransferase (APH) can be selected by cell growth in medium containing a selection agent for the selectable marker such as an aminoglycosidic antibiotic, *e.g.*, kanamycin, neomycin, or G418. See U.S. Pat. No. 4,965,199.

[0320] A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 (Stinchcomb *et al.*, *Nature*, 282:39 (1979)). The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1. Jones, *Genetics*, 85:12 (1977). The presence of the *trp1* lesion in the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan. Similarly, *Leu2*-deficient yeast strains (ATCC 20,622 or 38,626) are complemented by known plasmids bearing the *Leu2* gene.

[0321] In addition, vectors derived from the 1.6 μ m circular plasmid pKD1 can be used for transformation of *Kluyveromyces* yeasts. Alternatively, an expression system for large-scale production of recombinant calf chymosin was reported for *K. lactis*. Van den Berg, *Bio/Technology*, 8:135 (1990). Stable multi-copy expression vectors for secretion of mature recombinant human serum albumin by industrial strains of *Kluyveromyces* have also been disclosed. Fleer *et al.*, *Bio/Technology*, 9:968-975 (1991).

5. Promoter Component

[0322] Expression and cloning vectors generally contain a promoter that is recognized by the host organism and is operably linked to nucleic acid encoding an antibody. In some embodiments, the vector comprises one promoter controlling transcription of the self-crosslinking antibody. In some embodiments, the vector comprises one promoter operatively linked to a sequence of nucleic acids encoding both the self-crosslinking antibody and one or more free mediotopes. In another embodiment, the vector comprises a sequence of nucleotides

encoding the recombinant mediotope enabled antibody or antigen binding fragment thereof that is operatively linked to a first promoter and a sequence of nucleotides encoding the free mediotope that is operatively linked to a second promoter. The first and second promoters can be the same or different.

5 **[0323]** In some embodiments, it may be advantageous to express the free mediotope and the self-crosslinking antibody at different levels. For example, it may be advantageous to express the free mediotope at higher levels than the self-crosslinking antibody to prevent self-crosslinking during production, isolation, or storage. Thus, in some embodiments, one promoter might be a stronger promoter, may lead to a higher rate of transcription initiation, or
10 has a higher affinity for RNA polymerase than the other. In some embodiments, one or both of the promoters are conditional promoters.

[0324] Promoters suitable for use with prokaryotic hosts include the *phoA* promoter, β -lactamase and lactose promoter systems, alkaline phosphatase promoter, a tryptophan (*trp*) promoter system, and hybrid promoters such as the *tac* promoter. However, other known
15 bacterial promoters are suitable. Promoters for use in bacterial systems can contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding an antibody.

[0325] Promoter sequences are known for eukaryotes. Virtually all eukaryotic genes have an AT-rich region located approximately 25 to 30 bases upstream from the site where transcription is initiated. Another sequence found 70 to 80 bases upstream from the start of
20 transcription of many genes is a CNCAAT region where N may be any nucleotide. At the 3' end of most eukaryotic genes is an AATAAA sequence that may be the signal for addition of the poly A tail to the 3' end of the coding sequence. All of these sequences are suitably inserted into eukaryotic expression vectors.

[0326] Examples of suitable promoter sequences for use with yeast hosts include the
25 promoters for 3-phosphoglycerate kinase or other glycolytic enzymes, such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

[0327] Other yeast promoters, which are inducible promoters having the additional
30 advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes

associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657. Yeast enhancers also are advantageously used with yeast promoters.

5 **[0328]** Antibody transcription from vectors in mammalian host cells can be controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus (CMV), a retrovirus, hepatitis-B virus, Simian Virus 40 (SV40), or from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin
10 promoter, from heat-shock promoters, provided such promoters are compatible with the host cell systems.

[0329] The early and late promoters of the SV40 virus are conveniently obtained as an SV40 restriction fragment that also contains the SV40 viral origin of replication. The immediate early promoter of the human cytomegalovirus is conveniently obtained as a
15 HindIII E restriction fragment. A system for expressing DNA in mammalian hosts using the bovine papilloma virus as a vector is disclosed in U.S. Pat. No. 4,419,446. A modification of this system is described in U.S. Pat. No. 4,601,978. See also Reyes *et al.*, *Nature* 297:598-601 (1982) on expression of human β -interferon cDNA in mouse cells under the control of a thymidine kinase promoter from herpes simplex virus. Alternatively, the Rous Sarcoma
20 Virus long terminal repeat, PGK, EF1 α , NSE, UBC, CAGG, synapsin, β -actin, or GFAP can be used as the promoter.

[0330] In some embodiments, the expression is under the control of a conditional promoter, enhancer or transactivator. In some embodiments, expression of the self-crosslinking antibody is under the control of a conditional promoter, enhancer, or
25 transactivator and expression of the free mediotope is under the control of a constitutively active promoter. As an exemplary advantage, such embodiments can allow for the control of the amount of self-crosslinking antibody produced, the timing of expression, and the ratio of self-crosslinking antibody and free mediotope. In some embodiments, expression of the self-crosslinking antibody is under the control of a constitutively active promoter, enhancer, or
30 transactivator and expression of the free mediotope is under the control of a conditional promoter. As an exemplary advantage, such embodiments can allow for expression of the free mediotope only when necessary to modulate antibody self-crosslinking during production,

isolation, or storage. In some embodiments, the conditional promoter, enhancer or transactivator is an inducible promoter, enhancer or transactivator, a repressible promoter, enhancer or transactivator, or a tissue-specific promoter, enhancer or transactivator.

[0331] In some embodiments, expression of any of the peptides or nucleic acids

5 described herein may be externally controlled by treating the cell with a modulating factor, such as doxycycline, tetracycline or analogues thereof. Analogues of tetracycline include, for example, chlortetracycline, oxytetracycline, demethylchloro-tetracycline, methacycline, doxycycline and minocycline.

[0332] In some embodiments, inducible transcription and/or expression can be

10 implemented using a transactivator together with a transactivator induced promoter. In some embodiments, such a transactivator induced promoter comprises control elements for the enhancement or repression of transcription of the transgene or nucleic acid of interest. Control elements include, without limitation, operators, enhancers and promoters. In some
15 embodiments, a transactivator inducible promoter is transcriptionally active when bound to a transactivator, which in turn is activated under a specific set of conditions, for example, in the presence or in the absence of a particular combination of chemical signals, for example, by a modulating factor selected for example from the previous list.

[0333] The transactivator induced promoter may be any promoter herein mentioned

20 which has been modified to incorporate transactivator binding sequences, such as several tet-operon sequences, for example 3, 4, 5, 6, 7, 8, 9, or 10 tet-operon sequences. In some embodiments, the tet-operon sequences are in tandem.

[0334] Specific examples of transcription modulator domains that induce expression in

the presence of modulating factor include, but are not limited to, the transcription modulator domains found in the following transcription modulators: the Tet-On transcription modulator;
25 and the Tet-On Advanced transcription modulator and the Tet-On 3G transcription modulator; all of which are available from Clontech Laboratories, Mountain View, CA.

Specific examples of transcription modulator domains that induce expression in the absence of modulating factor include, but are not limited to, the transcription modulator domains found in the following transcription modulators: the Tet-off transcription modulator and the

30 Tet-Off Advanced transcription modulator, both of which are available from Clontech Laboratories, Mountain View, CA. These systems can be adapted and used according to

procedures that are well known in the art and that will be familiar to the ordinarily skilled artisan.

[0335] In some embodiments, the transactivator induced promoter comprises a plurality of transactivator binding sequences operatively linked to the inhibitory nucleic acid molecule.

5 [0336] The transactivator may be provided by a nucleic acid sequence, in the same expression vector or in a different expression vector, comprising a modulating factor-dependent promoter operatively linked to a sequence encoding the transactivator. The term “different expression vector” is intended to include any vehicle for delivery of a nucleic acid, for example, a virus, plasmid, cosmid or transposon. Suitable promoters for use in said
10 nucleic acid sequence include, for example, constitutive, regulated, tissue-specific or ubiquitous promoters, which may be of cellular, viral or synthetic origin, such as CMV, RSV, PGK, EF1 α , NSE, synapsin, β -actin, GFAP.

[0337] An exemplary transactivator according to some embodiments is the rtTA-Oct.2 transactivator composed of the DNA binding domain of rtTA2-M2 and of the Oct-2Q(Q $\rightarrow$ A) activation domain. Another exemplary transactivator according to some embodiments is the
15 rtTA-Oct.3 transactivator composed of the DNA binding domain of the Tet-repressor protein (E. coli) and of the Oct-2Q(Q $\rightarrow$ A) activation domain. Both are described in patent application WO 2007/004062.

6. *Enhancer Element Component*

20 [0338] Transcription of a DNA encoding an antibody of this invention by higher eukaryotes is often increased by inserting an enhancer sequence into the vector. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-
25 270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. See also Yaniv, *Nature* 297:17-18 (1982) on enhancing elements for activation of eukaryotic promoters. The enhancer may be spliced into the vector at a position 5' or 3' to the antibody-encoding sequence, but is preferably located at a site 5' from the promoter.

7. *Transcription Termination Component*

[0339] Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding antibody. One useful transcription termination component is the bovine growth hormone polyadenylation region. See WO94/11026 and the expression vector disclosed therein.

8. *Selection and Transformation of Host Cells*

[0340] Suitable host cells for cloning or expressing the DNA in the vectors herein are the prokaryote, yeast, or higher eukaryote cells described above. Suitable prokaryotes for this purpose include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 Apr. 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. One preferred *E. coli* cloning host is *E. coli* 294 (ATCC 31,446), although other strains such as *E. coli* B, *E. coli* X1776 (ATCC 31,537), and *E. coli* W3110 (ATCC 27,325) are suitable. These examples are illustrative rather than limiting.

[0341] Full length antibody, antibody fusion proteins, and antibody fragments can be produced in bacteria, in particular when glycosylation and Fc effector function are not needed, such as when the therapeutic antibody is conjugated to a cytotoxic agent (e.g., a toxin) that by itself shows effectiveness in tumor cell destruction. Full length antibodies have greater half-life in circulation. Production in *E. coli* is faster and more cost efficient. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. No. 5,648,237 (Carter et. al.), U.S. Pat. No. 5,789,199 (Joly et al.), U.S. Pat. No. 5,840,523 (Simmons et al.), which describes translation initiation region (TIR) and signal sequences for optimizing expression and secretion. See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*. After expression, the antibody may be isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., a protein A

or G column depending on the isotype. Final purification can be carried out similar to the process for purifying antibody expressed e.g., in CHO cells.

[0342] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*; *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilae* (ATCC 36,906), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070); *Candida*; *Trichoderma reesei* (EP 244,234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*. For a review discussing the use of yeasts and filamentous fungi for the production of therapeutic proteins, see, e.g., Gerngross, *Nat. Biotech.* 22:1409-1414 (2004).

[0343] Certain fungi and yeast strains may be selected in which glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See, e.g., Li et al., *Nat. Biotech.* 24:210-215 (2006) (describing humanization of the glycosylation pathway in *Pichia pastoris*); and Gerngross et al., *supra*.

[0344] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruit fly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the invention, particularly for transfection of *Spodoptera frugiperda* cells.

[0345] Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, duckweed (*Leninaceae*), alfalfa (*M. truncatula*), and tobacco can also be utilized as hosts. See, e.g., U.S.

Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIESTM technology for producing antibodies in transgenic plants).

[0346] Vertebrate cells may be used as hosts, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 cells or HEK-293 cells, including cells subcloned for growth in suspension culture, Graham *et al.*, *J. Gen Virol.* 36:59 (1977), or other variants including FREESTYLETM 293-F cells (Invitrogen, Carlsbad, CA)); baby hamster kidney cells (BHK, ATCC CCL 10); mouse sertoli cells (TM4, Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather *et al.*, *Annals N.Y. Acad. Sci.* 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

[0347] Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR⁻ CHO cells (Urlaub *et al.*, *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 255-268.

[0348] Host cells are transformed with the above-described expression or cloning vectors for antibody production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

9. Culturing the Host Cells

[0349] The host cells used to produce a self-crosslinking antibody may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham *et al.*, *Meth. Enz.* 58:44 (1979), Barnes *et al.*, *Anal. Biochem.*

102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469;
WO 90/03430; WO 87/00195; or U.S. Pat. Re. 30,985 may be used as culture media for the
host cells. Any of these media may be supplemented as necessary with hormones and/or
other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as
5 sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides
(such as adenosine and thymidine), antibiotics (such as GENTAMYCINTM drug), trace
elements (defined as inorganic compounds usually present at final concentrations in the
micro-molar range), and glucose or an equivalent energy source. Any other necessary
supplements may also be included at appropriate concentrations that would be known to
10 those skilled in the art. The culture conditions, such as temperature, pH, and the like, are
those previously used with the host cell selected for expression, and will be apparent to the
ordinarily skilled artisan.

B. Purification of Antibody

[0350] When using recombinant techniques, the antibody can be produced intracellularly,
15 in the periplasmic space, or directly secreted into the medium. If the antibody is produced
intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are
removed, for example, by centrifugation or ultrafiltration. Carter *et al.*, *Bio/Technology*
10:163-167 (1992) describe a procedure for isolating antibodies which are secreted to the
periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate
20 (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris
can be removed by centrifugation. Where the antibody is secreted into the medium,
supernatants from such expression systems are generally first concentrated using a
commercially available protein concentration filter, for example, an Amicon or Millipore
Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the
25 foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of
adventitious contaminants.

[0351] The antibody composition prepared from the cells can be purified using, for
example, hydroxylapatite chromatography, hydrophobic interaction chromatography, gel
electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being
30 among one of the typically preferred purification steps. The suitability of protein A as an
affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is
present in the antibody. Protein A can be used to purify antibodies that are based on human

$\gamma 1$, $\gamma 2$, or $\gamma 4$ heavy chains (Lindmark *et al.*, *J. Immunol. Meth.* 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human $\gamma 3$ (Guss *et al.*, *EMBO J.* 5:15671575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or
5 poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 domain, the Bakerbond ABXTM resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin
10 SEPHAROSETM chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

[0352] In general, various methodologies for preparing antibodies for use in research, testing, and clinical are well-established in the art, consistent with the above-described
15 methodologies and/or as deemed appropriate by one skilled in the art for a particular antibody of interest.

C. Compositions Comprising Self-Crosslinking Antibody-Agent Conjugates

[0353] In certain embodiments, the self-crosslinking antibodies are conjugated to one or more therapeutic or diagnostic agent, e.g., imaging agents, therapeutically effective agents or
20 compounds in therapeutically effective amounts or both. Provided are such complexes, in some embodiments comprising a plurality of mediotopes, one or more linkers, and one or more agents.

[0354] The current disclosure contemplates conjugating a therapeutic or diagnostic (e.g. imaging) agent or compound to a mediotope or variant thereof, a linker, and/or an antibody to
25 treat, prevent, diagnose or monitor a disease or condition. In one aspect, such conjugation of a self-crosslinking antibody to an agent provides a highly versatile platform technology that will significantly improve mAb based therapeutics and imaging methods to treat and detect disease.

[0355] Agents can be conjugated by any means known in the art. In some embodiments,
30 the agent is conjugated to a lysine, tyrosine, glutamic acid, aspartic acid, formylglycine or aldehyde tag, an unnatural amino acid, etc. A formylglycine or aldehyde tag can comprise a

6-amino acid (LCTPSR; SEQ ID NO: 247) or 13-amino acid (LCTPSRGSFLTGR, SEQ ID NO: 248) sequence that can be recognized and targeted by formylglycine-generating enzyme (FGE) to generate a reactive aldehyde group. The reactive aldehyde group can be useful in subsequent reactions comprising conjugating epitopes to agents. See Carrico et al.,

5 *Nature Chemical Biology* 3, 321-322 (2007).

[0356] The diagnostic and therapeutic agents include any such agent, which are well-known in the relevant art. Among the imaging agents are fluorescent and luminescent substances, including, but not limited to, a variety of organic or inorganic small molecules commonly referred to as "dyes," "labels," or "indicators." Examples include fluorescein, rhodamine, acridine dyes, Alexa dyes, and cyanine dyes. Enzymes that may be used as imaging agents in accordance with the embodiments of the disclosure include, but are not limited to, horseradish peroxidase, alkaline phosphatase, acid phosphatase, glucose oxidase, β -galactosidase, β -glucuronidase or β -lactamase. Such enzymes may be used in combination with a chromogen, a fluorogenic compound or a luminogenic compound to generate a detectable signal.

[0357] Radioactive substances that may be used as imaging agents in accordance with the embodiments of the disclosure include, but are not limited to, ^{18}F , ^{32}P , ^{33}P , ^{45}Ti , ^{47}Sc , ^{52}Fe , ^{59}Fe , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , ^{77}As , ^{86}Y , ^{90}Y , ^{89}Sr , ^{89}Zr , ^{94}Tc , ^{94}Tc , $^{99\text{m}}\text{Tc}$, ^{99}Mo , ^{105}Pd , ^{105}Rh , ^{111}Ag , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{142}Pr , ^{143}Pr , ^{149}Pm , ^{153}Sm , $^{154-158}\text{Gd}$, ^{161}Tb , ^{166}Dy , ^{166}Ho , ^{169}Er , ^{175}Lu , ^{177}Lu , ^{186}Re , ^{188}Re , ^{189}Re , ^{194}Ir , ^{198}Au , ^{199}Au , ^{211}At , ^{211}Pb , ^{212}Bi , ^{212}Pb , ^{213}Bi , ^{223}Ra and ^{225}Ac . Paramagnetic ions that may be used as additional imaging agents in accordance with the embodiments of the disclosure include, but are not limited to, ions of transition and lanthanide metals (e.g. metals having atomic numbers of 21-29, 42, 43, 44, or 57-71). These metals include ions of Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu.

[0358] When the imaging agent is a radioactive metal or paramagnetic ion, the agent may be reacted with another long-tailed reagent having a long tail with one or more chelating groups attached to the long tail for binding to these ions. The long tail may be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which the metals or ions may be added for binding. Examples of chelating groups that may be used according to the disclosure include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA),

DOTA, NOTA, NETA, TETA, porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups. The chelate is normally linked to the PSMA antibody or functional antibody fragment by a group, which enables the formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and gadolinium are useful for MRI, when used along with the antibodies and carriers described herein. Macrocyclic chelates such as NOTA, DOTA, and TETA are of use with a variety of metals and radiometals including, but not limited to, radionuclides of gallium, yttrium and copper, respectively. Other ring-type chelates such as macrocyclic polyethers, which are of interest for stably binding nuclides, such as ^{223}Ra for RAIT may be used. In certain embodiments, chelating moieties may be used to attach a PET imaging agent, such as an Al- ^{18}F complex, to a targeting molecule for use in PET analysis.

[0359] Exemplary therapeutic agents include, but are not limited to, drugs, chemotherapeutic agents, therapeutic antibodies and antibody fragments, toxins, radioisotopes, enzymes (e.g., enzymes to cleave prodrugs to a cytotoxic agent at the site of the tumor), nucleases, hormones, immunomodulators, antisense oligonucleotides, RNAi molecules (e.g., siRNA or shRNA), chelators, boron compounds, photoactive agents and dyes. The therapeutic agent may also include a metal, metal alloy, intermetallic or core-shell nanoparticle bound to a chelator that acts as a radiosensitizer to render the targeted cells more sensitive to radiation therapy as compared to healthy cells. Further, the therapeutic agent may include paramagnetic nanoparticles for MRI contrast agents (e.g., magnetite or Fe_3O_4) and may be used with other types of therapies (e.g., photodynamic and hyperthermal therapies and imaging (e.g., fluorescent imaging (Au and CdSe))).

[0360] Chemotherapeutic agents are often cytotoxic or cytostatic in nature and may include alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, mitotic inhibitors hormone therapy, targeted therapeutics and immunotherapeutics. In some embodiments the chemotherapeutic agents that may be used as therapeutic agents in accordance with the embodiments of the disclosure include, but are not limited to, 13-cis-retinoic acid, 2-chlorodeoxyadenosine, 5-azacitidine, 5-fluorouracil, 6-mercaptopurine, 6-thioguanine, actinomycin-D, adriamycin, aldesleukin, alemtuzumab, alitretinoin, all-transretinoic acid, alpha interferon, altretamine, amethopterin, amifostine, anagrelide, anastrozole, arabinosylcytosine, arsenic trioxide, amsacrine, aminocamptothecin,

aminogluthethimide, asparaginase, auristatin, dimethylvaline-valine-dolaisoleuine- dolaproine-phenylalanine-p-phenylenediamine (AFP), dovaline-valine-dolaisoleuine-dolaproine-phenylalanine (MMAF), monomethyl auristatin E (MMAE), auromycins, azacytidine, bacillus calmette-guerin (BCG), bendamustine, bevacizumab, etanercept, bexarotene, 5 bicalutamide, bismuth, bortezomib, bleomycin, busulfan, calcium leucovorin, citrovorum factor, capecitabine, canertinib, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, cortisone, cyclophosphamide, cytarabine, cc1065, darbepoetin alfa, dasatinib, daunomycin, decitabine, denileukin diftitox, dexamethasone, dexasone, dexrazoxane, dactinomycin, daunorubicin, decarbazine, docetaxel, dolostatin, doxorubicin, doxiluridine, 10 eniluracil, epirubicin, epoetin alfa, erlotinib, everolimus, exemestane, estramustine, ethidium bromide, etoposide, filgrastim, fluoxymesterone, fulvestrant, flavopiridol, floxuridine, fludarabine, fluorouracil, flutamide, gefitinib, gemcitabine, gemtuzumab, lintuzumab, ozogamicin, goserelin, granulocyte - colony stimulating factor, granulocyte macrophage-colony stimulating factor, hexamethylmelamine, hydrocortisone hydroxyurea, ibritumomab, 15 interferon alpha, interleukin – 2, interleukin-11, isotretinoin, ixabepilone, idarubicin, imatinib mesylate, ifosfamide, irinotecan, lapatinib, lenalidomide, letrozole, leucovorin, leuprolide, liposomal Ara-C, lomustine, mechlorethamine, megestrol, melphalan, mercaptopurine, mesna, methotrexate, methylprednisolone, mitomycin C, mitotane, mitoxantrone, maytansinoids, nelarabine, nilutamide, octreotide, oprelvekin, oxaliplatin, paclitaxel, 20 pamidronate, pemetrexed, panitumumab, PEG Interferon, pegaspargase, pegfilgrastim, PEG-L-asparaginase, pentostatin, plicamycin, prednisolone, prednisone, procarbazine, raloxifene, ricin, ricin A-chain, rituximab, romiplostim, raltitrexed, sapacitabine, sargramostim, satraplatin, sorafenib, sunitinib, semustine, streptozocin, taxol, tamoxifen, tegafur, tegafur-uracil, temsirolimus, temozolamide, teniposide, thalidomide, thioguanine, thiotepa, 25 topotecan, toremifene, tositumomab, trastuzumab, tretinoin, trinitrexate, alrubicin, vincristine, vinblastine, vindestine, vinorelbine, vorinostat, yttrium, or zoledronic acid.

[0361] Therapeutic antibodies and functional fragments thereof, that may be used as therapeutic agents in accordance with the embodiments of the disclosure include, but are not limited to, alemtuzumab, bevacizumab, cetuximab, edrecolomab, gemtuzumab, lintuzumab, 30 ibritumomab tiuxetan, panitumumab, rituximab, tositumomab, and trastuzumab and other antibodies associated with specific diseases listed herein.

[0362] Toxins that may be used as therapeutic agents in accordance with the embodiments of the disclosure include, but are not limited to, ricin, abrin, ribonuclease (RNase), DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtheria toxin, Pseudomonas exotoxin, and Pseudomonas endotoxin.

- 5 [0363] Radioisotopes that may be used as therapeutic agents in accordance with the embodiments of the disclosure include, but are not limited to, ^{32}P , ^{89}Sr , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{99}Mo , ^{131}I , ^{153}Sm , ^{177}Lu , ^{186}Re , ^{213}Bi , ^{223}Ra and ^{225}Ac .

D. Compositions Comprising Self-Crosslinking Antibodies and Free Meditope

- 10 [0364] Also provided herein are compositions comprising self-crosslinking antibodies and free meditopes. As described herein, such compositions may be advantageous in modulating or controlling self-crosslinking during expression, formulation, and storage, or for use with any of the methods described herein. Free meditope can be co-expressed with self-crosslinking antibody, as described above, or added to the composition separately.

- 15 [0365] In some embodiments, the composition comprises a high concentration of free meditope compared to the self-crosslinking antibody. For example, in some embodiments the ratio of self-crosslinking antibody to free meditope is between 1:1 and 1:1,000, including about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:10, 1:15, 1:20, 1:25, 1:50, 1:75, 1:100, 1:150, 1:200, 1:250, 1:300, 1:400, 1:500, and 1:750.

- 20 [0366] In some embodiments, the composition comprises free meditope with a higher affinity for the meditope binding site of the self-crosslinking antibody than the meditope attached to the self-crosslinking antibody via a linker. In some embodiments, the composition comprises free meditope with a lower affinity for the meditope binding site of the self-crosslinking antibody than the meditope attached to the self-crosslinking antibody via a linker. In some embodiments, the meditope binding site of the self-crosslinking antibody
25 comprises one or more substitutions that alter the binding affinity for one or more meditopes, as described above. For example, the meditope binding site might exhibit a greater affinity for a free meditope than the meditope fused to the self-crosslinking antibody, or vice versa.

- [0367] Various combinations of concentrations and affinities are also contemplated. Compositions comprising low concentrations of self-crosslinking antibodies and high
30 concentrations of free meditope, wherein the free meditope has a high affinity for the self-

crosslinking antibody's mediotope binding site, can be advantageous in some embodiments. For example, such embodiments may minimize self-crosslinking during production or storage of self-crosslinking antibodies, or may allow for the production, storage, and use of self-crosslinking antibodies with higher self-crosslinking capacities. In some embodiments, the composition comprises high concentrations of self-crosslinking antibodies and high concentrations of free mediotope with a high affinity for the self-crosslinking antibody's mediotope binding site. As an exemplary advantage, such embodiments may allow for more concentrated compositions of self-crosslinking antibodies.

[0368] As previously described, in some embodiments the formulation has a pH in which the free mediotope has an increased affinity for the mediotope binding site of a first self-crosslinking or mediotope enabled antibody. In some embodiments, the increased affinity of the free mediotope at the selected pH is higher than the affinity of the mediotope of a second self-crosslinking antibody for the mediotope binding site of the first self-crosslinking or mediotope enabled antibody. In some embodiments, such differences in affinity can be advantageous in preventing or reducing the self-crosslinking activity of antibody.

[0369] Additionally, in some embodiments the mediotope of a self-crosslinking antibody exhibits a higher affinity than the free mediotope for a mediotope binding site at a pH present at the site of the cognate antigen. In some embodiments, the site of the cognate antigen is a targeted cell or tissue, including a cell or tissue with a disease or disorder, including cancer.

E. Characterization of self-crosslinking antibodies

[0370] Binding properties of the mediotopes to mediotope-enabled antibodies can be characterized by any of a number of known methods, including SPR and ITC, for example, to ensure that conjugation to the self-crosslinking antibody does not affect the mediotope-Ig interaction. In some cases, such measurements can be limited in their ability to synergistic effects, given that these approaches generally do not involve antigen present on a cell surface (such as on the surface of a tumor cell). Thus, in some aspects, FACS analysis and/or cell viability assays are used to quantify the effect of the self-crosslinking antibody directly on cells expressing antigen recognized by the antibody (e.g., cells that overexpress EGFR in the context of cetuximab). In general, a cell line expressing (e.g., over-expressing) the antigen recognized by the self-crosslinking antibody is incubated with the self-crosslinking antibody under conditions whereby the antibody binds to the antigen expressed on the cells. In some cases, varying concentrations of the antibody are used. Appropriate incubation times and

washes are carried out. A non-self-crosslinking meditope-enabled antibody coupled to multivalent or monovalent meditopes may be used as positive and negative controls, respectively. The antibodies and meditopes may be labeled with agents detectable by flow cytometry or microscopy, which are well known. In some examples, a shift (in the case of FACS) or increased signal in the presence of a self-crosslinking antibody, for example compared to a non-self-crosslinking antibody, indicates a synergistic or additive effect. In another example, to further confirm the additive effects of the self-crosslinking antibody, a non-labeled, monovalent meditope is used in a competition assay, to determine whether it can compete with the labeled self-crosslinking antibody for binding to other antigen-bound self-crosslinking antibody.

[0371] In other examples, cell viability assays are used to determine the ability of a self-crosslinking antibody to enhance cell-killing effects. For example, a cell expressing the antigen of interest may be incubated with varying concentrations of the self-crosslinking antibody. Multivalent meditopes and monovalent meditopes bound to non-self-crosslinking meditope enabled antibodies again are useful as controls. In some examples, MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), is used to quantify the number or percentage of viable cells. Other approaches for measuring cell viability, proliferation, and/or death are known in the art and may be used.

[0372] In another example, for self-crosslinking antibodies that demonstrate activity in such assays, Western blot analysis or other biochemical or signaling approach is performed to investigate inhibition of signaling associated with a particular antigen, such as a cell surface receptor (e.g., in the case of cetuximab, to follow the phosphorylation status of EGFR, AKT, MAP which are part of the EGFR signaling pathway). Data from such studies may be compared with data from cells treated only with meditope-enabled antibody (i.e., without meditope), with monovalent meditopes, with multivalent meditopes, and/or with tyrosine kinase or other known inhibitors (AG1478, etc.). In some examples, an increase in cell death as a function of self-crosslinking antibody concentration is observed, demonstrating synergistic cell killing effects of the self-crosslinking antibody.

F. Selecting Biologically Active Antibodies

[0373] Antibodies produced as described above may be subjected to one or more "biological activity" assays to select an antibody with beneficial properties from a therapeutic perspective or selecting formulations and conditions that retain biological activity of the

antibody. The antibody may be tested for its ability to bind the antigen against which it was raised. In some embodiments, the binding of the antibody may be determined by saturation binding; ELISA; and/or competition assays (e.g. RIA's), for example. Also, the antibody may be subjected to other biological activity assays, e.g., in order to evaluate its effectiveness as a therapeutic. Such assays are known in the art and depend on the target antigen and intended use for the antibody.

[0374] To screen for antibodies which bind to a particular epitope on the antigen of interest, a routine cross-blocking assay such as that described in *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Alternatively, epitope mapping, e.g. as described in Champe et al., *J. Biol. Chem.* 270:1388-1394 (1995), can be performed to determine whether the antibody binds an epitope of interest.

G. Preparation of the Formulations

[0375] After preparation of the antibody of interest (e.g., techniques for producing antibodies which can be formulated as disclosed herein will be elaborated below and are known in the art), the pharmaceutical formulation comprising it is prepared. In certain embodiments, the antibody to be formulated has not been subjected to prior lyophilization and the formulation of interest herein is an aqueous formulation. In certain embodiments, the antibody is a full length antibody. In one embodiment, the antibody in the formulation is an antibody fragment, such as an F(ab')₂, in which case problems that may not occur for the full length antibody (such as clipping of the antibody to Fab) may need to be addressed. The therapeutically effective amount of antibody present in the formulation is determined by taking into account the desired dose volumes and mode(s) of administration, for example. From about 25 mg/mL to about 150 mg/mL, or from about 30 mg/mL to about 140 mg/mL, or from about 35 mg/mL to about 130 mg/mL, or from about 40 mg/mL to about 120 mg/mL, or from about 50 mg/mL to about 130 mg/mL, or from about 50 mg/mL to about 125 mg/mL, or from about 50 mg/mL to about 120 mg/mL, or from about 50 mg/mL to about 110 mg/mL, or from about 50 mg/mL to about 100 mg/mL, or from about 50 mg/mL to about 90 mg/mL, or from about 50 mg/mL to about 80 mg/mL, or from about 54 mg/mL to about 66 mg/mL is an exemplary antibody concentration in the formulation.

[0376] In some embodiments, the formulation further comprises free meditope. The free meditope can reduce or prevent self-crosslinking antibodies from self-crosslinking during

production, isolation, and/or storage. Such free meditope can be expressed and isolated along with the self-crosslinking antibodies, as described above, or produced and added to compositions and formulations separately. Some embodiments contain an excess of free-meditope peptide. In some embodiments, the amount of free meditope can be stoichiometrically related to the amount of self-crosslinking antibody. For example, in some embodiments, the ratio of self-crosslinking antibody to free meditope is between 1:1 and 1:1,000, including about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:10, 1:15, 1:20, 1:25, 1:50, 1:75, 1:100, 1:150, 1:200, 1:250, 1:300, 1:400, 1:500, and 1:750. In some embodiments, the free amount of meditope peptide is determined by concentration, including, for example from about 0.1 mg/mL to about 150 mg/mL.

[0377] An aqueous formulation is prepared comprising the antibody in a pH-buffered solution. The buffer of this invention has a pH in the range from about 5.0 to about 7.0. In certain embodiments the pH is in the range from about 5.0 to about 6.5, the pH is in the range from about 5.0 to about 6.4, in the range from about 5.0 to about 6.3, the pH is in the range from about 5.0 to about 6.2, the pH is in the range from about 5.0 to about 6.1, the pH is in the range from about 5.5 to about 6.1, the pH is in the range from about 5.0 to about 6.0, the pH is in the range from about 5.0 to about 5.9, the pH is in the range from about 5.0 to about 5.8, the pH is in the range from about 5.1 to about 6.0, the pH is in the range from about 5.2 to about 6.0, the pH is in the range from about 5.3 to about 6.0, the pH is in the range from about 5.4 to about 6.0, the pH is in the range from about 5.5 to about 6.0, the pH is in the range from about 5.6 to about 6.0, the pH is in the range from about 5.7 to about 6.0, or the pH is in the range from about 5.8 to about 6.0. In certain embodiments of the invention, the formulation has a pH of 6.0 or about 6.0. In certain embodiments of the invention, the formulation has a pH of 5.9 or about 5.9. In certain embodiments of the invention, the formulation has a pH of 5.8 or about 5.8. In certain embodiments of the invention, the formulation has a pH of 5.7 or about 5.7. In certain embodiments of the invention, the formulation has a pH of 5.6 or about 5.6. In certain embodiments of the invention, the formulation has a pH of 5.5 or about 5.5. In certain embodiments of the invention, the formulation has a pH of 5.4 or about 5.4. In certain embodiments of the invention, the formulation has a pH of 5.3 or about 5.3. In certain embodiments of the invention, the formulation has a pH of 5.2 or about 5.2.

[0378] Examples of buffers that will control the pH within this range include histidine (such as L-histidine) or sodium acetate. In certain embodiments, the buffer contains histidine acetate or sodium acetate in the concentration of about 15 mM to about 25 mM. In certain embodiments of the invention, the buffer contains histidine acetate or sodium acetate in the concentration of about 15 mM to about 25 mM, about 16 mM to about 25 mM, about 17 mM to about 25 mM, about 18 mM to about 25 mM, about 19 mM to about 25 mM, about 20 mM to about 25 mM, about 21 mM to about 25 mM, about 22 mM to about 25 mM, about 15 mM, about 16 mM, about 17 mM, about 18 mM, about 19 mM, about 20 mM, about 21 mM, about 22 mM, about 23 mM, about 24 mM, or about 25 mM. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.0. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.1. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.2. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.3. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.4. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.5. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.6. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.7. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.8. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 5.9. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 6.0. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 6.1. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 6.2. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 20 mM, pH 6.3. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.2. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.3. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.4. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.5. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.6. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.7. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.8. In one

embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 5.9. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 6.0. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 6.1. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 6.2. In one embodiment, the buffer is histidine acetate or sodium acetate in an amount of about 25 mM, pH 6.3.

[0379] The formulation can further comprise sucrose in an amount of about 60 mM to about 240 mM. In some embodiments, sucrose in the formulation is about 60 mM to about 230 mM, about 60 mM to about 220 mM, about 60 mM to about 210 mM, about 60 mM to about 200 mM, about 60 mM to about 190 mM, about 60 mM to about 180 mM, about 60 mM to about 170 mM, about 60 mM to about 160 mM, about 60 mM to about 150 mM, about 60 mM to about 140 mM, about 80 mM to about 240 mM, about 90 mM to about 240 mM, about 100 mM to about 240 mM, about 110 mM to about 240 mM, about 120 mM to about 240 mM, about 130 mM to about 240 mM, about 140 mM to about 240 mM, about 150 mM to about 240 mM, about 160 mM to about 240 mM, about 170 mM to about 240 mM, about 180 mM to about 240 mM, about 190 mM to about 240 mM, about 200 mM to about 240 mM, about 80 mM to about 160 mM, about 100 mM to about 140 mM, or about 110 mM to about 130 mM. In some embodiments, sucrose in the formulation is about 60 mM, about 70 mM, about 80 mM, about 90 mM, about 100 mM, about 110 mM, about 120 mM, about 130 mM, about 140 mM, about 150 mM, about 160 mM, about 170 mM, about 180 mM, about 190 mM, about 200 mM, about 210 mM, about 220 mM, about 230 mM, or about 240 mM.

[0380] In some embodiments, the antibody concentration in the formulation is about 40 mg/ml to about 125 mg/ml. In some embodiments, the antibody concentration in the formulation is about 40 mg/ml to about 120 mg/ml, about 40 mg/ml to about 110 mg/ml, about 40 mg/ml to about 100 mg/ml, about 40 mg/ml to about 90 mg/ml, about 40 mg/ml to about 80 mg/ml, about 40 mg/ml to about 70 mg/ml, about 50 mg/ml to about 120 mg/ml, about 60 mg/ml to about 120 mg/ml, about 70 mg/ml to about 120 mg/ml, about 80 mg/ml to about 120 mg/ml, about 90 mg/ml to about 120 mg/ml, or about 100 mg/ml to about 120 mg/ml. In some embodiments, the antibody concentration in the formulation is about 60 mg/ml. In some embodiments, the antibody concentration in the formulation is about 65 mg/ml. In some embodiments, the antibody concentration in the formulation is about 70

mg/ml. In some embodiments, the antibody concentration in the formulation is about 75 mg/ml. In some embodiments, the antibody concentration in the formulation is about 80 mg/ml. In some embodiments, the antibody concentration in the formulation is about 85 mg/ml. In some embodiments, the antibody concentration in the formulation is about 90 mg/ml. In some embodiments, the antibody concentration in the formulation is about 95 mg/ml. In some embodiments, the antibody concentration in the formulation is about 100 mg/ml. In some embodiments, the antibody concentration in the formulation is about 110 mg/ml. In some embodiments, the antibody concentration in the formulation is about 125 mg/ml.

10 **[0381]** In some embodiments, a surfactant is added to the antibody formulation. Exemplary surfactants include nonionic surfactants such as polysorbates (e.g. polysorbates 20, 80 etc.) or poloxamers (e.g. poloxamer 188, etc.). The amount of surfactant added is such that it reduces aggregation of the formulated antibody and/or minimizes the formation of particulates in the formulation and/or reduces adsorption. For example, the surfactant may be
15 present in the formulation in an amount from about 0.001% to about 0.5% (w/v). In some embodiments, the surfactant (e.g., polysorbate 20) is from about 0.005% to about 0.2%, from about 0.005% to about 0.1%, from about 0.005% to about 0.09%, from about 0.005% to about 0.08%, from about 0.005% to about 0.07%, from about 0.005% to about 0.06%, from about 0.005% to about 0.05%, from about 0.005% to about 0.04%, from about 0.008% to
20 about 0.06%, from about 0.01% to about 0.06%, from about 0.02% to about 0.06%, from about 0.01% to about 0.05%, or from about 0.02% to about 0.04%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.005% or about 0.005%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.006% or about 0.006%. In certain embodiments, the surfactant
25 (e.g., polysorbate 20) is present in the formulation in an amount of 0.007% or about 0.007%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.008% or about 0.008%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.009% or about 0.009%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.01% or about 0.01%. In certain embodiments, the surfactant (e.g., polysorbate
30 20) is present in the formulation in an amount of 0.02% or about 0.02%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.03% or about 0.03%. In certain embodiments, the surfactant (e.g., polysorbate 20) is

present in the formulation in an amount of 0.04% or about 0.04%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.05% or about 0.05%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.06% or about 0.06%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.07% or about 0.07%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.08% or about 0.08%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.1% or about 0.1%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.2% or about 0.2%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.3% or about 0.3%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.4% or about 0.4%. In certain embodiments, the surfactant (e.g., polysorbate 20) is present in the formulation in an amount of 0.5% or about 0.5%.

[0382] In one embodiment, the formulation contains the above-identified agents (e.g., antibody, buffer, sucrose, and/or surfactant) and is essentially free of one or more preservatives, such as benzyl alcohol, phenol, m-cresol, chlorobutanol and benzethonium Cl. In another embodiment, a preservative may be included in the formulation, particularly where the formulation is a multi-dose formulation. The concentration of preservative may be in the range from about 0.1% to about 2%, preferably from about 0.5% to about 1%. One or more other pharmaceutically acceptable carriers, excipients or stabilizers such as those described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980) may be included in the formulation provided that they do not adversely affect the desired characteristics of the formulation. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed and include; additional buffering agents; co-solvents; anti-oxidants including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g. Zn-protein complexes); biodegradable polymers such as polyesters; and/or salt-forming counterions. Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX[®], Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos.

2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[0383] The formulation herein may also contain more than one protein as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect the other protein. For example, a self-crosslinking antibody may be combined with one or more additional agents (e.g., a chemotherapeutic agent, anti-neoplastic agent, or imaging agent).

[0384] In some embodiments, the physical stability, chemical stability, or biological activity of the antibody in the formulation is evaluated or measured. Any methods known in the art and described in the Examples herein may be used to evaluate the stability and biological activity of the antibody in the formulation. For example, stability of the antibody in the formulation can be measured by, but not limited to, size exclusion chromatography (SEC or SE-HPLC), imaged capillary isoelectric focusing (ICIEF), peptide mapping, small-volume light obscuration (HIAC) assay, and capillary electrophoresis (CE) techniques such as CE-sodium dodecyl sulfate (CE-SDS) and CE-glycan analysis. In some embodiments, the antibody in the formulation is stable at -20°C for at least about 6 months, at least about 8 months, at least about 10 months, at least about 12 months, at least about 14 months, at least about 16 months, at least about 18 months, at least about 20 months, at least about 21 months, at least about 22 months, at least about 23 months, at least about 24 months, at least about 3 years, or at least about 4 years. In some embodiments, the antibody in the formulation is stable at 2°C to 8°C (e.g., 5°C) for at least about 6 months, at least about 8 months, at least about 10 months, at least about 12 months, at least about 14 months, at least about 16 months, at least about 18 months, at least about 20 months, at least about 21 months, at least about 22 months, at least about 23 months, or at least about 24 months. In some embodiments, the stability of the antibody (*i.e.*, an antibody monomer) is measured by size exclusion chromatography in the formulation after storage. In some embodiments, the stability of the antibody is (*i.e.*, an antibody monomer) measured by imaged capillary isoelectric focusing in the formulation after storage. In some embodiments, the percent of antibody monomer in the formulation as compared to total protein (e.g., including antibody and aggregates) is greater than about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94% or about 95% after storage at -20°C for at least about 6 months, at least about 12

months, at least about 18 months, or at least about 24 months. In some embodiments, the percent of antibody monomer in the formulation as compared to (*e.g.*, including antibody and aggregates) is greater than about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%,
5 about 93%, about 94% or about 95% after storage at 2°C to 8°C (*e.g.*, 5°C) for at least about 6 months, at least about 12 months, at least about 18 months, or at least about 24 months. In some embodiments, the percent of antibody monomer in the formulation as compared to (*e.g.*, including antibody and aggregates) is greater than about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 86%, about 87%, about 88%, about 89%, about
10 90%, about 91%, about 92%, about 93%, about 94% or about 95% after agitation at room temperature (*e.g.*, about 15°C to 25°C) for at least about 2 hours, at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, at least about 18 hours, at least about 20 hours, or at least about 24 hours. In some embodiments, the percent of total aggregates (*e.g.*, high
15 molecular weight species and low molecular weight species) in the formulation is less than any of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10% after storage at -20°C for at least about 6 months, at least about 12 months, at least about 18 months, or at least about 24 months. In
20 some embodiments, the percent of total aggregates (*e.g.*, high molecular weight species and low molecular weight species) in the formulation is less than any of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10% after storage at 2°C to 8°C (*e.g.*, 5°C) for at least about 6 months, at least about 12
25 months, at least about 18 months, or at least about 24 months. In some embodiments, the percent of total aggregates (*e.g.*, high molecular weight species and low molecular weight species) in the formulation is less than any of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10% after
30 agitation at room temperature (*e.g.*, about 15°C to 25°C) for at least about 2 hours, at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 14 hours, at least about 16 hours, at least about 18 hours, at least about 20 hours, or at least about 24 hours. In any of the embodiments herein, the stable

formulation can be stored in a glass vial, a metal alloy container, or an intravenous (IV) bag. In some embodiments, the metal alloy is 316L stainless steel or hastelloy.

[0385] The formulations to be used for in vivo administration should be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to, or following, preparation of the formulation.

III. METHODS OF USE

[0386] Also provided herein are methods and uses of the self-crosslinking antibodies. Among the provided methods are methods of delivering self-crosslinking antibodies and antigen binding fragments thereof, optionally comprising agents conjugated thereto, to cells and tissues expressing antigens recognized by the self-crosslinking antibodies. In some embodiments, the self-crosslinking antibodies crosslink mediotope-enabled antibodies, including mediotope-enabled self-crosslinking antibodies. In some embodiments, the antibodies target cell surface antigens. Exemplary antigens include antigens expressed by a disease or condition of a cell or tissue thereof, or cell surface receptors capable of receptor mediated endocytosis.

A. Methods for Altering the Distribution of a Cell Surface Antigen

[0387] Provided are methods for using self-crosslinking antibodies, including mediotope enabled self-crosslinking antibodies, to target cell surface antigens and produce changes in the distribution of those antigens on the surface of host cells. For example, the display of cell surface antigens, such as tumor associated antigens, receptors such as GPCRs, receptor tyrosine kinase, other signaling molecules such as CTLA4, and other epitopes present on cell surface proteins, can be manipulated and/or reorganized through the use of self-crosslinking antibodies that recognize epitopes on those antigens. Reorganization of the receptors and signaling molecules can have a profound effect on signaling pathways and cellular responses.

[0388] *In vivo*, this type of reorganization occurs through cell-cell contact, where ligands from one cell engage receptors on the other cell, effectively creating a multivalent interaction. Through this point of contact, the receptor/ligands are localized or brought into proximity to one another, creating a signaling “synapse”. The signaling synapse initiates post-translational modifications within the cell, and can, for example, alter actin and microtubule organization or protein phosphorylation, ultimately leading to specific transcriptional events.

[0389] Self-crosslinking antibodies can be used in a similar fashion to alter the distribution of cell surface antigens. In some embodiments, the methods enhance or increase co-localization, aggregation, or clustering of cell-surface antigens on target cells. In some aspects, the increase is an increase in degree, speed, and/or duration in comparison to that observed prior to or in the absence of the addition of the self-crosslinking antibody, or in the presence of the antibody without the mediotope crosslinker. Specifically, one or more self-crosslinking antibodies can be administered and permitted to bind to a targeted antigen on the surface of a cell in conjunction. This effect is illustrated by the use of two self-crosslinking mediotope-enabled antibodies. This combination allows for one mediotope fused via a linker to the Fab arm of a first mediotope-enabled antibody to engage with a Fab arm of a second mediotope enabled antibody. The binding permits the formation of a complex of linked antibodies bound to their cognate antigens. In this scenario, one would expect a "linear" arrangement of the two self-crosslinking mediotope-enabled antibodies bound to cell surface antigens. In some aspects, the mediotope is able to "latch-on" to adjacent antibodies, e.g., IgGs, to form a "daisy-chain"-like or web-like array of self-linking antibodies bound to cell surface antigens. The antibodies associate with each other, drawing or crosslinking the surface antigens towards one another, effectively altering the display of those antigens on the surface of the cell. Thus, the use of larger numbers of self-crosslinking antibodies can be used, for example, in antibodies targeting tumor antigens, given the high antigen density of tumor cells.

[0390] In some embodiments, each arm of the self-crosslinking antibody or antigen binding fragment thereof comprises a mediotope bound to the antibody or fragment thereof. As previously described, the linkers can be attached to one or both heavy chains, one or both light chains, or a combination of one or more heavy and light chains in some embodiments. Thus, in some embodiments, each mediotope on the self crosslinking antibody can independently bind to a mediotope binding site on one or more antibodies. For example, in some embodiments, the self-crosslinking antibody can bind to a mediotope binding site on each arm of another mediotope enabled antibody. In some embodiments, this alters or increases the binding affinity of a self-crosslinking antibody to the other antibody. As another example, in some embodiments, each mediotope of the self-crosslinking antibody can bind to a mediotope binding site on a different antibody. Such binding can increase the number of interconnected self-crosslinking antibodies, which can further alter binding geometry, surface antigen distribution, or antibody-antigen complexes.

[0391] In a different embodiment, the self-crosslinking antibodies can be used mark a specific cell for an immune response. In this case, clustering of receptors associated with self-crosslinking antibodies would present a "high" concentration of Fc domain for the FcR on T cells. Multiple investigations have demonstrated that the Fc domain can be specifically
5 tuned through a limited number of point mutations to elicit the appropriate response.

[0392] Provided are methods for delivering antibodies for enhancing or increasing internalization and/or degradation of cell-surface antigens on target cells. In some embodiments, the methods are carried out by administering to the cells one or more self-crosslinking antibodies that specifically bind to the cell surface antigen(s) and comprise a
10 mediotope coupled to the antibody via a linker. In some embodiments, internalization and/or degradation of the antigen is promoted, enhanced or increased. In some aspects, the increase in internalization is an increase in degree, speed, and/or duration in comparison to that observed prior to or in the absence of the addition of the self-crosslinking antibody, or in the presence of the antibody without the mediotope. In some embodiments, the methods alter
15 internalization or intracellular trafficking. In some embodiments, the methods alter intercellular or intracellular signaling.

[0393] An alternative approach for promoting or altering internalization rates is by promoting or controlling the aggregation of cell bound receptors, as in certain embodiments provided herein. In some embodiments herein, co-localization, clustering, aggregation,
20 internalization, and/or intracellular trafficking or sorting is effected, recapitulated, or enhanced or altered using self-crosslinking antibodies. Observed herein are differences in clustering and/or internalization of such surface receptors following administration to cells of self-crosslinking antibodies recognizing such receptor antigens in comparison to administration of non-self-crosslinking antibodies, including antibodies that do not comprise
25 mediotopes fused via linkers. Among the provided embodiments are self-crosslinking antibodies that promote co-localization and clustering of surface antigens recognized by the mediotope enabled antibodies, and/or internalization/trafficking/sorting of such antigens, including cell-surface antigens, including receptors. Cell surface proteins on a host cell forced to internalize would be less available for interaction with their cognate ligands, which
30 could impact the ability of the host cell to respond to that ligand.

[0394] Studies have demonstrated that the size of a particle localized to the cell membrane is important for some mechanisms of internalization (see *Biochem J.* 2004 Jan

1;377(Pt 1):159-69; *J Nanobiotechnology*. 2014 Feb 3;12:5. doi: 10.1186/1477-3155-12-5), suggesting the size of an associated ligand may affect some internalization pathways. The use of self-crosslinking antibodies would create the appearance of a ligand with a larger particle size as compared to a single antibody bound to a cell surface antigen. In some
5 embodiments, the larger particle size can enhance antigen or cell surface receptor internalization.

[0395] In another embodiment, the efficacy of antibody treatments can be altered and improved i) by manipulating the binding affinity of the mediotope coupled to an antibody for the mediotope binding site of a mediotope enabled antibody, ii) by selecting a mediotope enabled
10 antibody with a preferred binding affinity for its cognate epitope on a target antigen, or iii) by manipulating both features to optimize the lifetime as well as the specificity of targeting of the self-crosslinking mediotope enabled antibody complex. Specifically, the lifetime of an interaction is related to the kinetic off-rate. In some instances, it can be envisioned that the longest possible lifetime would be advantageous. In other cases, a moderate lifetime ($\tau =$
15 10 ms to 10 minutes) would be advantageous. In the latter case, there are specific receptors (e.g., EGFR or Her2) that are overexpressed on tumor tissues, but also expressed on certain healthy tissues, albeit at a lower level (10, 100 or 1000 fold). Clinically, it may be desirable to bind to the tumor and not bind to the healthy tissue. Using a combination of self-crosslinking antibodies with a moderate life-time enhances the selectivity. Specifically, at
20 low concentrations of antigen as found in a normal cell, a mediotope enabled antibody could bind to the antigen. However, the likelihood of a second mediotope enabled antibody engaged to antigen is low, preventing antibody crosslinking. In states with high concentrations of antigen, including some disease states, the likelihood of an adjacent mediotope enabled antibody engaged antigen is higher, allowing bridging between two or more self-crosslinking
25 antibody-associated antigens.

[0396] As previously described, in some embodiments, the methods provide an increased degree and/or speed of internalization of a cell-surface antigen. Increased or more rapid internalization can be advantageous when an antibody is delivered to promote downregulation of a surface receptor or other surface antigen associated with or causative in
30 the progression of disease. It can also be advantageous, for example, by reducing the amount of a receptor or other surface antigen on a cell's surface, for example, by targeting it for

degradation. Some such receptors, including co-receptors, are capable of effecting or mediating cell signaling.

[0397] Therefore, the methods described herein can reduce, interfere with, or eliminate harmful cell signaling pathways in some embodiments. In some embodiments, the

5 compositions and methods described herein can increase antigen internalization by 1.5-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 75-, 100-, 200-, 300-, 400-, 500-fold or more.

In some embodiments, the compositions and methods described herein can reduce the amount of antigen present on a cell's surface by 1.5-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 75-, 100-, 200-, 300-, 400-, 500-fold or more. In some embodiments, the compositions and

10 methods described herein can increase antibody internalization by 1.5-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 75-, 100-, 200-, 300-, 400-, 500-fold or more, including the internalization of antibodies with low internalization rates.

[0398] A slower degree or less rapid internalization may be desirable in some contexts, such as those in which the antibody is delivered to promote effector functions such as ADCC and/or complement-mediated lysis, and/or to engage and promote signaling via the cell-
15 surface receptor antigens. In some embodiments, the method promotes or enhances the degree of a signal via the cell surface antigen and/or an effector function mediated via the bound antibody.

[0399] In some embodiments, a non-internalizing antigen is one in which the binding of a
20 monospecific bivalent antibody without a mediotope bound via a linker results in no internalization of the antigen, a degree of internalization that is no more than that resulting from metabolic turnover or in the absence of an antibody specific for the antigen, or that is not greater than 2-fold greater than that resulting from metabolic turnover or in the absence of an antigen-specific antibody. In some embodiments, the antigen following incubation with a
25 monospecific bivalent antibody without a mediotope bound via a linker does not internalize at a rate that is 3-, 4-, 5-, 6-, 7-, 8-, or 9-fold greater than that resulting from metabolic turnover or in the absence of an antigen-specific antibody.

[0400] In some embodiments, the non-internalizing antigen is one in which the binding of a natural binding partner or ligand for the cell-surface antigen alone results in no
30 internalization of the antigen, or a degree of internalization that is no more than that resulting from metabolic turnover or in the absence of the binding partner or ligand, or that is not

greater than 2-fold greater than that resulting from metabolic turnover or in the absence of ligand/binding partner. In some embodiments, the antigen following incubation of cells with a natural ligand or binding partner for the antigen does not internalize at a rate that is 3-, 4-, 5-, 6-, 7-, 8-, or 9-fold greater than that resulting from metabolic turnover or in the absence of the ligand or binding partner. In some embodiments, the antigen is internalized following binding of a monospecific bivalent antibody without a mediotope bound via a linker or natural ligand or binding partner at a half-time that is at least 10, 11, 12, 13, 14, 15, or 16 hours or more.

B. Methods for Increasing the Efficacy of an Antibody Therapy

[0401] Also provided are methods for delivering antibodies to cells, including antibodies comprising agents coupled thereto. In some embodiments, the methods are carried out by administering to the cells one or more self-crosslinking antibodies that specifically bind to the cell surface antigen(s) and comprise a mediotope coupled to the antibody via a linker.

[0402] In some embodiments, the methods increase antibody internalization by a cell.

Increased or more rapid internalization can be advantageous, for example, in the context of ADC or other uses in which the antibody is used to deliver an agent to a cell or in which the antibody is delivered to promote downregulation of a surface receptor or other surface antigen associated with or causative in the progression of disease, such as cancer, for example, by targeting it for degradation.

[0403] In other embodiments, the provided methods utilize properties of cells and alter the internalization and sorting pathway of conjugated biologics to efficiently release an agent associated with the self-crosslinking antibody. As previously discussed, studies have demonstrated that the size of a particle localized to the cell membrane is important for some mechanisms of internalization, suggesting the size of an associated ligand may affect some internalization pathways. The use of self-crosslinking antibodies would create the appearance of a ligand with a larger particle size as compared to a single antibody bound to a cell surface antigen.

[0404] Also provided are methods and uses of such self-crosslinking antibodies in delivering mediotopes, including free mediotopes, including multivalent mediotopes and mediotopes fused to other proteins or protein domains. Some mediotopes can be coupled to agents, for example, in therapeutic and imaging methods. Exemplary methods are those

effecting delivery of an agent, such as a therapeutic or imaging agent, coupled to a mediotope, including a multivalent mediotope, optionally including mediotopes not fused to an antibody via a linker.

[0405] Some potentially useful antibodies that recognize specific antigens abundant on the surface of target cells are "poorly internalizable" (Matzku et al. *Int. J. Cancer*. 1988 2:11-14; Reilly et al. *Clin. Pharmacokinet*. 1995 28:126-142). Poor or suboptimal internalization diminishes intracellular delivery and accumulation in target organs or tissues (Matzku et al. *Int. J. Cancer*. 1988 2:11-14; Reilly et al. *Clin. Pharmacokinet*. 1995 28:126-142).

Therefore, these "poorly internalizable" antibodies are not optimized for intracellular targeting. Accordingly, there is a need for antibody systems that enhance antibody targeting and internalization by cells.

[0406] Some antibodies exert a therapeutic effect after entering a cell. In some embodiments, increased or more rapid internalization can increase an antibody's potency or efficacy. Therefore, in some embodiments, lower dosages can be used to achieve the same therapeutic effect. In some embodiments, administration of a self-crosslinking antibody can achieve the same therapeutic effect as administration of antibody alone using 1.5-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 75-, 100-, 200-, 300-, 400-, or 500- fold less drug.

[0407] In some embodiments, increased or more rapid internalization results in increased or more rapid delivery of an antibody to endosomes. Some antibodies comprise linkers comprising a proteolytic cleavage site. The linkers can be conjugated to agents, including imaging or therapeutic agents, which are then released by the antibody upon internalization. In some embodiments, linker cleavage occurs in endosomes or lysosomes. Therefore, increased or more rapid delivery of an antibody to endosomes or lysosomes can increase an antibody's potency or efficacy.

[0408] In some embodiments, the mediotope, the linker, or the antibody is coupled to a therapeutic or diagnostic agent, such as a chemotherapeutic, cytotoxin, or radiolabeled agent, such as for use in ADC or radioimmunotherapy (RIT). In some embodiments, the methods described herein are useful to enhance delivery of an agent or other methods for antibody-mediated delivery to a cell or tissue expressing an antigen targeted by the antibody. In some embodiments, the methods are advantageous in that they promote clustering and therefore internalization of antigens, antibodies bound to the antigens, and agents associated with the

antibodies, in the context of non-internalizing antigens, such as carcinoembryonic antigen (CEA), tumor-associated glycoprotein (TAG-72), KS1/4 (see Schmidt et al., *Cancer Immunol Immunother.* Dec 2008; 57(12): 1879–1890; Myer et al. *Cancer Res* 1993;53:3956-3963).

[0409] Similarly, with antibodies conjugated to various agents, such as imaging agents, the ability to cluster or co-localize cell and/or internalize surface antigens can be important. For example, drug-conjugated biologics such as antibody-drug conjugates (ADCs) are generally designed with a goal of selectively delivering an agent, e.g., an active drug, within the targeted tissue, often within a cell of the targeted tissue or targeted cell, such as a tumor cell. The targeting biologic, e.g., the antibody, is generally designed to preferentially bind to the cell of interest; selective binding to antigens present only on the target cells or tissues and/or present at very low amounts or infrequently on other tissues, can be especially desirable. Particularly for drug-conjugated antibodies directly targeting diseased cells, e.g., tumor cells, it can be desirable or important that the agent-conjugated antibody is internalized within the target cell following binding to the target antigen on the cell surface. See, e.g., Trail et al., *Antibodies* 2013, 2, 113-129; H.L. Perez, et al., *Drug Discov Today* (2013). In some contexts, antibodies that result in internalization of antigens are also desirable in the context of radioimmunotherapy (RIT). See Boudousq V et al., *PLoS ONE* 8(7): e69613 (2013). In general, the conjugated agent, e.g., drug, is released and is active within the target cell. In some contexts, for example in targeting of certain extracellular matrix components and/or antigens specific to the tumor environment, internalization may not be necessary. See Ackerman et al., *Cancer Immunol Immunother.* Jul 2008; 57(7): 1017–1027.

[0410] In some embodiments, the provided methods utilize properties of tumor cells and alter the internalization and sorting pathway of conjugated biologics to efficiently release the agent. In some embodiments, the methods effect co-localization, clustering, aggregation, internalization, and/or intracellular trafficking or sorting of the antigen and/or meditope-enabled antibodies, and/or recapitulation or enhancement or alteration thereof. Observed herein are differences in clustering and/or internalization of self-crosslinking antibodies compared to non-self-crosslinking antibodies following administration to cells.

[0411] Despite the successful development of TDM1, an anti-Her2 ADC that is marketed as KADCYLA®, only a small fraction of the conjugated drug (~2%) is delivered to the tumor. The precise reason for such a low delivery yield is not clear, however, it likely stems from the different internalization routes utilized by the cell (e.g., clathrin-mediated

endocytosis and/or caveolae-mediated endocytosis and/or macropinocytosis) as well as routing of the endocytosed material once inside the cell (recycling endosomes or late endosomes or lysosomes). Drugs conjugated to the antibody through a disulfide linker may be released due to the reducing environment of the cellular cytoplasm. Alternatively, some drug conjugates, such as auristatin, may be released by specific proteases active in endosomal vesicles. Other studies using different linkers indicate that the lysosome is an effective means in releasing the drug, independent of conjugation chemistry. Yet disulfides can be reduced in serum and proteases can be active in healthy tissue. In some embodiments, the provided methods, antibodies (including self-crosslinking antibodies), and mediotopes provide improvements such as more specific and effective delivery of agents, such as toxins to treat disease.

[0412] In tumor immunotherapy, many antigens are merely tumor-associated or expressed at higher levels on tumor cells/environments, as opposed to being tumor-specific. For example, while Her2 and EGFR are significantly overexpressed in tumor tissues such as Her2+ breast cancer and colorectal cancers, they are also expressed in healthy tissues, which can result in on-target, off-tissue toxicities. Other types of antigens (such as tumor-specific antigens and oncofetal antigens, e.g., carcinoembryonic antigen (CEA)) are expressed solely in tumor tissues and/or otherwise minimally or at only certain stages of development. Combinations of monoclonal antibodies (mAbs) that recognize unique epitopes on the same antigen can produce synergistic effects, including enhancement of various antibody effector functions (e.g., ADCC, complement-dependent lysis, signaling inhibition), enhancement of cell death, and in the case of cancer-targeting antibodies, enhancement of tumor growth inhibition. See, for example, Dechant M et al., "Complement-dependent tumor cell lysis triggered by combinations of epidermal growth factor receptor antibodies," *Cancer Res*, 2008 Jul 1;68(13):4998-5003; Scheuer W et al., "Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models," *Cancer Res*, 2009 Dec 15;69(24):9330-6; Cardarelli PM et al., "Binding to CD20 by anti-B1 antibody or F(ab')(2) is sufficient for induction of apoptosis in B-cell lines," *Cancer Immunol Immunother*, 2002 Mar;51(1):15-24. Epub 2001 Dec 18.

[0413] In some aspects, the self-crosslinking antibody is used instead of a bispecific antibody, e.g., to achieve synergy in combination with a mediotope-enabled antibody. In some aspects, the self-crosslinking antibody provides advantages compared to use of a bispecific

antibody recognizing two separate epitopes on the same antigen. For example, production of the self-crosslinking antibody can be more efficient and cost-effective when compared to manufacturing a bispecific antibody. In some aspects, the self-crosslinking antibodies also are comparatively more easily targeted to disease sites, such as tumors. Given the nature of the meditope binding site (within the meditope binding site, separate from the antibody CDRs), and the broadly applicable methods provided herein for meditope-enabling any antibody of choice, the self-crosslinking antibody and meditope enabled antibody also have the advantage of being readily applicable to a large range of therapeutic antibodies, without the need to generate a bispecific antibody with therapeutically acceptable characteristics, and the associated and significant cost of its development.

[0414] In some embodiments, the compounds and methods are useful in deriving synergistic tumor inhibition (Kamat, V., et al., *Cancer Biol Ther* 7, 726-733 (2008); Koefoed K, et al. (2011) *MAbs* 3(6):584-595; Spangler JB, et al. (2010) *Proc Natl Acad Sci USA* 107(30):13252-13257), as observed in the trastuzumab-pertuzumab combination (Baselga J, et al. (2012). *N Engl J Med* 366(2):109-119). In some examples, self-crosslinking antibodies function as second “mAb”-like molecules, but with the flexibility of being able to pair up with any compatible meditope enabled antibody. In some aspects, this reduces the cost of identifying and developing a second therapeutic mAb. In some embodiments, multivalent meditope variants (e.g., generated by altering valency and/or linker geometry) further enhance specificity and synergistic effects.

[0415] Similarly, in some embodiments, two self-crosslinking meditope-enabled antibodies, each of which specifically binds to a different antigen expressed on the surface of the same cell, are used in place of a bivalent antibody. In some embodiments, the methods provide enhanced antigen (e.g., receptor) aggregation, and/or a certain level aggregation regardless of the ratio of the density or presence of the two antigens relative to one another on the cell surface. In some aspects, the methods enhance cell-surface clustering of antigens and/or co-localization. In one embodiment, two or more self-crosslinking antibodies are used to achieve such clustering together with recognizing multiple different antigens. Thus, in some embodiments, as compared to a bispecific antibody, in which clustering would occur only where each arm of the antibody bound its respective antigen, clustering in such an embodiment may be achieved even where the antigen bound by one of the antibodies is present at a much higher density on the cell surface compared to the antigen bound by

another. Furthermore, in some embodiments, the use of two self-crosslinking antibodies can also enhance efficacy where the distance between two cell surface antigens exceeds the distance between the two arms of a bispecific antibody. In such embodiments, the linker length can be varied to accommodate the actual or expected distances between cell surface antigens, as described above.

[0416] In some embodiments, the self-crosslinking antibodies provide advantages over and/or improvements in bivalent antibodies. In some embodiments, the self-crosslinking antibody is a bispecific mediotope-enabled antibody, e.g., to enhance aggregation of two antigens, e.g., cell-surface antigens, bound by the different arms of the bispecific antibody, for example, to enhance affinity, signaling induced by the antibody, effector functions, and/or internalization, as compared to use of the bispecific antibody alone. Thus, in some aspects, the self-crosslinking bispecific mediotope-enabled antibody provides an increased level of efficacy, for example, by causing an additional degree of clustering as compared to the bispecific antibody alone.

[0417] Antibodies and binding compounds (e.g., mediotopes) provided have practical utility and in some embodiments can overcome hurdles associated with available mAb-based technologies. In some embodiments, the provided compounds and methods address the problem of antigenicity that can arise with non-native reagents, which for example, expose new surfaces, which can be antigenic, and/or concerns with stability and the scalability in the manufacturing of such molecules (Nelson AL (2010) Antibody fragments: hope and hype. *MAbs* 2(1):77-83). Cetuximab is used successfully in the clinic and is stable and produced at scale. In some embodiments, the unique combination of residues that line the mediotope binding site is distant in sequence (i.e., unlikely to be a peptide T-cell epitope) and located within a deep cavity (i.e., unlikely to be a surface exposed B-cell epitope)). Thus, in some embodiments, mAbs containing the mediotope binding site are not immunogenic.

[0418] In some embodiments, the mediotope binding site is used as a specific point of conjugation, useful in avoiding issues of heterogeneity and conjugation efficiency that typically affect the development of effective ADCs by available methods. A toxin-bearing mediotope in some embodiments can direct a reactive chemical to the Fab cavity, favoring specificity and unit stoichiometry.

[0419] In some aspects, moderate affinity of mediotopes (e.g., cQFD and cQYN mediotopes) is advantageous, such as when considering a multivalent approach ((Mammen M, Choi S, & Whitesides G (1998) Polyvalent interactions in biological systems: Implications for design and use of multivalent ligands and inhibitor. *Angew. Chem., Int. Ed. Eng* 37:2755)), in some embodiments, different un-natural amino acids, cyclization strategies, and/or screening methods are used to improve affinity and/or pharmacokinetics / pharmacodynamics / toxicity. As demonstrated herein, in some embodiments, it is equally possible to tailor the mediotope binding site to accommodate changes in the mediotope.

C. Therapeutic and diagnostic uses and pharmaceutical compositions

[0420] In one embodiment, the self-crosslinking antibody is used to deliver therapeutic agents, diagnostic agents (e.g., imaging agents), or a combination thereof for treatment, diagnosis (e.g., imaging) a disease or condition. A self-crosslinking antibody-drug conjugate may be used in a method for directing treatment to a particular type of cell or population of cells in a disease or condition that can be targeted by a therapeutic antibody. Such a method of treatment may include administering a therapeutically effective amount of a pharmaceutical composition to a subject having the disease or condition via any suitable route of administration. The pharmaceutical composition may include a self-crosslinking antibody or functional fragment thereof.

[0421] In some embodiments, the provided self-crosslinking antibodies and complexes thereof are used in treatment, diagnosis or imaging of a disease or condition, including any cancer, disease or other condition that may be treated or targeted using a therapeutic antibody. Cancers avoid immune surveillance by actively suppressing the immune system. One method envisioned for counteracting this immunosuppression is through vaccination using epitopes of antigens that are either uniquely expressed or over-expressed by the tumor cells. For example, self-crosslinking antibodies that block signaling pathways, sequester growth factor and/or induce an immune response have been successfully implemented in the clinic to treat cancer and other diseases.

[0422] Thus, the diseases and conditions include any cancer, as well as other diseases and conditions, including those targeted using therapeutic monoclonal antibodies (mAbs), including, but not limited to, leukemia and lymphomas (which can be treated or imaged using, e.g., self-crosslinking versions of alemtuzumab, bectumomab, gemtuzumab, lintuzumab, FBT A05, ibritumomab tiuzetan, ofatumumab, rituximab, tositumomab), breast

cancer (which can be treated or imaged using, e.g., self-crosslinking versions of trastuzumab, adecatumumab, ertumaxomab) prostate cancer (which can be treated or imaged using, e.g., self-crosslinking versions of adecatumumab, capromab pendetide, etaracizumab), colorectal cancer (which can be treated or imaged using, e.g., self-crosslinking versions of labetuzumab, panitumumab, altumumab pentetate, votumumab), gastrointestinal cancers (which can be treated or imaged using, e.g., self-crosslinking versions of arcitumumab, catumaxomab), ovarian cancer (which can be treated or imaged using, e.g., self-crosslinking versions of abagovomab, catumaxomab, etaracizumab, igovomab, oregovomab), lung cancer (which can be treated or imaged using, e.g., self-crosslinking versions of anatumumab mafenatox), pancreatic cancer (which can be treated or imaged using, e.g., self-crosslinking versions of clivatuzumab tetraxetan), renal cancer (which can be treated or imaged using, e.g., self-crosslinking versions of girentuximab), melanoma cancer (which can be treated or imaged using, e.g., self-crosslinking versions of etaracizumab, ipilimumab, TRBS07), glioma (which can be treated or imaged using, e.g., self-crosslinking versions of nimotuzumab), bone metastases (which can be treated or imaged using, e.g., self-crosslinking versions of denosumab), head and neck cancer (which can be treated or imaged using, e.g., self-crosslinking versions of zalutumumab), cardiovascular disease (which can be treated or imaged using, e.g., self-crosslinking versions of abciximab), autoimmune disorders (which can be treated or imaged using, e.g., self-crosslinking versions of adalimumab, infliximab), rheumatoid arthritis (which can be treated or imaged using, e.g., self-crosslinking versions of atlizumab, golimumab, infliximab), transplant rejection (which can be treated or imaged using, e.g., self-crosslinking versions of basiliximab, daclizumab, muromonab-CD3), Crohn's disease (which can be treated or imaged using, e.g., self-crosslinking versions of certolizumab, fontolizumab, natalizumab, infliximab, visilizumab), hemoglobinuria (which can be treated or imaged using, self-crosslinking versions of eculizumab), psoriasis (which can be treated or imaged using, e.g., self-crosslinking versions of efalizumab, infliximab, ustekinumab), multiple sclerosis (which can be treated or imaged using, e.g., self-crosslinking versions of natalizumab, ustekinumab), asthma (which can be treated or imaged using, e.g., self-crosslinking versions of benralizumab, mepolizumab, omalizumab), respiratory syncytial virus (RSV) (which can be treated or imaged using, e.g., self-crosslinking versions of palivizumab), macular degeneration (which can be treated or imaged using, e.g., self-crosslinking versions of ranibizumab), appendicitis (which can be treated or imaged using, e.g., self-crosslinking versions of fanolesomab) and any other condition that may be targeted

or treated with an antibody. The above-listed antibodies and related diseases or disorders are examples only and do not limit the platform.

[0423] In certain embodiments, the mediotope-enabled self-crosslinking antibody can be bound by one or more free mediotopes, mediotope variants, multivalent mediotope tethering agents or multivalent mediotope variant tethering agents. Such mediotopes may be conjugated to one or more imaging agents, therapeutically effective agents or compounds in therapeutically effective amounts or both. Administration of mediotope-enabled self-crosslinking antibody bound by mediotopes or variants thereof with the therapeutically effective compound may treat, prevent, diagnose or monitor a disease or condition. Such conjugation of a high affinity and/or multivalent mediotope coupled to mediotope-enabled mAbs provides a highly versatile platform technology that will significantly improve mAb based therapeutics and imaging methods to treat and detect disease.

[0424] In some embodiments, the provided methods and compounds are useful in antibody engineering, antibody-drug conjugates (ADCs), antibody-directed enzyme prodrug therapies (ADEPT), immune system engagement (e.g., Fc modifications (Desjarlais JR & Lazar GA (2011) Modulation of antibody effector function. *Exp Cell Res* 317(9):1278-1285), chemokine fusion, bi-specific T-cell engagers (Wolf E, Hofmeister R, Kufer P, Schlereth B, & Baeuerle PA (2005) BiTEs: bispecific antibody constructs with unique anti-tumor activity. *Drug Discov Today* 10(18):1237-1244) and disease imaging (e.g., immunoPET and pre-targeted radionuclide imaging (Goldenberg DM, et al. (2012) Pretargeted molecular imaging and radioimmunotherapy. *Theranostics* 2(5):523-540; Pagel JM, et al. (2006) Comparison of a tetravalent single-chain antibody-streptavidin fusion protein and an antibody-streptavidin chemical conjugate for pre-targeted anti-CD20 radioimmunotherapy of B-cell lymphomas. *Blood* 108(1):328-336).

[0425] In some aspects, the provided methods and compounds overcome issues observed in available such methods, for example, those using post-translational chemical modifications or manipulation of the gene sequence, which can for example lead to undesirable consequences that are detrimental to therapeutic and imaging applications. For example, with ADCs targeting cytotoxins to disease sites using available methods, chemical conjugation of the toxin (typically involves lysines, reduced cysteines, or sugars on the mAb) can produce a heterogeneous mixture, which can adversely affect the specificity and stability of the mAb and alter its bio-distribution.

[0426] In other embodiments, a method for imaging tumors or other tissues is provided. In such methods, a self-crosslinking antibody that is labeled with an imaging agent is administered via any suitable route of administration and will bind to the therapeutic antibodies that are bound to the target tumor or tissue. Examples of imaging agents include but are not limited to radiolabels (e.g., ^3H , ^{14}C , ^{35}S , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{125}I , ^{131}I , ^{177}Lu , ^{166}Ho , and ^{153}Sm), metal or magnetic labels (e.g., gold, iron, gadolinium), biotin, chelating agents (e.g., 1,4,7,10-tetraazacyclododecane-N,N', N'', N'''-tetraacetic acid ("DOTA")) or any agent described above. In one embodiment, the imaging agent used with the method described herein is DOTA.

[0427] As another example, reducing the size of the mAb to Fab fragments (e.g., single chain Fab variable domain (scFvs)) to facilitate tumor penetration and enhance imaging using available methods can reduce the valency and thus affect both the affinity and the tissue specificity compared to the original mAb. In other cases, with available methods, as part of a pre-targeted imaging protocol to enhance detection, mAbs conjugated with streptavidin or multiple Fabs/scFvs stitched together through a scaffold (e.g., "lock-and-dock") can be immunogenic, unstable in serum, and technically difficult and expensive to produce, especially at scales necessary for clinical use. The provided compounds and methods in some embodiments are useful in overcoming such difficulties, for example, by providing an alternative mAb platform and improved mAb-based delivery systems for cancer and other diseases and conditions.

D. Modulating the Effects of Self-Crosslinking Antibodies

[0428] Also provided are methods for altering the effects of a self-crosslinking antibody with a free meditope. In some embodiments, the free meditope can compete with a meditope fused to self-crosslinking antibodies for binding to meditope binding sites. Generally, the methods comprise contacting a meditope binding site of a meditope enabled antibody with a free meditope. Binding between the meditope binding site and free meditope can occupy the meditope binding site, thereby inhibiting, reducing, or preventing a meditope from a self-crosslinking antibody from contacting or binding to the meditope binding site. In some embodiments, the free meditope can displace or disrupt a meditope fused to a self-crosslinking antibody via a linker. Because the binding between a meditope and a meditope binding site is generally non-covalent, such binding can be temporary or reversible.

[0429] In some embodiments, the methods reverse or reduce the effects of a self-crosslinking antibody. Such effects include, for example, reversing or reducing the ability of the self-crosslinking antibody to alter the distribution, co-localization, or internalization of a cell surface antigen. Such effects also include, for example, reversing or reducing the ability of the self-crosslinking antibody to alter or increase the rate of antibody internalization, antibody efficacy, or decrease the dosage of antibody therapy needed to achieve a desired therapeutic effect.

[0430] As an exemplary advantage, such methods may allow for the modulation of certain treatments over time. For example, in some embodiments a self-crosslinking antibody with a long half-life is administered, but the effects of the antibody are modulated by the administration of free meditope with a shorter half-life. In some embodiments, the free meditope's shorter half-life allows for the temporary inhibition of antibody self-crosslinking until the free meditope levels drop due to degradation or clearance. When the free meditope levels drop, the peptides are less effective at inhibiting self-crosslinking, and self-crosslinking can resume. Such half-lives can be minutes, hours, days, or weeks long depending on the free meditope's structure and the conditions under which it is used.

[0431] These effects can be useful in modulating or minimizing side effects that may be a byproduct of antibody therapy, including self-crosslinking antibody therapy. For example, in some embodiments a free meditope is administered simultaneously with, shortly before, or shortly after the administration of a self-crosslinking antibody. In some embodiments, the methods include using a composition comprising both the self-crosslinking antibody and free meditope, or a first composition comprising the self-crosslinking antibody and a second composition comprising the free meditope. In some embodiments, the free meditope reduces or prevents self-crosslinking, and therefore aggregation, before the antibody binds to its cognate antigen. In some embodiments, this can reduce the amount of self-crosslinking that occurs in the blood, which can reduce the amount of self-crosslinking antibody that may deposit in capillaries. In some embodiments, reducing self-crosslinking and aggregation reduces the amount of antibody cleared by the kidney or liver. Thus, administering self-crosslinking antibody with free meditope, including, for example, a free-meditope peptide with a shorter half-life than the self-crosslinking antibody, can temporarily reduce or delay self-crosslinking. Such a reduction or delay can allow time for the self-crosslinking antibody to bind to its cognate antigen before beginning to self-crosslink with other antibodies, thereby

reducing self-crosslinking or aggregation in blood vessels, tissues or organs that are not intended as antibody targets.

[0432] In another exemplary method, free meditope can be administered to a subject who has already received self-crosslinking antibody to reverse, reduce, or alter the effects of the self-crosslinking antibody. Such methods may be useful in reducing the therapeutic effects or side effects caused by self-crosslinking antibodies. In some embodiments, it may be useful to temporally control self-crosslinking. As previously described, self-crosslinking antibodies can be used to alter the distribution of an antigen on a cell's surface or increase the rates of antibody or antigen internalization. In some embodiments it may be advantageous to control or reduce these effects by reducing or inhibiting self-crosslinking. Such methods can include the administration of free meditopees.

[0433] In some embodiments, the free meditope has a long half-life, thereby permanently or semi-permanently altering self-crosslinking. In some embodiments, a free meditope with a half-life that is shorter than the half-life of the self-crosslinking antibody is administered. In some embodiments, administration of a free meditope with a short half-life causes the temporary reduction or inhibition of self-crosslinking. In some embodiments, the subject receives a plurality of free meditope administrations. Such administrations can be delivered as "booster doses" to prolong or extend the inhibiting or reducing effects of the free meditope. Alternatively, such administrations can be delivered over longer periods of time, thereby allowing the self-crosslinking abilities of the antibody to be inhibited and restored over time. In such an embodiment, high levels of free meditope can inhibit self-crosslinking. As the free meditope is cleared or degrades, less is available to occupy meditope binding sites of self-crosslinking antibodies, thereby restoring antibody self-crosslinking. A subsequent administration of additional free-meditope peptide can once again reduce or inhibit antibody self-crosslinking.

[0434] The extent of the inhibition or reduction of self-crosslinking be modulated in some embodiments by administering higher or lower dosages of free meditope. In some embodiments, administering a larger dose of free meditope will have a greater inhibitory effect than a smaller dose. Such dosages can be calculated, for example, as a ratio of free meditope to self-crosslinking antibody, as an amount necessary to produce a therapeutic effect for a desired amount of time, as a relative or absolute IC₅₀, or as an amount calculated by weight or volume.

[0435] The extent of the inhibition or reduction of self-crosslinking can be modulated in some embodiments by administering free meditoes with specific affinities for a meditoep binding site. For example, in some embodiments, a free meditoep with a high affinity has a higher, stronger, or longer effect on inhibiting or reducing self-crosslinking than a free meditoep with a lower affinity. In some embodiments, a free meditoep with a higher affinity binds to a meditoep binding site stronger or with a longer off-rate than a free meditoep with a lower affinity. In some embodiments, antibody self-crosslinking can be reduced or inhibited with lower amounts of free meditoes with higher affinities as compared to the amounts of free meditoes with lower affinities needed to achieve the same effect.

[0436] In some embodiments, a free meditoep with a lower affinity can be used to have a more modest or temporary effect on self-crosslinking. In some embodiments, such meditoes can be used to adjust the efficacy of a particular antibody therapy.

[0437] In some embodiments, the free meditoep is administered a plurality of times, including, for example, optionally 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times. In some embodiments, the administrations take place over a period of minutes, hours, days, months, or years. In some embodiments, a plurality of free meditoes are administered, which plurality can comprise free meditoes that are the same or different. For example, in some embodiments, a first free meditoep can comprise a first affinity for a meditoep binding site, and a second free meditoep can comprise a second affinity for the meditoep binding site. The first and second free meditoes can differ in half-life or IC₅₀. Administering the first and/or second free meditoep can allow for additional mechanisms for altering meditoep self-crosslinking.

IV. METHODS OF ADMINISTRATION

[0438] The formulation is administered to a mammal in need of treatment with the antibody, preferably a human, in accord with known methods, such as intravenous administration (e.g., as a bolus or by continuous infusion over a period of time), by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. In one embodiment, the formulation is administered to the mammal by intravenous administration. For such purposes, the formulation may be injected using a syringe or via an IV line, for example. In one embodiment, the formulation is administered to the mammal by subcutaneous administration.

[0439] The appropriate dosage ("therapeutically effective amount") of the antibody will depend, for example, on the condition to be treated, the severity and course of the condition, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, the type of antibody used, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments and may be administered to the patient at any time from diagnosis onwards. The antibody may be administered as the sole treatment or in conjunction with other drugs or therapies useful in treating the condition in question.

[0440] As a general proposition, the therapeutically effective amount of the antibody administered to human will be in the range of about 0.01 to about 50 mg/kg of patient body weight whether by one or more administrations. In some embodiments, the antibody used is about 0.01 to about 45 mg/kg, about 0.01 to about 40 mg/kg, about 0.01 to about 35 mg/kg, about 0.01 to about 30 mg/kg, about 0.01 to about 25 mg/kg, about 0.01 to about 20 mg/kg, about 0.01 to about 15 mg/kg, about 0.01 to about 10 mg/kg, about 0.01 to about 5 mg/kg, or about 0.01 to about 1 mg/kg administered daily, for example. In some embodiments, the antibody is administered at 15 mg/kg. However, other dosage regimens may be useful. In one embodiment, a self-crosslinking antibody described herein is administered to a human at a dose of about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg or about 1400 mg on day 1 of 21-day cycles. The dose may be administered as a single dose or as multiple doses (e.g., 2 or 3 doses), such as infusions. The dose of the antibody administered in a combination treatment may be reduced as compared to a single treatment. The progress of this therapy is easily monitored by conventional techniques.

[0441] In some embodiments, the disease or disorder is cancer. In some embodiments, the cancer is locally advanced or metastatic. In some embodiments, the cancer is selected from the group consisting of a solid tumor, a hematologic cancer, bladder cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, gastric cancer, glioma, head cancer, leukemia, liver cancer, lung cancer (e.g., non-small cell lung cancer), lymphoma, myeloma, neck cancer, ovarian cancer, melanoma, pancreatic cancer, renal cancer, salivary cancer, stomach cancer, thymic epithelial cancer, thyroid cancer, and squamous cell carcinoma of the head and neck.

[0442] In some embodiments, the disease or disorder is infection. In some embodiments, the infection is a persistent infection. In some embodiments, the infection is a viral infection, a bacterial infection, a fungal infection, a helminth infection, or a protozoan infection. In some embodiments, the viral infection is selected from the group consisting of cytomegalovirus Epstein-Barr virus, hepatitis B, hepatitis C virus, herpes virus, measles virus, influenza, human immunodeficiency virus, human T lymphotropic virus, lymphocytic choriomeningitis virus, respiratory syncytial virus, and/or rhinovirus. In some embodiments, the bacterial infection is selected from the group consisting of *Helicobacter* spp., *Mycobacterium* spp., *Porphyromonas* spp., *Chlamydia* spp., *Salmonella* spp., *Listeria* spp., *Streptococcus* spp., *Haemophilus* spp., *Neisseria* spp., *Klebsiella* spp., *Borrelia* spp., *Bacterioides* spp., and *Treponema* spp. In some embodiments, the protozoan infection is selected from the group consisting of *Leishmania* spp., *Plasmodium falciparum*, *Schistosoma* spp., *Toxoplasma* spp., *Trypanosoma* spp., and *Taenia* spp. In some embodiments, the fungal infection is selected from the group consisting of blastomycosis, coccidioidomycosis, histoplasmosis, candidiasis, cryptococcosis, aspergillosis, mucormycosis and pneumocystosis.

[0443] In some embodiments, the disease or disorder is an inflammatory disease. In some embodiments, the inflammatory disease is selected from the group consisting of acute disseminated encephalomyelitis, Addison's disease, Alzheimer's disease, ankylosing spondylitis, antiphospholipid antibody syndrome, atherosclerosis, autoimmune hemolytic anemia, autoimmune hepatitis, arthritis, Behcet's disease, Berger's disease, Bullous pemphigoid, Celiac disease, Chagas' disease, cholangitis, Crohn's disease, Dermatomyositis, Diabetes mellitus type 1, glomerulonephritis, Goodpasture's syndrome, graft-versus-host disease, Graves' disease, Guillain-Barré syndrome, Hashimoto's disease, hives, hyper IgE syndrome, idiopathic thrombocytopenic purpura, lupus erythematosus, lupus nephritis, multiple sclerosis, myasthenia gravis, organ transplant rejection, Parkinson's disease, pemphigus, pernicious anaemia, polymyositis, primary biliary cirrhosis, psoriasis, Raynaud's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, temporal arteritis, thyroiditis, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis.

[0444] In some embodiments, the formulation containing the antibody may be administered in conjunction with another therapeutic agent to a subject or an individual for treating a disease or disorder. For example, for treating cancer, the self-crosslinking antibody

formulation described herein may administered in conjunction with another anti-cancer treatment (e.g., a chemotherapy or a different antibody treatment).

V. ARTICLES OF MANUFACTURE OR KITS

[0445] Also provided herein are articles of manufacture or kits comprising a container
5 which holds the aqueous pharmaceutical formulation of any of the embodiments described herein and optionally provides instructions for its use. Suitable containers include, for example, bottles, vials, bags and syringes. The container may be formed from a variety of materials such as glass, plastic (such as polyvinyl chloride or polyolefin), or metal alloy (such as stainless steel or hastelloy). An exemplary container is a 300 cc metal alloy container
10 (e.g., for storing at -20°C). Another exemplary container may be 10-50 cc glass vial (e.g., for storing at 2-8°C). For example, the container may be 10 cc, 15 cc, 20 cc, or 50 cc glass vials. The container holds the formulation and the label on, or associated with, the container may indicate directions for use. The article of manufacture may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters,
15 needles, syringes, and package inserts with instructions for use. In some embodiments, the article of manufacture further includes one or more of another agent (e.g., a chemotherapeutic agent, and anti-neoplastic agent). Suitable containers for the one or more agent include, for example, bottles, vials, bags and syringes.

[0446] Having described the invention with reference to the embodiments and illustrative
20 examples, those in the art may appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to
25 those of ordinary skill in the art and are described in numerous publications. Further, all references cited above and in the examples below are hereby incorporated by reference in their entirety, as if fully set forth herein.

[0447] The following documents are hereby incorporated by reference in their entirety for all purposes: United States Application Serial Number 61/597,708, filed February 10, 2012;
30 United States Application Serial Number 13/270,207, filed October 10, 2011, now U.S. Patent No. 8,658,774; International Application Number PCT/US2011/055656 filed October 10, 2011; International Application Number PCT/US12/32938 filed April 10, 2012; United

States Application Serial Number 13/443,804, filed April 10, 2012, now U.S. Patent No. 8,962,804; United States Application Serial Number 61/749,830, filed February 10, 2012, and United States Application Serial Number 13/764,762, filed February 11, 2013.

VI. DEFINITIONS

5 **[0448]** An “antibody,” as used herein, refers to an immunoglobulin molecule that specifically binds to, or is immunologically reactive with an antigen or epitope, and includes both polyclonal and monoclonal antibodies, as well as functional antibody fragments, including but not limited to fragment antigen binding (Fab) fragments, F(ab')₂ fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain variable
10 fragments (scFv) and single domain antibodies (e.g., sdAb, sdFv, nanobody) fragments. The term “antibody” includes genetically engineered or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric antibodies, fully human antibodies, humanized antibodies, mediotope-enabled antibodies and heteroconjugate antibodies (e.g., bispecific antibodies, diabodies, triabodies, tetrabodies, tandem di-scFv,
15 tandem tri-scFv). Unless otherwise stated, the term “antibody” should be understood to encompass functional antibody fragments thereof.

[0449] The terms “complementarity determining region,” and “CDR,” are known in the art to refer to non-contiguous sequences of amino acids within antibody variable regions, which confer antigen specificity and binding affinity. In general, there are three CDRs in
20 each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). “Framework regions” and “FR” are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each light chain variable region (FR-L1, FR-L2,
25 FR-L3, and FR-L4).

[0450] The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme), Al-
30 Lazikani et al., (1997) JMB 273,927-948 (“Chothia” numbering scheme), MacCallum et al., J. Mol. Biol. 262:732-745 (1996), “Antibody-antigen interactions: Contact analysis and binding site topography,” J. Mol. Biol. 262, 732-745.” (Contact” numbering scheme),

Lefranc MP et al., “IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains,” *Dev Comp Immunol*, 2003 Jan;27(1):55-77 (“IMGT” numbering scheme), and Honegger A and Plückthun A, “Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool,” *J Mol Biol*, 2001 Jun 8;309(3):657-70, (AHo numbering scheme).

[0451] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, “30a,” and deletions appearing in some antibodies. The two schemes place certain insertions and deletions (“indels”) at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0452] Table 4, below, lists the positions of CDR-L1, CDR-L2, CDR-L3 and CDR-H1, CDR-H2, CDR-H3 as identified by the Kabat, Chothia, and Contact schemes, respectively. For CDR-H1, residue numbering is given listed using both the Kabat and Chothia numbering schemes. It is noted that because the Kabat numbering scheme places insertions at H35A and H35B, the end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34, depending on the length of the loop.

Table 4

CDR	Kabat	Chothia	Contact
CDR-L1	L24--L34	L24--L34	L30--L36
CDR-L2	L50--L56	L50--L56	L46--L55
CDR-L3	L89--L97	L89--L97	L89--L96
CDR-H1 (Kabat Numbering ¹)	H31--H35B	H26-- H32..34	H30-- H35B
CDR-H1 (Chothia Numbering ²)	H31--H35	H26--H32	H30--H35
CDR-H2	H50--H65	H52--H56	H47--H58
CDR-H3	H95--H102	H95--H102	H93-- H101

1 - Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD

2 - Al-Lazikani et al., (1997) *JMB* 273,927-948

[0453] Thus, unless otherwise specified, a “CDR” or “complementary determining region,” or individual specified CDRs (e.g., “CDR-H1, CDR-H2), of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) complementary determining region as defined by any of the known schemes.

5 Likewise, unless otherwise specified, a “FR” or “framework region,” or individual specified FRs (e.g., “FR-H1, FR-H2), of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) framework region as defined by any of the known schemes. In some instances, the scheme for identification of a particular CDR, FR, or FRs or CDRs is specified, such as the CDR as defined by the Kabat, Chothia, or
10 Contact method. In other cases, the particular amino acid sequence of a CDR or FR is given.

[0454] The term “meditope-enabled” antibody and “meditope enabled antibody” and “meditope enabled antibody” refer to an antibody or functional fragment thereof that is able to bind to a meditope, via a meditope binding site. Examples of meditope-enabled antibodies include, but are not limited to, cetuximab and others described herein. A “meditope binding
15 site” is a region of the meditope-enabled antibody containing the amino acid residues that interact with a bound meditope, which residues include framework region (FR) residues of the heavy and light chains. With reference to a Fab fragment or a Fab portion of an antibody, the meditope binding site is located within the central cavity of the Fab fragment or portion.

[0455] The “central cavity,” with respect to the three-dimensional structure of a Fab,
20 refers to the internal cavity of the Fab, lined by portions of the heavy and light chain variable and constant regions. The central cavity thus is lined by residues of the VH, VL, CH1, and CL regions and does not include the antigen binding site.

[0456] In some embodiments, the meditope binding site includes residues 40, 41, 83, and 85 of the light chain of a meditope-enabled antibody, according to Kabat numbering, and/or
25 residues 39, 89, 105, and 108 of the heavy chain of the meditope-enabled antibody, according to Kabat numbering.

[0457] In some embodiments, the meditope binding site is located within a cavity formed by residues 8, 9, 10, 38, 39, 40, 41 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102,
103, 104, 105, 142, 162, 163, 164, 165, 166, 167, 168, and 173 of the light chain and 6, 9, 38,
30 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 111, 110,

147, 150, 151, 152, 173, 174, 175, 176, 177, 185, 186, and 187 of the heavy chain of the antibody, according to Kabat numbering.

[0458] With respect to a Fab portion of a mediotope-enabled antibody, the mediotope binding site includes residues within the central cavity. The mediotope-binding site typically
5 further includes constant region residues.

[0459] A “therapeutic agent,” as used herein, is an atom, molecule, or compound that is useful in treatment of a disease or condition.

[0460] A “therapeutically effective amount,” “therapeutically effective concentration” or “therapeutically effective dose” is the amount of a compound that produces a desired
10 therapeutic effect in a subject, such as preventing or treating a target condition, alleviating symptoms associated with the condition, producing a desired physiological effect, or allowing imaging or diagnosis of a condition that leads to treatment of the disease or condition. The precise therapeutically effective amount is the amount of the composition that
15 amount will vary depending upon a variety of factors, including, but not limited to, the characteristics of the therapeutic compound (including activity, pharmacokinetics, pharmacodynamics, and bioavailability), the physiological condition of the subject (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), the nature of the pharmaceutically acceptable carrier or carriers in
20 the formulation, and the route of administration. One skilled in the clinical and pharmacological arts will be able to determine a therapeutically effective amount through routine experimentation, namely by monitoring a subject's response to administration of a compound and adjusting the dosage accordingly. For instance, in some embodiment, the therapeutically effective amount of an antibody is from about 1 to about 1000 mg/m², or
25 alternatively from 1 to about 1000 mg/m², from 1 to about 1000 mg/m², from 1 to about 1000 mg/m², from 10 to about 900 mg/m², from 20 to about 800 mg/m², from 30 to about 700 mg/m², from 40 to about 600 mg/m², from 50 to about 500 mg/m², from 100 to about 400 mg/m², from 1 to about 500 mg/m², from 10 to about 400 mg/m², from 50 to about 300 mg/m², from 100 to about 1000 mg/m², from 150 to about 900 mg/m², from 200 to about 800
30 mg/m², from 250 to about 700 mg/m². For additional guidance, see Remington: The Science and Practice of Pharmacy 21st Edition, Univ. of Sciences in Philadelphia (USIP), Lippincott Williams & Wilkins, Philadelphia, PA, 2005.

[0461] A “pharmaceutically acceptable carrier” refers to a pharmaceutically acceptable material, composition, or vehicle that is involved in carrying or transporting a compound of interest from one tissue, organ, or portion of the body to another tissue, organ, or portion of the body. For example, the carrier may be a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, or some combination thereof. Each component of the carrier must be “pharmaceutically acceptable” in that it must be compatible with the other ingredients of the formulation. It also must be suitable for contact with any tissue, organ, or portion of the body that it may encounter, meaning that it must not carry a risk of toxicity, irritation, allergic response, immunogenicity, or any other complication that outweighs its therapeutic benefits.

[0462] A “route of administration” may refer to any administration pathway known in the art, including but not limited to aerosol, enteral, nasal, ophthalmic, oral, parenteral, rectal, transdermal, or vaginal. “Transdermal” administration may be accomplished using a topical cream or ointment or by means of a transdermal patch. “Parenteral” refers to a route of administration that is generally associated with injection, including infraorbital, infusion, intraarterial, intracapsular, intracardiac, intradermal, intramuscular, intraperitoneal, intrapulmonary, intraspinal, intrasternal, intrathecal, intrauterine, intravenous, subarachnoid, subcapsular, subcutaneous, transmucosal, or transtracheal.

[0463] “In combination” or “in combination with,” when used herein in the context of multiple agents, therapeutics, or treatments, means in the course of treating the same disease or condition in a subject administering two or more agents, drugs, treatment regimens, treatment modalities or a combination thereof (e.g., an antibody in combination with a meditope or a meditope), in any order. This includes simultaneous administration (or “coadministration”), administration of a first agent prior to or after administration of a second agent, as well as in a temporally spaced order of up to several days apart. Such combination treatment may also include more than a single administration of any one or more of the agents, drugs, treatment regimens or treatment modalities. Further, the administration of the two or more agents, drugs, treatment regimens, treatment modalities or a combination thereof may be by the same or different routes of administration.

[0464] A “therapeutic antibody” may refer to any antibody or functional fragment thereof that is used to treat cancer, autoimmune diseases, transplant rejection, cardiovascular disease or other diseases or conditions such as those described herein. Examples of therapeutic antibodies that may be used according to the embodiments described herein include, but are

not limited to murine antibodies, murinized or humanized chimera antibodies or human antibodies including, but not limited to, Erbitux (cetuximab), ReoPro (abciximab), Simulect (basiliximab), Remicade (infliximab); Orthoclone OKT3 (muromonab-CD3); Rituxan (rituximab), Bexxar (tositumomab) Humira (adalimumab), Campath (alemtuzumab),
 5 Simulect (basiliximab), Avastin (bevacizumab), Cimzia (certolizumab pegol), Zenapax (daclizumab), Soliris (eculizumab), Raptiva (efalizumab), Mylotarg (gemtuzumab), lintuzumab, Zevalin (ibritumomab tiuxetan), Tysabri (natalizumab), Xolair (omalizumab), Synagis (palivizumab), Vectibix (panitumumab), Lucentis (ranibizumab), and Herceptin (trastuzumab).

10 **[0465]** “Treating” or “treatment” of a condition may refer to preventing the condition, slowing the onset or rate of development of the condition, reducing the risk of developing the condition, preventing or delaying the development of symptoms associated with the condition, reducing or ending symptoms associated with the condition, generating a complete or partial regression of the condition, or some combination thereof.

15 **[0466]** As used herein, the terms “including,” “containing,” and “comprising” are used in their open, non-limiting sense.

[0467] As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

[0468] To provide a more concise description, some of the quantitative expressions given
 20 herein are not qualified with the term “about”. It is understood that, whether the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value.

25 **[0469]** As used herein, “alkyl” refers to a saturated, straight- or branched-chain hydrocarbon group having from 1 to 12 carbon atoms. Representative alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-
 30 pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, and the like, and longer alkyl

groups, such as heptyl, octyl, and the like. The term “C_{x-y}alkyl,” where x and y are integers, refers to an alkyl with x-y carbon atoms.

[0470] As used herein, an “alkenyl” refers to a straight- or branched-chain hydrocarbon group having one or more double bonds therein and having from 2 to 12 carbon atoms.

5 Illustrative alkenyl groups include, but are not limited to, ethylenyl, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, and the like. The term “C_{x-y}alkenyl,” where x and y are integers, refers to an alkenyl with x-y carbon atoms.

[0471] The term “alkylenyl” or “alkylene” refers to a divalent alkyl group. The term
10 “alkenylene” or “alkenylene” refers to a divalent alkenyl group.

[0472] As used herein, “alkynyl” refers to a straight- or branched-chain hydrocarbon group having one or more triple bonds therein and having from 2 to 10 carbon atoms.

Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, 4-butyl-2-
15 hexynyl, and the like.

[0473] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be
20 oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited

to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-
25 CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -C
H=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃.

[0474] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified,
30 but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g.,

alkyleneoxy, alkylendioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'$ represents both $-C(O)_2R'$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-C(O)R'$, $-C(O)NR'$, $-NR'R''$, $-OR'$, $-SR'$, and/or $-SO_2R'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-NR'R''$ or the like, it will be understood that the terms heteroalkyl and $-NR'R''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-NR'R''$ or the like.

[0475] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl,” respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0476] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one

ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. A 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene” and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. Non-limiting examples of heteroaryl groups include pyridinyl, pyrimidinyl, thiophenyl, furanyl, indolyl, benzoxadiazolyl, benzodioxolyl, benzodioxanyl, thianaphthanyl, pyrrolopyridinyl, indazolyl, quinoliny, quinoxaliny, pyridopyrazinyl, quinazolinonyl, benzoisoxazolyl, imidazopyridinyl, benzofuranyl, benzothiophenyl, phenyl, naphthyl, biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, furylthienyl, pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, isoquinolyl, thiadiazolyl, oxadiazolyl, pyrrolyl, diazolyl, triazolyl, tetrazolyl, benzothiadiazolyl, isothiazolyl, pyrazolopyrimidinyl, pyrrolopyrimidinyl, benzotriazolyl, benzoxazolyl, or quinolyl. The examples above may be substituted or unsubstituted and divalent radicals of each heteroaryl example above are non-limiting examples of heteroarylene.

[0477] The term “boronic ester” refers to a substituent $-B(OR)_2$, wherein each R group is independently a C_{1-4} alkyl, or the two R groups taken together form a C_{2-6} alkylene.

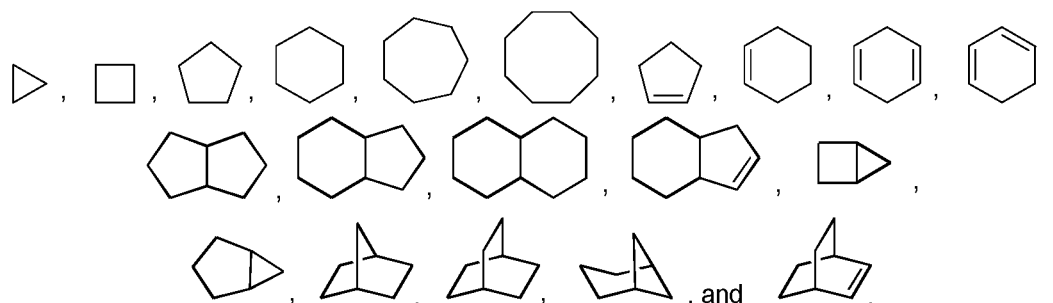
[0478] The term “acetal” refers to a $-CH(OR)_2$ group, wherein each R group is independently a C_{1-4} alkyl, or the two R groups taken together form a C_{2-6} alkylene.

Exemplary acetal groups include dimethylacetal or diethylacetal, or a cyclic acetal. The term “ketal” refers to a $-C(OR)_2-$ group, wherein each R group is independently a C_{1-4} alkyl, or the

two R groups taken together form a C₂₋₆alkylene. Exemplary ketals include dimethylketal or diethylketal, or a cyclic ketal.

[0479] The term “halo” represents chloro, fluoro, bromo, or iodo. In some embodiments, halo is chloro, fluoro, or bromo. The term “halogen” as used herein refers to fluorine, chlorine, bromine, or iodine. The term “ortho ester” refers to a –C(OR)₃ group, wherein each R group is independently a C₁₋₄alkyl, or two of the R groups taken together form a C₂₋₆alkylene. The term “oxo” means an =O group and may be attached to a carbon atom or a sulfur atom. The term “phosphonate ester” refers to a –P(O)(OR)₂ group, wherein each R group is independently a C₁₋₄alkyl, or the two R groups taken together form a C₂₋₆alkylene.

[0480] As used herein, the term “cycloalkyl” refers to a saturated or partially saturated, monocyclic, fused polycyclic, bridged polycyclic, or spiro polycyclic carbocycle having from 3 to 15 ring carbon atoms. A non-limiting category of cycloalkyl groups are saturated or partially saturated, monocyclic carbocycles having from 3 to 6 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



[0481] As used herein, the term “5-membered heteroaryl” refers to a monocyclic, aromatic heterocycle having five ring atoms that are selected from carbon, oxygen, nitrogen, and sulfur. Examples of 5-membered heteroaryl groups include, but are not limited to, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, and thiadiazolyl. Particular examples of 5-membered heteraryls include those that may be formed by 1,3-cycloaddition reactions such as a Huisgen reaction between an azide and a propargyl group.

[0482] As used herein, the term “substituted” means that the specified group or moiety bears one or more suitable substituents. As used herein, the term “unsubstituted” means that

the specified group bears no substituents. As used herein, the term “optionally substituted” means that the specified group is unsubstituted or substituted by the specified number of substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. As used herein, the expression “one or more substituents” denotes one to maximum possible number of substitution(s) that can occur at any valency-allowed position on the system. In a certain embodiment, “one or more substituents” means 1, 2, 3, 4, or 5 substituents. In another embodiment, one or more substituent means 1, 2, or 3 substituents.

[0483] A “substituent group” or “substituent” as used herein, means a group selected from the following moieties:

- (A) oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
- (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:
 - i. oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
 - ii. alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:
 1. oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl,

unsubstituted heterocycloalkyl, unsubstituted aryl,
unsubstituted heteroaryl, and

2. alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0484] A “size-limited substituent” or “size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0485] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted

heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0486] In other embodiments herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₂₀ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₈ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0487] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₈ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₇ cycloalkylene, each

substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene.

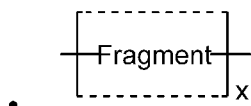
5 **[0488]** Any atom that is represented herein with an unsatisfied valence is assumed to have the sufficient number of hydrogen atoms to satisfy the atom's valence. When any variable, such as alkyl, R³, or R⁵, appears in more than one place in any formula or description provided herein, the definition of that variable on each occurrence is independent of its definition at every other occurrence. Numerical ranges, as used herein, are intended to
10 include sequential whole numbers. For example, a range expressed as "from 0 to 4" or "0-4" includes 0, 1, 2, 3 and 4. When a multifunctional moiety is shown, the point of attachment to the core is indicated by a line or hyphen. For example, -OH refers to a moiety in which an oxygen atom is the point of attachment of the hydroxyl group to the remainder of the molecule.

15 **[0489]** Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. E.g., compounds of any formula herein may have asymmetric or chiral centers and therefore exist in different stereoisomeric forms. All stereoisomers, including optical isomers, enantiomers, and diastereomers, of the compounds of the general formula, and mixtures thereof, are considered
20 to fall within the scope of the formula. Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. All such isomeric forms, and mixtures thereof, are contemplated herein as part of the present invention. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more tautomeric or
25 atropisomeric forms, and mixtures thereof.

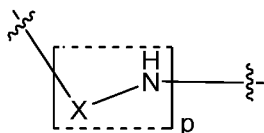
[0490] Diastereomeric mixtures may be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers may be separated by converting the enantiomeric mixture into a diastereomeric mixture by
30 reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride, or formation of a mixture of diastereomeric salts), separating the diastereomers and converting (e.g., hydrolyzing or de-salting) the individual

diastereomers to the corresponding pure enantiomers. Enantiomers may also be separated by use of chiral HPLC column. The chiral centers of compounds of the present invention may be designated as “R” or “S” as defined by the IUPAC 1974 Recommendations, or by “D” or “L” designations consistent with the peptide literature.

- 5 [0491] As used herein, a box around a portion of a structure, drawn with a subscript, indicates that the structural fragment that appears within the box is repeated according to the subscript. For example, the substructure:



- 10 where x is 0, 1, or 2, indicates the fragment is absent from the structure, or is –Fragment–, or is –Fragment-Fragment–. For example, within Formula VII, the following substructure:



where p is 0 or 1, means that the –X-NH– group within the box is absent from the structure (p is 0), or is present once (p is 1).

- 15 [0492] The compounds of the invention can form pharmaceutically acceptable salts, which are also within the scope of this invention. A “pharmaceutically acceptable salt” refers to a salt of a free acid or base of a compound described herein that is non-toxic, is physiologically tolerable, is compatible with the pharmaceutical composition in which it is formulated, and is otherwise suitable for formulation and/or administration to a subject. Reference to a compound herein is understood to include reference to a pharmaceutically
20 acceptable salt of said compound unless otherwise indicated.

- [0493] Compound salts include acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, where a given compound contains both a basic moiety, such as, but not limited to, a pyridine or imidazole, and an acidic moiety, such as, but not limited to, a carboxylic acid, one of skill in the art will
25 recognize that the compound may exist as a zwitterion (“inner salt”); such salts are included within the term “salt” as used herein. Salts of the compounds of the invention may be

prepared, for example, by reacting a compound with an amount of a suitable acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0494] Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate (“mesylate”), ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counterions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

[0495] Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like.

[0496] Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, *t*-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

[0497] Acids and bases generally considered suitable for the formation of pharmaceutically useful salts from pharmaceutical compounds are discussed, e.g., by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, MD, available from FDA). These disclosures are incorporated herein by reference thereto.

[0498] Any compound described herein is intended to refer also to any unsolvated form, or a hydrate, solvate, or polymorph of such a compound, and mixtures thereof, even if such forms are not listed explicitly. "Solvate" means a physical association of a compound of the invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Suitable solvates include those formed with pharmaceutically acceptable solvents such as water, ethanol, and the like. In some embodiments, the solvent is water and the solvates are hydrates.

[0499] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (for example with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly suitable for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced

dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

5 VII. EXAMPLES

[0500] The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1 Meditope Fc Binding

[0501] A mediotope-Fc construct was generated by fusing a mediotope to the N-terminus of
 10 an Fc domain via a poly-glycine-serine linker. The gene for this mediotope-Fc construct was constructed by DNA2.0 (cQFD mediotope connected to human IgG gamma heavy chain 3 (accession# AAW65947) residues 22-241 via a 37-residue linker, cloned into pAcGP67A vector (BD Biosciences) and produced in Sf9 cells. The protein was purified using Protein A and size exclusion chromatography. The mediotope-Fc included a polypeptide having an
 15 amino acid sequence as set forth in SEQ ID NO: 57 (shown below with a leader ("G") in position 1, mediotope bolded, linker italicized, Fc portion in plain text):

[0502] **GCQFDLSTRRLRCGGSRS***GGTSGGGSVPGSGSSGSTSGSGKSSEGS***QASTH**
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
 20 **KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT**
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFC**SVMHEALHNHYTQKSLSLSPGK** (SEQ ID NO: 57).

[0503] Using this construct, it was demonstrated by size exclusion chromatography (SEC) that cetuximab Fab, EGFRdIII and mediotope form a complex. The mediotope-Fc
 25 construct was added to a stoichiometric complex of EGFRdIII and cetuximab Fab and observed a new peak, which eluted much earlier than the Fab-EGFRdIII complex, consistent with an increase in the hydrodynamic mass. SDS-PAGE of this new peak showed the presence of all three proteins. These studies further confirmed that the mediotope did not significantly interfere with antigen recognition.

Example 2 Generation of a Meditope-Enabled Trastuzumab

[0504] A meditope binding site was grafted onto a human mAb framework to generate a meditope-enabled antibody (meditope enabled antibody), specifically, a meditope enabled antibody trastuzumab. The sequences of cetuximab and trastuzumab were aligned and sequence identity mapped onto the atomic model of trastuzumab (1N8Z, see Cho et al., Nature 421, 756-760(2003)). Based on this mapping and the superposition of cQFD-cetuximab and trastuzumab structures, thirteen (13) residues were identified that differ between cetuximab and trastuzumab and whose side chains either make direct contact with the meditope or may indirectly affect meditope binding. These residues were: Thr40, Asn41, Asp85 in the light chain (see above), Arg39, and Arg45 in the light chain, which coordinate a non-bonded phosphate group and in some examples stabilize the loop containing Thr40 and Asn41 in the light chain, Val9 and Ile10 which participate in forming a shallow hydrophobic surface near the side chain of Leu10 in the meditope, and Gly42, Ser43, Ile83 and Ala100 of the light chain, as well as Ser40 and Ile89 in the heavy chain. The light chain sequence of this meditope enabled antibody is set forth in SEQ ID NO: 303 and the heavy chain is shown in SEQ ID NO: 304 (without the meditope peptide sequence and the linker sequence).

[0505] Equivalent positions in the trastuzumab sequence were mutated (to Thr40, Asn41, Asp85, Arg39, Arg45, Ile9, Leu10, Gly42, Ser43, Ile83 and Ala100 in the light chain and Ser40 and Ile89 in the heavy chain, based on Kabat numbering), and the protein produced and purified. Using SPR, it was shown that the cQFD meditope bound to the grafted trastuzumab Fab with similar affinity as cetuximab ($K_D = 1.2 \mu\text{M}$). It was also observed that the meditope-enabled trastuzumab Fab bound to soluble HER2 with similar affinity as the Fab isolated from the commercial source, confirming that the mutations had no deleterious effect on antigen binding. It was demonstrated by size exclusion chromatography that the meditope-enabled trastuzumab, sHER2, and meditope-Fc co-eluted.

[0506] To further confirm that the point mutations did not significantly perturb the overall structure of the Fab, the Fab of the trastuzumab meditope enabled antibody was crystallized with and without the cQFD meditope. Well diffracting crystals were obtained in the presence of Protein A and Protein L to aid crystallization. The structures of the apo-meditope enabled antibody trastuzumab and the meditope-containing complex were solved at 1.95 and 2.0 Å, respectively. The parental trastuzumab Fab bound to Protein A and Protein L was also crystallized and solved to 2.08 Å resolution. Superposition of either the apo-parental

trastuzumab Fab or HER2-bound parental trastuzumab Fab (22) onto “apo”-meditope enabled antibody trastuzumab revealed only minor changes in the overall structure (RMSD = 0.22 Å and 0.56 Å over 433 and 431 Cα atoms, respectively). Superposition of the “apo”- and meditope-liganded meditope enabled antibody trastuzumab showed that meditope occupancy stabilized the heavy chain loop (residues 39-44) in an open conformation, similar to what was observed for cetuximab, and accounted in part for the slightly higher RMSD. More importantly, residues (Thr40, Asn41 and Asp85) identified by the sequence mapping in the “apo”- and meditope-liganded meditope enabled antibody were essentially in the same positions as their counterparts in cetuximab, and formed similar interactions with the meditope. Important side chain rotamers of the meditope were also essentially the same as they were in the cQFD-cetuximab structure. As with cetuximab, significant alterations in the CDR loops were not observed.

[0507] These data demonstrate successful grafting of a meditope binding site onto a human Fab framework without significantly affecting antigen binding. The successful grafting of the meditope site further validates the initial cetuximab-meditope model obtained through diffraction data and the specificity of the interaction. The data further confirm the feasibility of enhancing meditope binding affinity through avidity, and show that a bivalent meditope is specific and binds with high affinity, but only in the presence of the cognate meditope enabled antibody, to cells overexpressing the antigen.

Example 3 Increasing antibody internalization using meditope fusion antibody crosslinking

[0508] SnAP-bodies (meditope enabled antibodies including a meditope fused to the N-terminus of the heavy chain via a linker) were assessed for their ability to be internalized by cells expressing a target antigen.

A. Antibody Production

[0509] Three different antibodies were produced in a mammalian expression system. Each antibody included a meditope-enabled gemtuzumab light chain including the amino acid sequence of SEQ ID NO: 254. SnAP-body variant 1 had a heavy chain including a meditope-enabled gemtuzumab IgG1 heavy chain sequence fused to a meditope via a linker (SEQ ID NO: 255). SnAP-body variant 2 had a heavy chain including a meditope-enabled gemtuzumab IgG1 heavy chain sequence fused to a meditope via a linker (SEQ ID NO: 256).

The control antibody had a mediotope-enabled gemtuzumab IgG1 heavy chain amino acid sequence (SEQ ID NO: 257), but without a mediotope or a linker fused to its N-terminus.

[0510] Nucleic acids encoding SEQ ID NOS: 254-257 were cloned into CMV-based pCEP4 expression vectors containing an EBV origin of replication (Invitrogen). The

5 expression vectors were transfected into a human embryonic kidney 293 cell line (HEK-293) comprising the Epstein-Barr virus (EBV) at 1 µg endotoxin-free DNA/10⁶ cells using a polyethylenimines transfection reagent (FuGENE® HD, Promega). The cells were cultured for six to seven days in FREESTYLE™ 293 expression media (Invitrogen, Carlsbad, CA) supplemented with 25 µg/ml Hygromycin B (Thermo Fischer Scientific) and 0.1 %
10 Pluronic® F68 (Thermo Fischer Scientific). The cell culture supernatant was then sterilized using a 0.22 µm filter and stored at 4 °C until purification.

[0511] Antibodies were purified with a protein A column followed by a size exclusion chromatography (SEC) column, yielding 95% purity and endotoxin levels ≤ 1EU/mg. The antibodies were formulated in a sterile buffer containing 20mM histidine and 5% sucrose
15 at a final concentration of 5 mg/ml. Concentration was determined by spectrophotometry (Nanodrop 2000c; Thermo Fisher). Production of intact antibody was confirmed by visualization on a standard protein gel.

B. Antibody Labeling

[0512] SnAP-body variant 1, SnAP-body variant 2, and the control antibody were labeled
20 with pHrodo™ Red SE (Thermo Fisher Scientific, Waltham, MA) according to manufacturer's instructions. The pHrodo™ dye is pH sensitive; its fluorescence increases as pH decreases. Thus, quantifying the fluorescence of pHrodo™-labeled antibodies indicates the rates of antibody endocytosis. Briefly, pHrodo™ was prepared in dry dimethyl sulfoxide (DMSO) (Invitrogen) to achieve a final concentration of 2-5 µM of dye. 2mg of antibody
25 was dissolved in 2mL of phosphate buffered saline (PBS) at pH 9. pHrodo™ dye was then added slowly in four 50ul increments to the antibody solution and incubated with each addition for 15 minutes with rocking at room temperature.

C. Fluorescence Microscopy

[0513] HL-60 cells expressing CD33 were incubated on ice prior to the addition of
30 antibody. Cells were stained for fluorescence microscopy with pHrodo™-labeled SnAP-body variant 1, SnAP-body variant 2, or control antibody to determine receptor-mediated

antibody endocytosis rates. Labeled cells were incubated for 15 minutes in a 37 °C water bath. Cells were washed with ice-cold buffer (PBS supplemented with 1% BSA), resuspended in 100µl buffer, and fixed by adding 100µl of 4% paraformaldehyde. Cells were then added to Nunc® Lab-Tek® II chambered slide systems with 8 wells per slide (0.7
5 cm²/well) for imaging. Slides were subsequently mounted in Fluoromount G (Southern Biotechnology, Birmingham, AL).

[0514] Cells were imaged with a confocal microscope using appropriate wavelength settings for pHrodo™-labeled antibodies, as shown in Fig. 7A. Z sectioning permitted visualization of the internalized materials and all quantitative measurements were taken at the
10 same defined section height. More than 30 cells were visualized and quantified at each time point with three focal fields for each visualization event. Fluorescence for each imaged cell was calculated using ImageJ, averaged for each condition, and normalized to the control. Total staining for SnAP-body variant 1 was more than 2.5 times greater than the control. Total staining for SnAP-body variant 2 was more than 2.0 times greater than the control, as
15 shown in Figure 7B. The results indicate that HL-60 cells internalize self-crosslinking SnAP-bodies at more than twice the rate of the non-crosslinking control antibody.

Example 4 Increasing antibody internalization using mediotope fusion antibody crosslinking

[0515] HL-60 cells expressing CD33 were incubated on ice prior to the addition of antibody. Cells were stained for flow cytometric analysis with pHrodo™-labeled SnAP-body
20 variant 1, SnAP-body variant 2, or control antibody, as described in Example 1, to determine receptor-mediated antibody endocytosis rates. Labeled cells were incubated for 15 minutes in a 37 °C water bath. Cells were washed with ice-cold buffer (PBS supplemented with 1% BSA), resuspended in 100µl buffer.

[0516] Cells were analyzed using a CytoFLEX flow cytometer (Becton Dickinson) and
25 analyzed in a histogram using FloJo, version 9. The data for the self-crosslinking antibodies (SnAP-body variants 1 and 2) show additional peaks with increased intensity as compared to the control, indicating that the HL-60 cells internalize the self-crosslinking antibodies at an increased rate as compared to the control (Fig. 8).

Example 5 Increasing antibody crosslinking using meditope-antibody fusions

[0517] Four different antibodies were produced in a mammalian expression system. Each antibody included a meditope-enabled gemtuzumab light chain including the amino acid sequence of SEQ ID NO: 254. SnAP-body variant 1 and 2 were produced as described in Example 1. SnAP-body variant 3 had a heavy chain including a meditope-enabled gemtuzumab IgG1 heavy chain sequence fused to a meditope via a linker (SEQ ID NO: 279). The control antibody had a meditope-enabled gemtuzumab IgG1 heavy chain amino acid sequence (SEQ ID NO: 257), but without a meditope or a linker fused to its N-terminus. Sequences were clones into expression vectors and expressed as described in Example 1.

[0518] Antibodies were then purified and analyzed by size-exclusion chromatography using SRT-10C SEC columns from Sepax technologies. The columns contained 5-10 μ m silica particles coated with hydrophilic and neutral nanometer-thick films. The particles also contained 100 $\text{\AA}$ pores. Columns were first equilibrated with histidine-sucrose buffer (histidine 20 mM pH6, sucrose 5%). The sample was loaded and eluted at 1 ml/min in the same buffer. The chromatogram was recorded with an UV detector set at 280 nM.

[0519] The data show that the gemtuzumab control antibody eluted as a single monomeric peak (Fig. 9A), whereas the self-crosslinking SnAP-body variants 1, 2, and 3 were able to form dimers and multimers, as evidenced by the smaller early peaks (Figs. 9B-9D, respectively).

Example 6 Antibody self-crosslinking can be concentration dependent

[0520] SnAP-body variant 1, SnAP-body variant 2, and the control gemtuzumab antibody from Example 1 were each prepared as 1nM and 100nM samples in a phosphate buffered saline solution. The PBS contained 137 nM of NaCl, 2.7 mM of KCl, 10 mM of Na₂HPO₄, and 1.8 mM of KH₂PO₄. Each sample was then mixed with an equal volume of 2X sample buffer made of 62.5 mM Tris-HCl, pH 6.8, 25% glycerol, and 1% Bromophenol Blue. The samples were then loaded into a polyacrylamide gel (3–12% polyacrylamide gradient NativePAGE® Bis-Tris Gels (Thermo Fisher)) in a gel electrophoresis chamber containing running buffer (50 mM BisTris, 50 mM Tricine, pH 6.8). The gels were run at a constant 150 V for 90-115 minutes. Gels were then stained with a Pierce silver staining kit from Thermo Scientific (cat # 24612) according to the manufacturer's instructions.

[0521] The results showed that self-crosslinking antibodies formed multimers, including dimers, trimers, and tetramers, in a concentration-dependent manner (Fig. 10). The control gemtuzumab antibody only formed monomers, and did not self-crosslink.

Example 7 Antibody self-crosslinking can be modulated by free-meditope peptide

5 [0522] SnAP-body variant 1, SnAP-body variant 2, SnAP-body variant 3, and the control gemtuzumab antibody from Examples 1 and 3 were each prepared in duplicate as 100nM samples in a phosphate buffered saline solution. Free mediotope (cQFD, SEQ ID NO: 1) was then added to one of the samples at a final concentration of 1 μ M and incubated for 30 minutes. Each sample was then mixed with an equal volume of 2X sample buffer made of
10 62.5 mM Tris-HCl, pH 6.8, 25% glycerol, and 1% Bromophenol Blue. The samples were then loaded into a polyacrylamide gel (3–12% polyacrylamide gradient NativePAGE® Bis-Tris Gels (Thermo Fisher)) in a gel electrophoresis chamber containing running buffer (50 mM BisTris, 50 mM Tricine, pH 6.8). The gels were run at a constant 150 V for 90–115 minutes. Gels were then stained with a Pierce silver staining kit from Thermo Scientific (cat
15 # 24612) according to the manufacturer's instructions.

[0523] The results show that free mediotope can interfere with the self-crosslinking ability of self-crosslinking antibodies. SnAP-body variants 1, 2, and 3 each exhibited the ability to form dimers, trimers, and tetramers in the absence of free mediotope (Fig. 11). However, there were little to no detectable multimers when an excess of free mediotope was added.

20 Example 8 Efficacy of SnAP-Bodies in an Ovarian Xenograft Model in Nude Mice

[0524] This study was performed to evaluate the efficacy of ADC constructs against HER2 expressing SK-OV-3-Luc ovarian xenograft subcutaneous model using both bioluminescent imaging and traditional tumor caliper measurement. Sixty-five female athymic nudes, 4 weeks old of age were obtained from Charles River. SK-OV-3-Luc cells
25 were expanded using standard tissue culture technique. On the day of implantation, 2.5×10^6 cells in incomplete media with 30% matrigel were implanted to the right lower flank of each mouse. Animals were stratified into 7 groups of 8 mice for treatment based on the total flux (Perkin Elmer IVIS Lumina XRMS II) at day 10 pi. Animals were weighed twice weekly in conjunction with tumor measurements. Bioluminescent Imaging were performed once a
30 week. Tumor mass were calculated using the following formula:

Mass (mg) = Tumor volume (mm³)=d²xD/2, where d and D are the shortest and longest diameter in mm, respectively.

[0525] Animals were treated according to the following table (BIW: twice a week; QW: once a week, DM1: Mertansine, MMAD: Monomethyl auristatin D, ADC: antibody-drug conjugate):

Group	Agent	Dose (mg/kg)	NO. of Mice	Schedule	Route
1: Vehicle	Saline	n/a	8	BIW x 8w	<i>ip</i>
2: mAb alone	Trastuzumab (Trast)	9	8	BIW x 6w	<i>ip</i>
3: Trast-DM1	Kadcyla	3	8	BIW x 8w	<i>ip</i>
4: MBI Trast-DM1	MBI HER2 ADC (DM1)	3	8	BIW x 8w	<i>ip</i>
5: MBI Snap mAb	MBI HER2 Snapbody (no toxin)	3	8	BIW x 8w	<i>ip</i>
6: MBI Trast-MMAD	MBI HER2 ADC (MMAD)	5	8	BIW x 6w	<i>ip</i>
7: chemotherapeutic	Paclitaxel	20	8	BIW x 3w	<i>ip</i>

[0526] Sequences of the MBI Her2 Snapbody are provided is SEQ ID NOS: 303 and 304.

The light chain and heavy chain of MBI Her2 antibody are the same as the Snapbody but but the Her2 antibody does not include the mediotope and the linker sequences (see description in

Example 2 as well). Results were demonstrated in FIG. 12. Tumors were detectable by bioluminescence at day 10 pi. Tumor volume of the vehicle group kept increasing till the end of the study. When compared to the vehicle group on day 66 pi, HER2 expressing tumors in Group 2 (G2, treated with Trastuzumab at 9 mg/kg) showed complete regression. Kadcyla (trastuzumab conjugated to maytansinoid toxin) showed efficacy at 3 mg/kg. All ADC and Snap-body treatment groups showed tumor growth reduction or repression. Tumor responded to Paclitaxel (20 mg/kg) earlier, but showed minimal (2.80 % TGI, day 52 pi) inhibition overall. Most animals showed no adverse effect to each treatment throughout the study and body weight of all groups kept increasing till the end of the study (FIG. 13).

[0527] The study demonstrates the efficacy of ADC constructs against HER2 expressing ovarian xenograft subcutaneous model. The individual antibodies and ADC showed expected efficacy. All MBI ADC and Snap-body treatment groups showed tumor growth reduction or repression. Kadcyla (traditional ADC conjugation) and MBI DM1 conjugated ADC showed comparable results as well, demonstrating that the SnAP-body technology retains the activity of the antibodies.

[0528] The present invention is not intended to be limited in scope to the particular disclosed embodiments, which are provided, for example, to illustrate various aspects of the invention. Various modifications to the compositions and methods described will become apparent from the description and teachings herein. Such variations may be practiced without
5 departing from the true scope and spirit of the disclosure and are intended to fall within the scope of the present disclosure.

CLAIMS

1. A recombinant meditope enabled antibody or antigen binding fragment thereof, comprising:

a heavy chain comprising a heavy chain variable (VH) region, a heavy chain constant region (CH) or portion thereof, and a light chain comprising a light chain variable (VL) region, wherein each chain comprises an amino terminus;

a meditope binding site;

a linker comprising a carboxy terminus, a rigid, alpha helical segment, a first flexible, unstructured segment, and an amino terminus, wherein the carboxy terminus of the linker is coupled to the amino terminus of the heavy chain or the light chain; and

a cyclic peptide, wherein the cyclic peptide is coupled to the amino terminus of the linker, and wherein the cyclic peptide does not bind to the meditope binding site.

2. The recombinant meditope enabled antibody or antigen binding fragment thereof of claim 1, wherein the carboxy terminus of the linker and the cyclic peptide are separated by a distance of between 10-120 angstroms, including about 10-100 angstroms and 10-80 angstroms.

3. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-2, wherein the rigid, alpha helical segment of the linker comprises the carboxy terminus of the linker.

4. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-3, wherein the first flexible, unstructured segment of the linker comprises the amino terminus of the linker.

5. The recombinant meditope enabled antibody of any one of claims 1-3, wherein the amino terminus of the light chain or heavy chain is coupled to a carboxy terminus of the rigid, alpha helical segment of the linker;

a carboxy terminus of the first flexible, unstructured segment of the linker is coupled to an amino terminus of the rigid, alpha helical segment of the linker;

and the cyclic peptide is coupled to an amino terminus of the first flexible, unstructured segment of the linker.

6. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-5, wherein the linker further comprises a second flexible, unstructured segment.

5

7. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 6, wherein the second flexible, unstructured segment of the linker comprises the carboxy terminus of the linker.

10

8. The recombinant meditope enabled antibody of claim 6 or 7, wherein the amino terminus of the light chain or heavy chain is coupled to a carboxy terminus of the second flexible, unstructured segment of the linker;

a carboxy terminus of the rigid, alpha helical segment of the linker is coupled to an amino terminus of the second flexible, unstructured segment of the linker;

15

a carboxy terminus of the first flexible, unstructured segment of the linker is coupled to an amino terminus of the rigid, alpha helical segment of the linker; and the cyclic peptide is coupled to an amino terminus of the linker.

20

9. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-8, wherein the rigid alpha helical segment comprises a sequence selected from the group consisting of SEQ ID NOS: 266-274.

25

10. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-9, wherein the first flexible, unstructured segment of the linker comprises SEQ ID NO: 265.

30

11. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 6-10, wherein the second flexible, unstructured segment of the linker comprises SEQ ID NO: 265.

12. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-11, wherein the cyclic peptide is capable of binding to a meditope binding site of a second meditope enabled antibody.

13. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-12, wherein the cyclic peptide comprises a meditope.

14. The meditope of claim 13, comprising a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

15. The meditope of claim 1, comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, and 207, or a cyclic peptide derived therefrom.

16. The recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-15, wherein:

the heavy chain variable (VH) region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 260-261;

the light chain variable (VL) region comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 258-259;

5 the rigid, alpha helical segment comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 266-274;

the first flexible, unstructured segment comprises an amino acid sequence of SEQ ID NO: 265; and

the cyclic peptide comprises an amino acid sequence selected from the group
10 consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom.

17. A recombinant mediotope enabled antibody or antigen binding fragment thereof
15 comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 255, 256, 277, 278, 279, 280, or 282.

18. The recombinant mediotope enabled antibody or antigen binding fragment of
20 any one of claims 1-17, wherein the mediotope enabled antibody or antigen binding fragment specifically binds to a cell surface antigen.

19. The recombinant mediotope enabled antibody or antigen binding fragment of
any one of claims 1-18, wherein the mediotope enabled antibody or antigen binding fragment specifically binds to an antigen expressed by a disease or condition of a cell or tissue thereof.

25

20. The recombinant mediotope enabled antibody or antigen binding fragment
claim 19, wherein the disease or condition is a cancer.

21. The mediotope enabled antibody or antigen binding fragment of any one of
30 claims 1-20, wherein the mediotope enabled antibody or antigen binding fragment competes for antigen binding with, or binds to the same epitope as an antibody or antigen-binding fragment thereof selected from the group consisting of abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab,

benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, fontolizumab, gemtuzumab, lintuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab, anrukinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab, mavrili-
 mumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, and urelumab; or

the meditope-enabled antibody or fragment specifically binds to an antigen selected from the group consisting of: CA-125, glycoprotein (GP) IIb/IIIa receptor, TNF-alpha, CD52, TAG-72, Carcinoembryonic antigen (CEA), interleukin-6 receptor (IL-6R), IL-2, interleukin-2 receptor a-chain (CD25), CD22, B-cell activating factor, interleukin-5 receptor (CD125), VEGF, VEGF-A, CD30, IL-1beta, prostate specific membrane antigen (PSMA), CD3, EpCAM, EGF receptor (EGFR), MUC1, human interleukin-2 receptor, Tac, RANK ligand, C5 or other complement proteins, CD11a, alpha-v beta-3 integrin, HER2, neu, CD15, CD20, Interferon gamma, CD33, CA-IX, CTLA-4, IL-5, CD3 epsilon, CAM, Alpha-4-integrin, IgE, IgE Fc region, an RSV antigen, F (or fusion) protein of respiratory syncytial virus (RSV), NCA-90 (granulocyte cell antigen), IL-6, GD2, GD3, IL-12, IL-23, IL-17, CTAA16.88, beta-amyloid, IGF-1 receptor (IGF-1R), delta-like ligand 4 (DLL4), alpha subunit of granulocyte macrophage colony stimulating factor receptor, hepatocyte growth factor, IFN-alpha, nerve growth factor, IL-13, CD326, CD19, PD-L1, CD47, and CD137.

22. The meditope enabled antibody or antigen binding fragment of any one of claims 1-21, wherein the meditope enabled antibody or antigen binding fragment is coupled to a therapeutic agent or diagnostic agent.

23. The meditope enabled antibody or antigen binding fragment of any one of claims 1-22, wherein the cyclic peptide is coupled to a therapeutic agent or diagnostic agent.

24. The meditope enabled antibody or antigen binding fragment of claim 22 or 23, wherein the therapeutic agent is selected from the group consisting of a chemotherapeutic

agent, a therapeutic antibody, a toxin, a radioactive isotope, an enzyme, a chelator, a boron compound, a photoactive agent, a dye, a metal, a metal alloy, and a nanoparticle; or

the diagnostic agent is an imaging agent selected from the group consisting of a fluorescent substance, a luminescent substance, a dye, and a radioactive isotope.

5

25. A method of crosslinking a first mediotope enabled antibody or antigen binding fragment thereof and a second mediotope enabled antibody or antigen binding fragment thereof, wherein the second mediotope enabled antibody is a recombinant mediotope enabled antibody of any one of claims 1-24 the method comprising contacting a mediotope binding site
10 of the first mediotope enabled antibody or antigen binding fragment thereof with a mediotope of the second mediotope enabled antibody, thereby resulting in crosslinking of the first and second mediotope-enabled antibodies.

26. A method for altering the distribution of a cell surface antigen, comprising:
15 contacting a cell comprising a cell surface antigen with a plurality of the recombinant mediotope enabled antibodies or antigen binding fragments of any one of claims 1-24, wherein the recombinant mediotope enabled antibodies or antigen binding fragments are capable of binding to the cell surface antigen; and

contacting a mediotope binding site of a first mediotope enabled antibody or antigen
20 binding fragment thereof of the plurality of mediotope enabled antibodies with a mediotope from a second mediotope enabled antibody from the plurality of mediotope enabled antibodies, resulting in crosslinking of the first and second mediotope-enabled antibodies, whereby crosslinking the first and second mediotope enabled antibodies alters the distribution of the cell surface antigen.

25

27. A method for increasing co-localization of a cell surface antigen or cell surface receptor, comprising:

contacting a cell comprising a cell surface antigen with a plurality the of recombinant mediotope enabled antibodies or antigen binding fragments of any one of claims 1-24, wherein
30 the recombinant mediotope enabled antibodies or antigen binding fragments are capable of binding to the cell surface antigen; and

contacting a mediotope binding site of a first mediotope enabled antibody or antigen binding fragment thereof of the plurality of mediotope enabled antibodies with a mediotope from a second mediotope enabled antibody from the plurality of mediotope enabled antibodies,

resulting in crosslinking of the first and second meditope-enabled antibodies, whereby crosslinking the first and second meditope enabled antibodies increases the co-localization of the cell surface antigen or receptor.

5 28. A method for increasing cellular internalization of a meditope enabled antibody, comprising:

 contacting a cell comprising a cell surface antigen with a plurality of the recombinant meditope enabled antibodies or antigen binding fragments of any one of claims 1-24, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of
10 binding to the cell surface antigen; and

 contacting a meditope binding site of a first meditope enabled antibody or antigen binding fragment thereof of the plurality of meditope enabled antibodies with a meditope from a second meditope enabled antibody from the plurality of meditope enabled antibodies, resulting in crosslinking of the first and second meditope-enabled antibodies, whereby
15 crosslinking the first and second meditope enabled antibodies increases cellular internalization of the first and second meditope enabled antibodies bound to the cell surface antigen.

 29. A method for increasing cellular internalization of a cell surface antigen,
20 comprising:

 contacting a cell comprising a cell surface antigen with a plurality of the recombinant meditope enabled antibodies or antigen binding fragments of any one of claims 1-24, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of
25 binding to the cell surface antigen; and

 contacting a meditope binding site of a first meditope enabled antibody or antigen binding fragment thereof of the plurality of meditope enabled antibodies with a meditope from a second meditope enabled antibody from the plurality of meditope enabled antibodies, resulting in crosslinking of the first and second meditope-enabled antibodies, whereby crosslinking of the first and second meditope enabled antibodies increases cellular
30 internalization of the first and second cell surface antigen.

 30. A method of increasing the efficacy of an antibody therapy, comprising:
 administering to a subject in need thereof an effective amount of a plurality of the recombinant meditope enabled antibody or antigen binding fragment of any one of claims 1-

24, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of binding to a cell surface antigen;

contacting a cell comprising the cell surface antigen with a first recombinant meditope enabled antibody or fragment of the plurality of recombinant meditope enabled antibodies or antigen binding fragments;

contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment with a meditope from a second meditope enabled antibody of the plurality of recombinant meditope enabled antibodies, resulting in crosslinking of the first and second meditope-enabled antibodies, whereby crosslinking the first and second antibodies increases the efficacy of the antibody therapy.

31. A method of decreasing a dosage of an antibody therapy needed to achieve a desired therapeutic effect in a subject comprising:

administering to a subject in need thereof an effective amount of a plurality of the recombinant meditope enabled antibodies or antigen binding fragments of any one of claims 1-24, wherein the recombinant meditope enabled antibodies or antigen binding fragments are capable of binding to a cell surface antigen;

contacting a cell comprising the cell surface antigen with a first recombinant meditope enabled antibody or fragment of the plurality of recombinant meditope enabled antibodies or antigen binding fragments;

contacting a meditope binding site of the first meditope enabled antibody or antigen binding fragment with a meditope from a second meditope enabled antibody of the plurality of recombinant meditope enabled antibodies, resulting in crosslinking of the first and second antibodies, whereby crosslinking the first and second antibodies decreases the dosage of the antibody therapy needed to achieve the desired therapeutic effect in a subject.

32. The method of any one of claims 25-31, wherein the first and second meditope enabled antibodies are the same or different.

33. The method of any one of claims 25-31, wherein at least one of the first or second meditope enabled antibodies or antigen-binding fragments specifically binds to an antigen expressed by a disease or condition of a cell or tissue thereof.

34. The method of claim 33, wherein the disease or condition is a cancer.

35. The method of any one of claims 26-34, wherein the cell surface antigen is a receptor capable of receptor-mediated endocytosis.

5 36. The method of any one of claims 26-35, wherein the cell surface antigen comprises a plurality of cell surface antigens.

37. The method of claim 36, wherein a first cell surface antigen of the plurality of cell surface antigens is different than a second cell surface antigen of the plurality of cell surface antigens, and wherein the first recombinant mediotope enabled antibody specifically binds to the first cell surface antigen and the second recombinant mediotope enabled antibody specifically binds to the second cell surface antigen.

10 38. The method of claim 37, wherein a first cell surface molecule comprises the first cell surface antigen and the second cell surface antigen.

39. The method of claim 37, wherein a first cell surface molecule comprises the first cell surface antigen and a second cell surface molecule comprises the second cell surface antigen.

20 40. The method of any one of claims 25-39, further comprising contacting a mediotope binding site of the second mediotope enabled antibody or fragment with a mediotope of a third mediotope enabled antibody or fragment, wherein the third mediotope enabled antibody or fragment is a recombinant mediotope enabled antibody or antigen binding fragment thereof of any one of claims 1-24, thereby resulting in crosslinking of the second and third mediotope-enabled antibodies.

41. A method of inhibiting the crosslinking of a first mediotope enabled antibody or antigen binding fragment thereof and a second mediotope enabled antibody or antigen binding fragment thereof, wherein the second mediotope enabled antibody is a recombinant mediotope enabled antibody or antigen binding fragment thereof of any one of claims 1-24, the method comprising contacting a mediotope binding site of the first mediotope enabled antibody or antigen binding fragment thereof with a free mediotope, thereby inhibiting a mediotope of the second mediotope enabled antibody from contacting the mediotope binding site of the first

meditope enabled antibody, resulting in inhibiting the crosslinking of the first and second mediotope-enabled antibodies.

42. A method of reducing the crosslinking of a first mediotope enabled antibody or antigen binding fragment thereof and a second mediotope enabled antibody or antigen binding fragment thereof, wherein the second mediotope enabled antibody is a recombinant mediotope enabled antibody or antigen binding fragment thereof of any one of claims 1-24, the method comprising contacting a mediotope binding site of the first mediotope enabled antibody or antigen binding fragment thereof with a free mediotope, thereby reducing the ability of a mediotope of the second mediotope enabled antibody to contact the mediotope binding site of the first mediotope enabled antibody, resulting in reducing the crosslinking of the first and second mediotope-enabled antibodies.

43. A method of disrupting the crosslinking of a first mediotope enabled antibody or antigen binding fragment thereof and a second mediotope enabled antibody or antigen binding fragment thereof, wherein the second mediotope enabled antibody is a recombinant mediotope enabled antibody or antigen binding fragment thereof of any one of claims 1-24, the method comprising contacting a mediotope binding site of the first mediotope enabled antibody or antigen binding fragment thereof with a free mediotope, thereby displacing a mediotope of the second mediotope enabled antibody from the mediotope binding site of the first mediotope enabled antibody, resulting in disrupting the crosslinking of the first and second mediotope-enabled antibodies.

44. A method of reversing the crosslinking of a first mediotope enabled antibody or antigen binding fragment thereof and a second mediotope enabled antibody or antigen binding fragment thereof, wherein the second mediotope enabled antibody is a recombinant mediotope enabled antibody or antigen binding fragment thereof of any one of claims 1-24, the method comprising contacting a mediotope binding site of the first mediotope enabled antibody or antigen binding fragment thereof with a free mediotope, thereby displacing a mediotope of the second mediotope enabled antibody from the mediotope binding site of the first mediotope enabled antibody, resulting in reversing the crosslinking of the first and second mediotope-enabled antibodies.

45. A method of treatment, comprising administering an effective amount of a recombinant meditope enabled antibody of any one of claims 1-24 to a subject having a disease or condition.

5 46. The method of treatment of claim 45, wherein the disease or condition is cancer.

47. The method of treatment of claim 45 or 46, further comprising administering a chemotherapeutic agent to the subject.

10 48. Use of the recombinant meditope enabled antibody of any one of claims 1-24 in the manufacture of a medicament for the treatment of a disease or condition.

15 49. Use of a combination of the antibody drug conjugate of any one of claims 1-24 and a chemotherapeutic agent in the manufacture of a medicament for the treatment a disease or condition.

50. The use of claim 48 or claim 49, wherein the disease or condition is cancer.

20 51. A method of reducing the effects of a meditope-enabled self-crosslinking antibody on a subject who has been administered the antibody, the method comprising administering free meditope to the subject.

25 52. The method of claim 51, wherein the free meditope comprises a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

30 X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

5 X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

10 X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

15 53. The method of claim 51, wherein the free meditope comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom.

20

54. The method of any one of claims 51-53, wherein the method comprises administering free meditope to the subject a plurality of times, optionally 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times.

25

55. The method of any one of claims 51-54, wherein the half-life of the free meditope is the same or about the same as the half-life of the meditope-enabled self-crosslinking antibody.

30

56. The method of any one of claims 51-54, wherein the half-life of the free meditope is longer than the half-life of the meditope-enabled self-crosslinking antibody.

57. The method of any one of claims 51-54, wherein the half-life of the free meditope is shorter than the half-life of the meditope-enabled self-crosslinking antibody.

58. A method of temporally controlling the effects of a meditope-enabled self-crosslinking antibody comprising:

administering a meditope-enabled self-crosslinking antibody to a subject in need thereof;

5 administering one or more free meditopes to the subject, wherein the free meditope binds to a meditope binding site on the meditope-enabled self-crosslinking antibody, thereby reducing the ability of the antibody to self-crosslink.

59. The method of claim 58, wherein the step of administering one or more free meditopes to the subject occurs after the step of administering the meditope-enabled self-crosslinking antibody.

60. The method of claim 58 or claim 59, wherein the method further comprises administering one or more free meditopes a plurality of times.

61. The method of claim 60, wherein the administering one or more free meditopes a plurality of times takes place over a period of minutes, hours, days, months, or years.

62. The method of any one of claims 58-61, wherein the half-life of the one or more free meditopes is shorter than the half-life of the meditope-enabled self-crosslinking antibody.

63. The method of claim 62, further comprising cessation of the administration of one or more free meditopes, thereby restoring the ability of the antibody to self-crosslink as the levels of free meditopes decrease.

64. The method of claim 63, further comprising the restoration of the administration of one or more free meditopes one or more times, wherein the free meditope binds to a meditope binding site on the meditope-enabled self-crosslinking antibody, thereby reducing the ability of the antibody to self-crosslink.

65. A nucleic acid molecule comprising a sequence of nucleotides encoding the recombinant meditope enabled antibody or antigen binding fragment thereof of any one of claims 1-21.

5 66. The nucleic acid molecule of claim 65, further comprising a sequence of nucleotides encoding a free meditope.

67. The nucleic acid molecule of claim 66, wherein the free meditope comprises a peptide having the formula:

10 X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

15 X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

20 X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

25 X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X11 is Lys; and

30 X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

68. The nucleic acid molecule of claim 66, wherein the free meditope comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43,

44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom.

69. The nucleic acid molecule of any one of claims 66-68, wherein the free
5 meditope encoded by the nucleic acid molecule is capable of binding to the meditope binding site on the recombinant meditope enabled antibody or antigen binding fragment thereof encoded by the nucleic acid molecule.

70. The nucleic acid molecule of any one of claims 65-69, further comprising at
10 least one promoter operatively linked to control expression of the recombinant meditope enabled antibody or antigen binding fragment thereof.

71. The nucleic acid molecule of any one of claims 66-69, further comprising at
15 least one promoter operatively linked to control expression of the recombinant meditope enabled antibody or antigen binding fragment thereof and the free meditope.

72. The nucleic acid molecule of any one of claims 66-69 or 71, wherein the
sequence of nucleotides encoding the recombinant meditope enabled antibody or antigen
binding fragment thereof and the sequence of nucleotides encoding the free meditope are
20 separated by an internal ribosome entry site (IRES), a sequence of nucleotides encoding a self-cleaving peptide, or a sequence of nucleotides encoding a peptide that causes ribosome skipping, optionally a T2A peptide.

73. The nucleic acid molecule of any one of claims 66-69 or 71, wherein the
25 sequence of nucleotides encoding the recombinant meditope enabled antibody or antigen binding fragment thereof is operatively linked to a first promoter and the sequence of nucleotides encoding the free meditope is operatively linked to a second promoter, wherein the first and second promoter can be the same or different.

30 74. The nucleic acid molecule of any one of claims 70-73, wherein at least one of the one or more promoters is a conditional promoter.

75. The nucleic acid molecule of claim 74, wherein the conditional promoter is an inducible promoter.

76. The nucleic acid molecule of claim 74, wherein the conditional promoter comprises a Lac operator sequence, a tetracycline operator sequence, a galactose operator sequence or a doxycycline operator sequence, or is an analog thereof.

5

77. The nucleic acid molecule of any one of claims 74, wherein the conditional promoter is a repressible promoter.

78. The nucleic acid molecule of claim 74, wherein the conditional promoter
10 comprises a Lac repressor or a tetracycline repressor, or is an analog thereof.

79. The nucleic acid molecule of any one of claims 70-78, wherein at least one of the one or more promoters is selected from the group consisting of CMV, RSV, PGK, EF1 α , NSE, SV40, UBC, CAGG, synapsin, β -actin, and GFAP.

15

80. A vector comprising the nucleic acid molecule of any one of claims 65-79.

81. The vector of claim 80, wherein the vector is a pCEP4 vector, a viral vector, a retroviral vector, a lentiviral vector, or a gamma retroviral vector.

20

82. A cell comprising the nucleic acid molecule of any one of claims 65-79 or vector of claims 80-81.

83. A cell comprising a first nucleic acid or vector comprising a sequence of
25 nucleotides encoding the recombinant mediotope enabled antibody or antigen binding fragment thereof of any one of claims 1-21 and a second nucleic acid or vector comprising a sequence of nucleotides encoding a free mediotope.

84. The cell of claim 83, wherein the free mediotope comprises a peptide having
30 the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

5 X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

X7 is Thr, Ser or Cys;

10 X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

15 X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

20 85. The cell of claim 83, wherein the free meditope comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, or 207, or a cyclic peptide derived therefrom.

25 86. The cell of any one of claims 83-85, wherein the first vector further comprises a first promoter operatively linked to control expression of the recombinant meditope enabled antibody or antigen binding fragment thereof and the second vector further comprises a second promoter operatively linked to control expression of the free meditope, wherein the first promoter and second promoter can be the same or different.

30

87. The cell of any one of claims 83-86, wherein at least one of the first promoter or the second promoter is a conditional promoter.

88. The cell of any one of claims 82-87, wherein the cell is a eukaryotic cell.

89. The cell of any one of claims 82-88, wherein the cell is a mammalian cell.

90. The cell of any one of claims 82-89, wherein the cell is a CHO cell, a HEK-
5 293 cell, or a 293T cell.

91. A method of making a meditope-enabled self-crosslinking antibody or antigen binding fragment thereof, the method comprising

- 10 i) culturing the host cell of any one of claims 82-90 under conditions suitable for expression of the sequence of nucleotides encoding the recombinant meditope-enabled antibody or antigen binding fragment thereof; and
- ii) isolating the antibody or antigen binding fragment thereof.

92. A method of making a meditope-enabled self-crosslinking antibody or antigen
15 binding fragment thereof, the method comprising

- i) culturing the host cell of any one of claims 82-90 under conditions suitable for expression of both the sequence of nucleotides encoding the recombinant meditope-enabled antibody or antigen binding fragment thereof and the sequence of nucleotides encoding the free meditope; and
- 20 ii) isolating the antibody or antigen binding fragment thereof and free meditope.

93. The method of claim 91 or claim 92, wherein the antigen binding fragment is a Fab, Fab', Fv, scFv, or F(ab')₂ fragment.

25 94. The method of any one of claims 91-93, further comprising conjugating a drug to the antibody or antigen binding fragment thereof.

95. An antibody or antigen binding fragment thereof produced by the method of any one of claims 91-93.

30

96. An antibody drug conjugate produced by the method of claim 94.

97. A composition comprising a plurality of the recombinant meditope enabled antibodies or antigen binding fragments thereof of any one of claims 1-24, 95 or 96, or

encoded by the nucleic acids of any one of claims 65-79, or expressed by the vector of any one of claims 80-81, expressed by the cell of any one of claims 82-87, or produced by the method of any one of claims 91-94.

5 98. The composition of claim 97, further comprising a plurality of free mediotopes.

 99. The composition of claim 98, wherein the free mediotope comprises the free mediotope encoded by the nucleic acids of any one of claims 66-79, expressed by the vector of any one of claims 80-81, expressed by the cell of any one of claims 82-87, or produced by the
10 method of any one of claims 92-94.

 100. The composition of claim 98, wherein the free mediotope comprises a peptide having the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (formula V)

15 wherein:

X1 is Cys, Gly, β -alanine, diaminopropionic acid, β -azidoalanine, or null;

X2 is Gln or null;

X3 is Phe, Tyr, β,β' -diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-
20 containing residue, or a boronic acid-containing residue;

X4 is Asp or Asn;

X5 is Leu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 is Ser or Cys;

25 X7 is Thr, Ser or Cys;

X8 is Arg, a modified Arg, or a hydratable carbonyl-containing residue or boronic acid-containing residue;

X9 is Arg or Ala;

X10 is Leu; Gln; Glu; β,β' -diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-
30 containing residue;

X11 is Lys; and

X12 is Cys, Gly, 7-aminoheptanoic acid, β -alanine, diaminopropionic acid, propargylglycine, aspartic acid, isoaspartic acid, or null.

101. The composition of claim 98, wherein the free meditope comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 2, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 186, 187, 188, 189, and 207, or a cyclic peptide derived therefrom.

102. The composition of any one of claims 98-101, wherein the ratio of the recombinant meditope enabled antibody or antigen binding fragment thereof to the free meditope is between 1:1 and 1:1,000,000,000,000, including about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:10, 1:15, 1:20, 1:25, 1:50, 1:75, 1:100, 1:150, 1:200, 1:250, 1:300, 1:400, 1:500, 1:750, 1:1000, 1:2000, 1:3,000, 1:4,000, 1:5,000, 1:10,000, 1:25,000, 1:50,000, 1:100,000, 1:250,000, 1:500,000, 1:1,000,000, 1:1,000,000,000, and 1:1,000,000,000,000.

103. The composition of any one of claims 98-102, wherein the free meditope binds the meditope binding site of a recombinant meditope enabled antibody or antigen binding fragment thereof of the plurality of recombinant meditope enabled antibodies with a dissociation constant of less than at or about 10 μ M, less than at or about 5 μ M, or less than at or about 2 μ M, less than at or about 1 μ M, less than at or about 500, 400, 300, 200, 100 nM, 200 picomolar or less..

104. The composition of any one of claims 98-103, wherein the plurality of recombinant meditope enabled antibodies or antigen binding fragments thereof comprises a first and second recombinant meditope enabled antibodies or antigen binding fragments thereof; and

wherein the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is greater than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof.

105. The composition of claim 104, wherein the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding

fragment thereof that is between 2X and 1,000,000X greater than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant mediotope enabled antibody or antigen binding fragment thereof for the mediotope binding site of the first recombinant mediotope enabled antibody or antigen binding fragment thereof.

5

106. The composition of any one of claims 98-103, wherein the plurality of recombinant mediotope enabled antibodies or antigen binding fragments thereof comprises a first and second recombinant mediotope enabled antibodies or antigen binding fragments thereof; and

10

wherein the free mediotope has an affinity for a mediotope binding site of the first recombinant mediotope enabled antibody or antigen binding fragment thereof that is less than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant mediotope enabled antibody or antigen binding fragment thereof for the mediotope binding site of the first recombinant mediotope enabled antibody or antigen binding fragment thereof.

15

107. The composition of claim 106, wherein the free mediotope has an affinity for a mediotope binding site of the first recombinant mediotope enabled antibody or antigen binding fragment thereof that is between 2X and 1,000,000X less than the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant mediotope enabled antibody or antigen binding fragment thereof for the mediotope binding site of the first recombinant mediotope enabled antibody or antigen binding fragment thereof.

20

108. The composition of any one of claims 97-107, wherein the plurality of recombinant mediotope enabled antibodies or antigen binding fragments thereof comprises a first and second recombinant mediotope enabled antibodies or antigen binding fragments thereof; and

25

wherein the cyclic peptide coupled to the amino terminus of a linker of the second recombinant mediotope enabled antibody or antigen binding fragment thereof binds the mediotope binding site of the first recombinant mediotope enabled antibody or antigen binding fragment thereof with dissociation constant of less than at or about 10 μ M, less than at or about 5 μ M, or less than at or about 2 μ M, less than at or about 1 μ M, less than at or about 500, 400, 300, 200, 100 nM, 200 picomolar or less.

30

109. The composition of any one of claims 97-108, wherein the composition has a pH of between 1 and 7.35 or between 7.45 and 13.

110. The composition of claim 109, wherein the plurality of recombinant meditope enabled antibodies or antigen binding fragments thereof comprises a first recombinant meditope enabled antibody or antigen binding fragment thereof and a second recombinant meditope enabled antibody or antigen binding fragment thereof;

wherein the affinity of a cyclic peptide coupled to the amino terminus of a linker of the second recombinant meditope enabled antibody or antigen binding fragment thereof for the meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof is higher at a physiological pH than it is at a non-physiological pH.

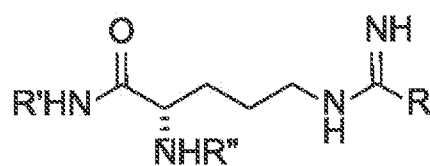
111. The composition of any one of claims 98-110, wherein the free meditope has an affinity for a meditope binding site of the first recombinant meditope enabled antibody or antigen binding fragment thereof that is lower at a physiological pH than it is at a non-physiological pH.

112. The composition of claim 110 or claim 111, wherein the physiological pH is the pH at a cell or a tissue of a disease or a condition.

113. A pharmaceutical composition comprising:
a pharmaceutically acceptable carrier and the recombinant meditope enabled antibody or antigen binding fragment thereof of any one of claims 1-24, encoded by the nucleic acid of any one of claims 65-79 or vectors of claims 80-81, expressed by the cell of any one of claims 82-90, produced by the method of any one of claims 91-94; or
the composition of any one of claims 97-112.

114. The pharmaceutical composition of claim 113 in human unit dose form.

Fig. 1



Modified Arg8

R = alkyl, substituted alkyl, aromatic or NHR'''
where R''' = alkyl, substituted alkyl, aromatic

Fig. 2

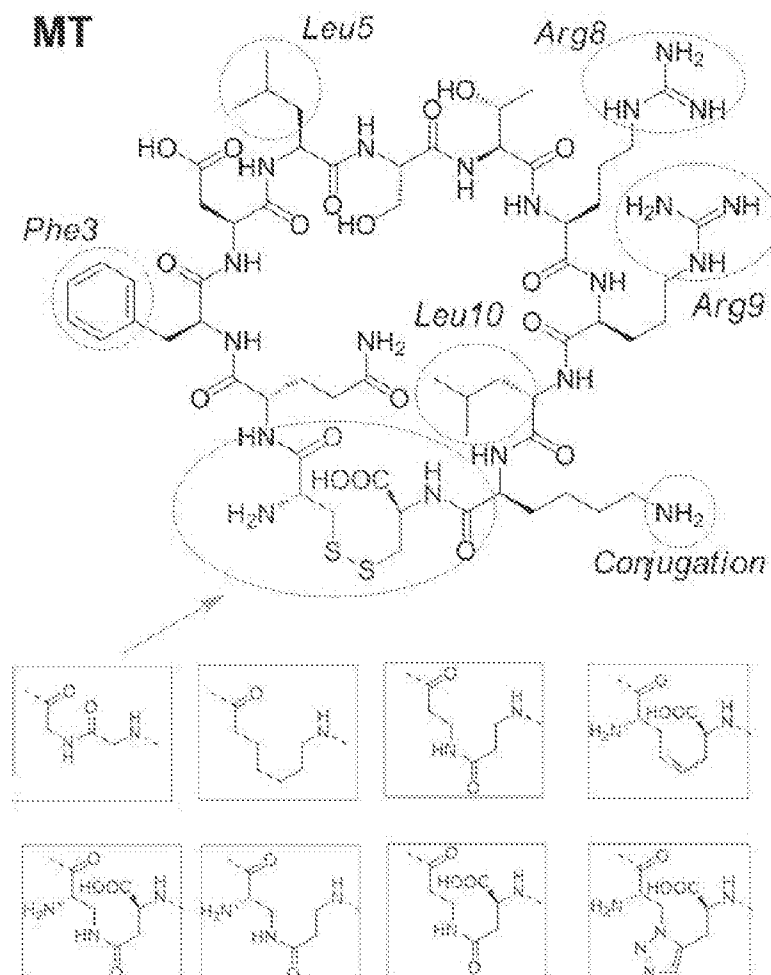
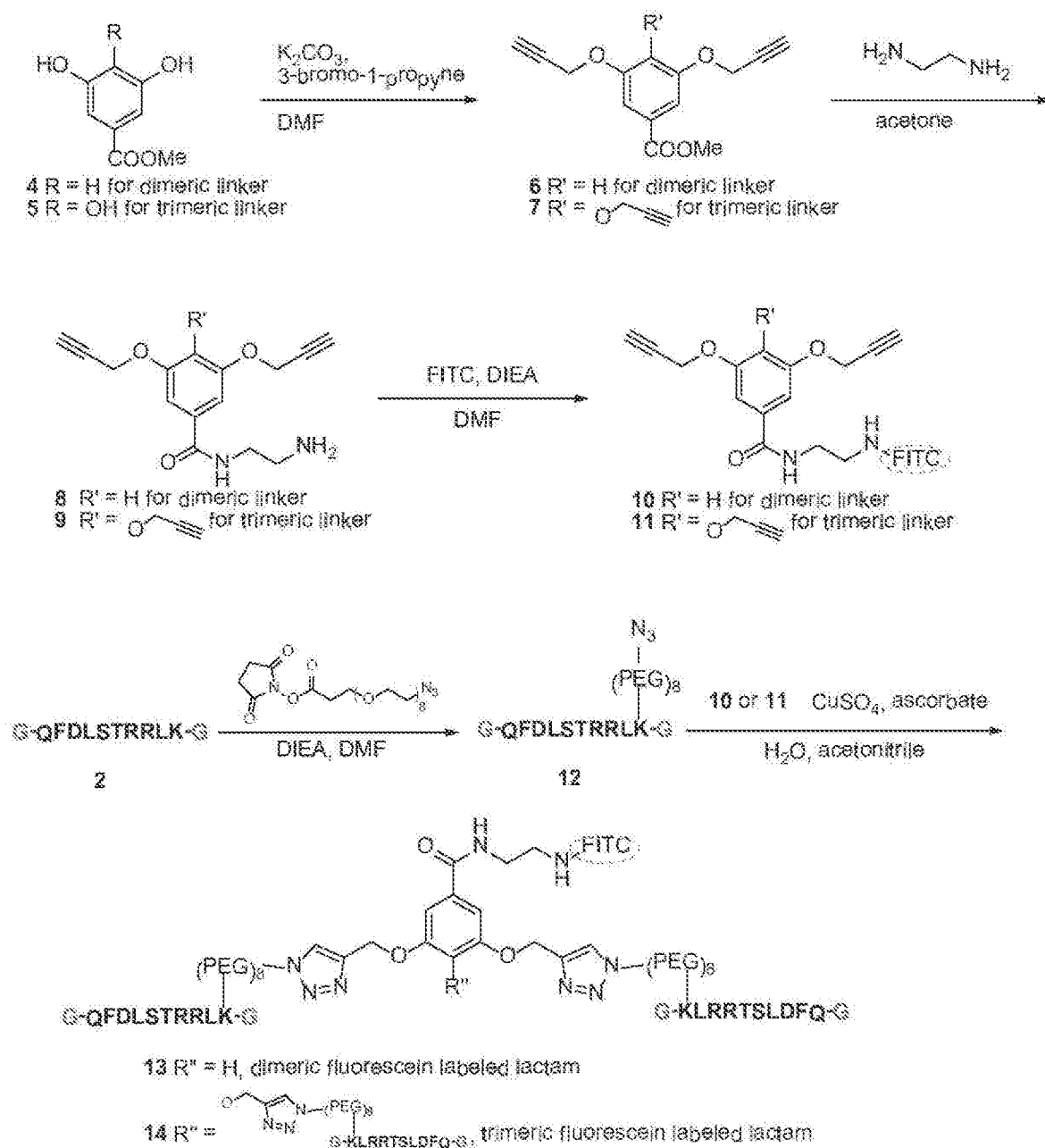


Fig. 3



3/14

Fig. 4A

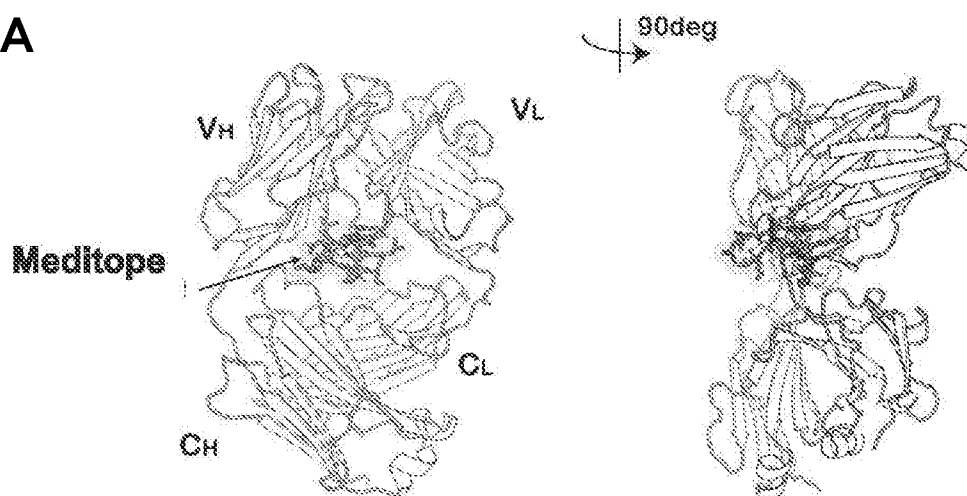


Fig. 4B

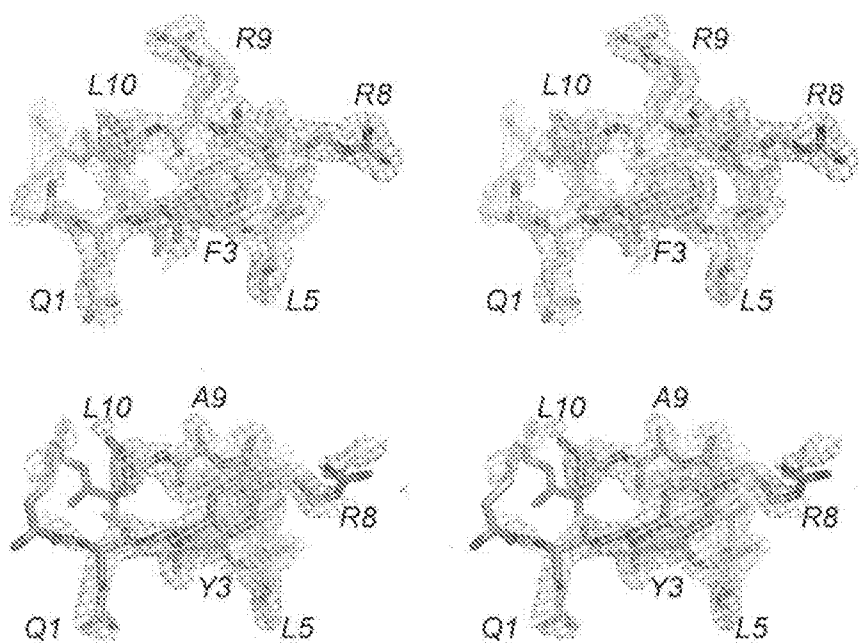


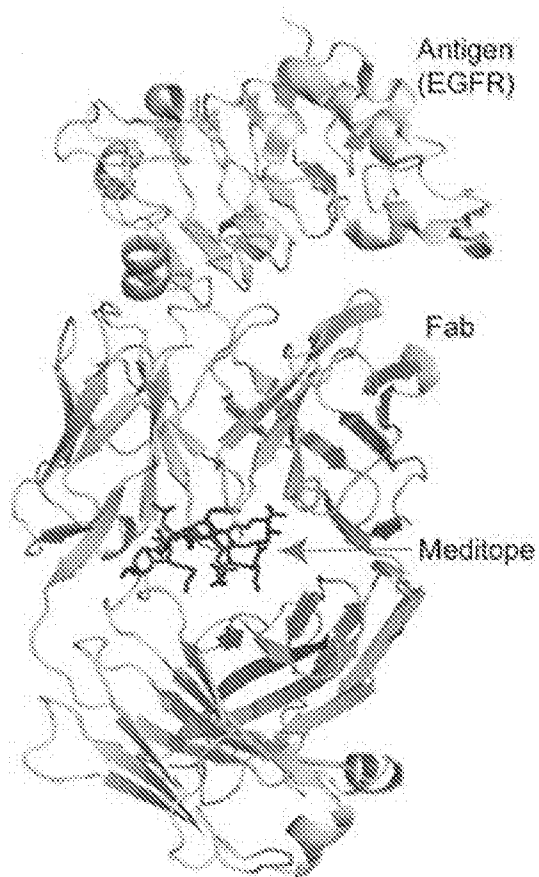
Fig. 5

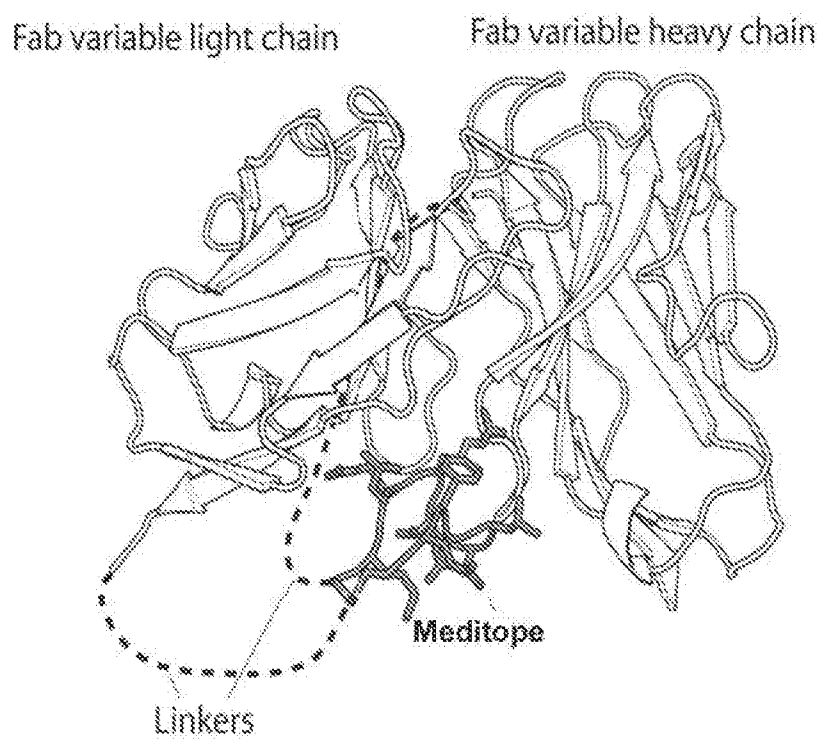
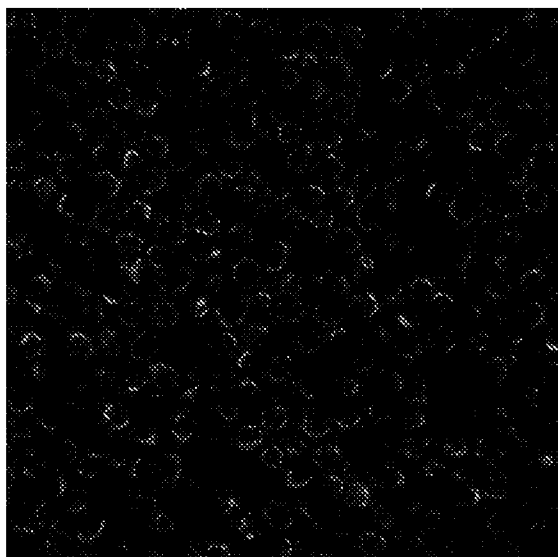
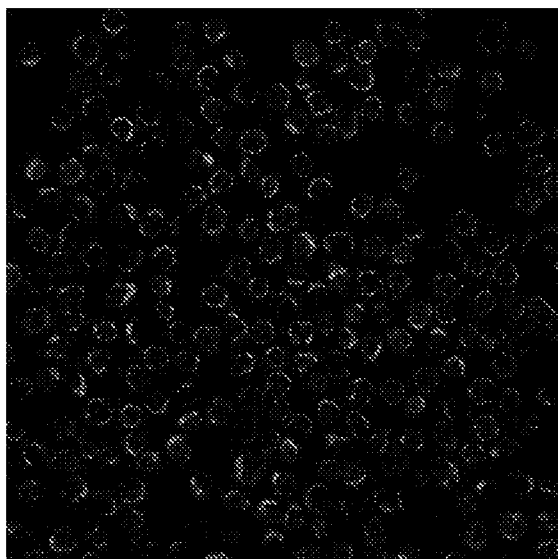
Fig. 6

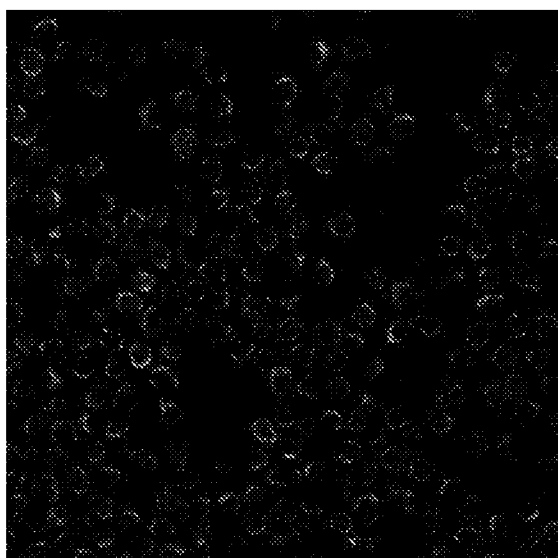
Fig. 7A



Control Antibody



SnAP-body Variant 1



SnAP-body Variant 2

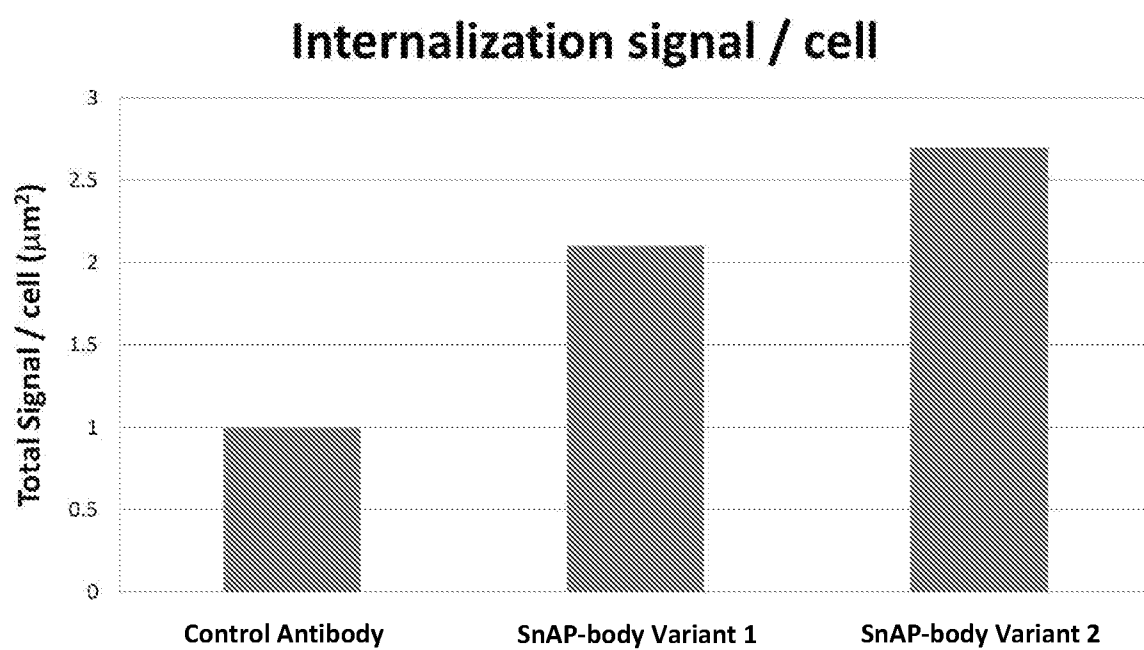
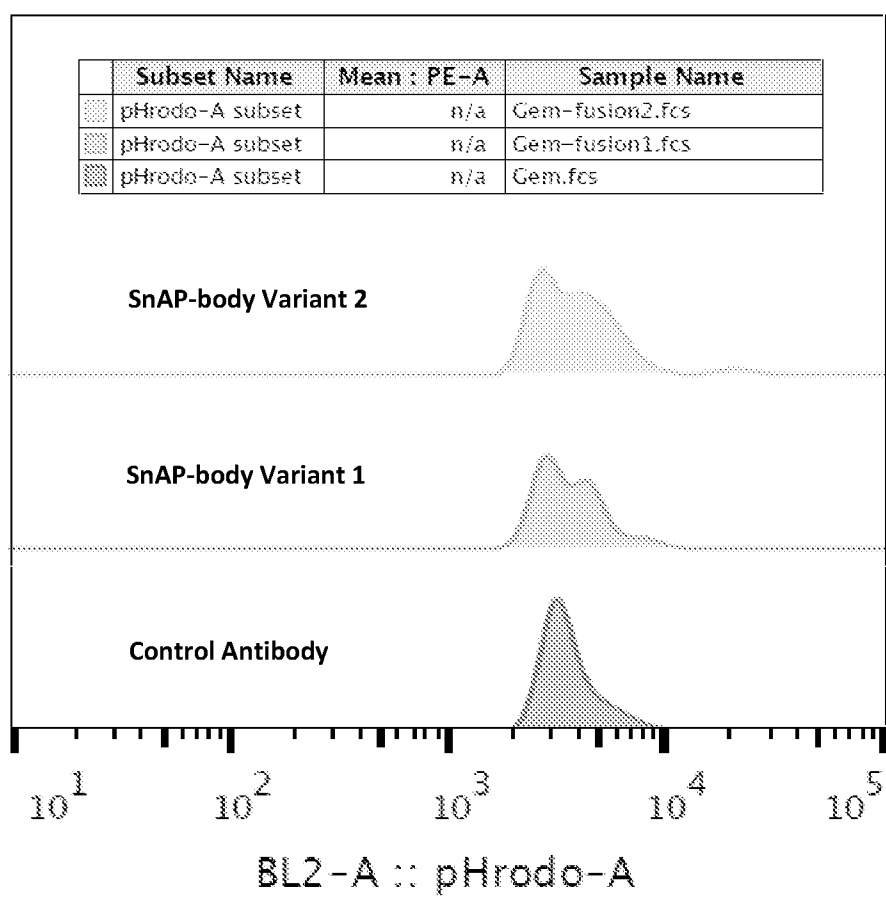
Fig. 7B

Fig. 8



9/14

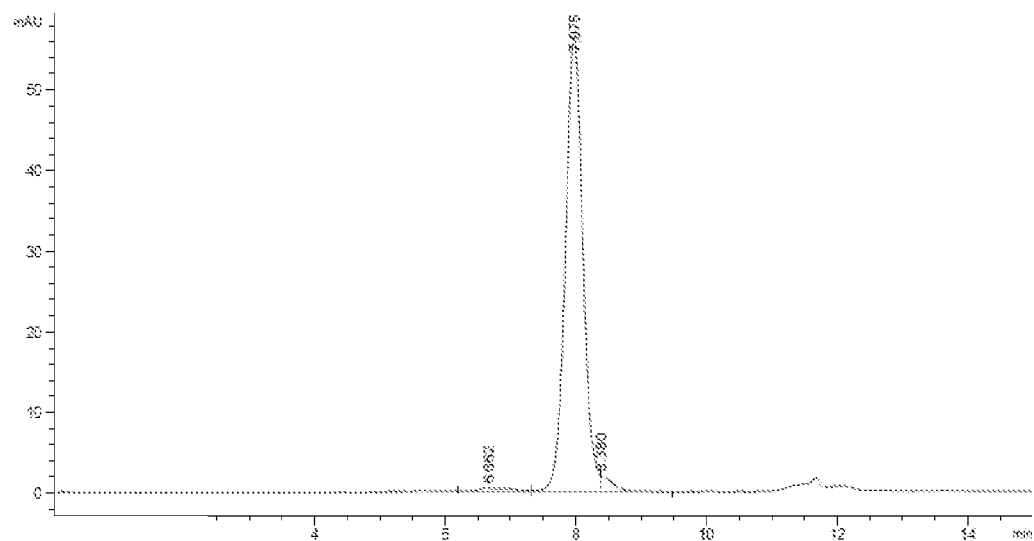
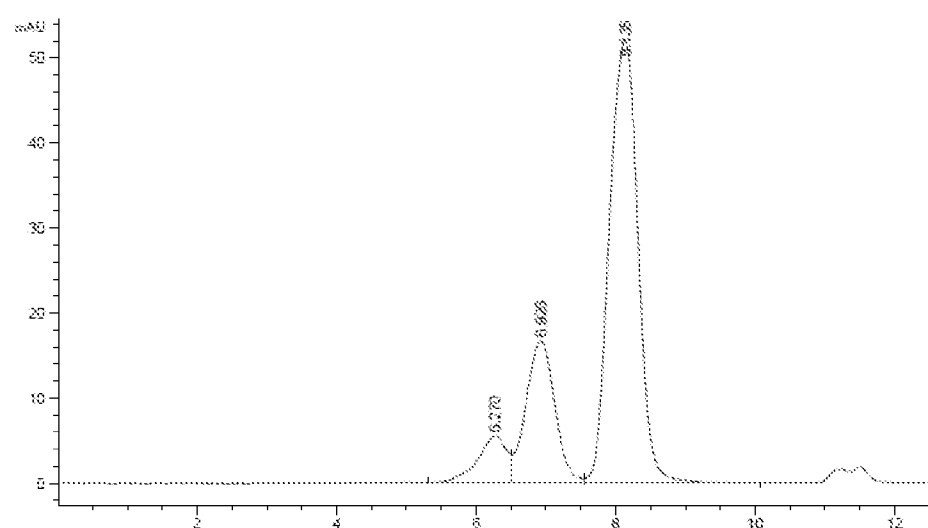
Fig. 9A**Fig. 9B**

Fig. 9C

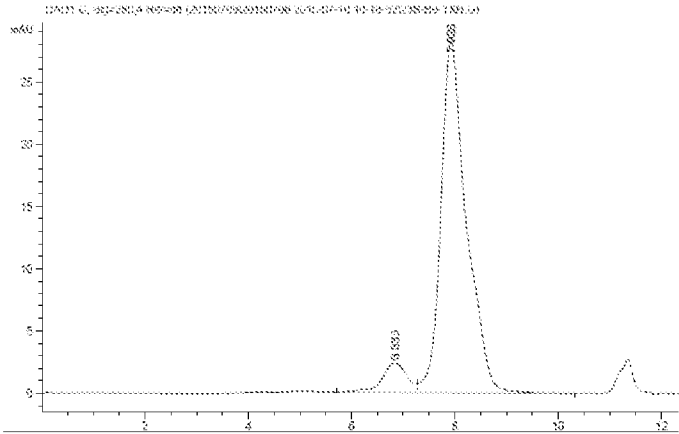


Fig. 9D

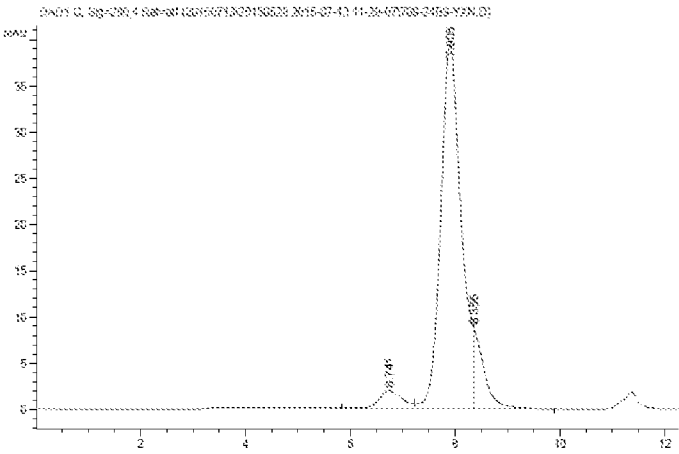


Fig. 10

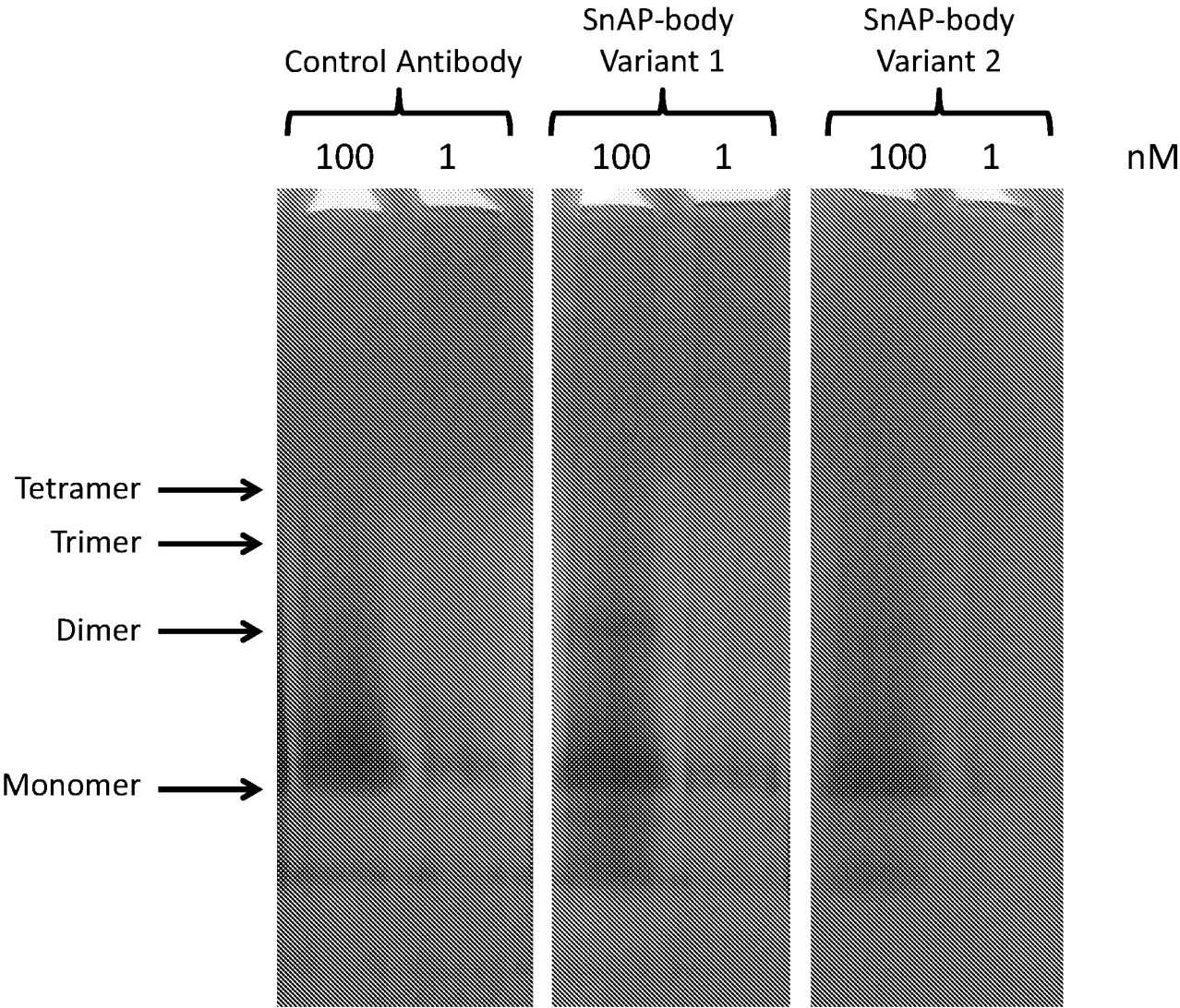
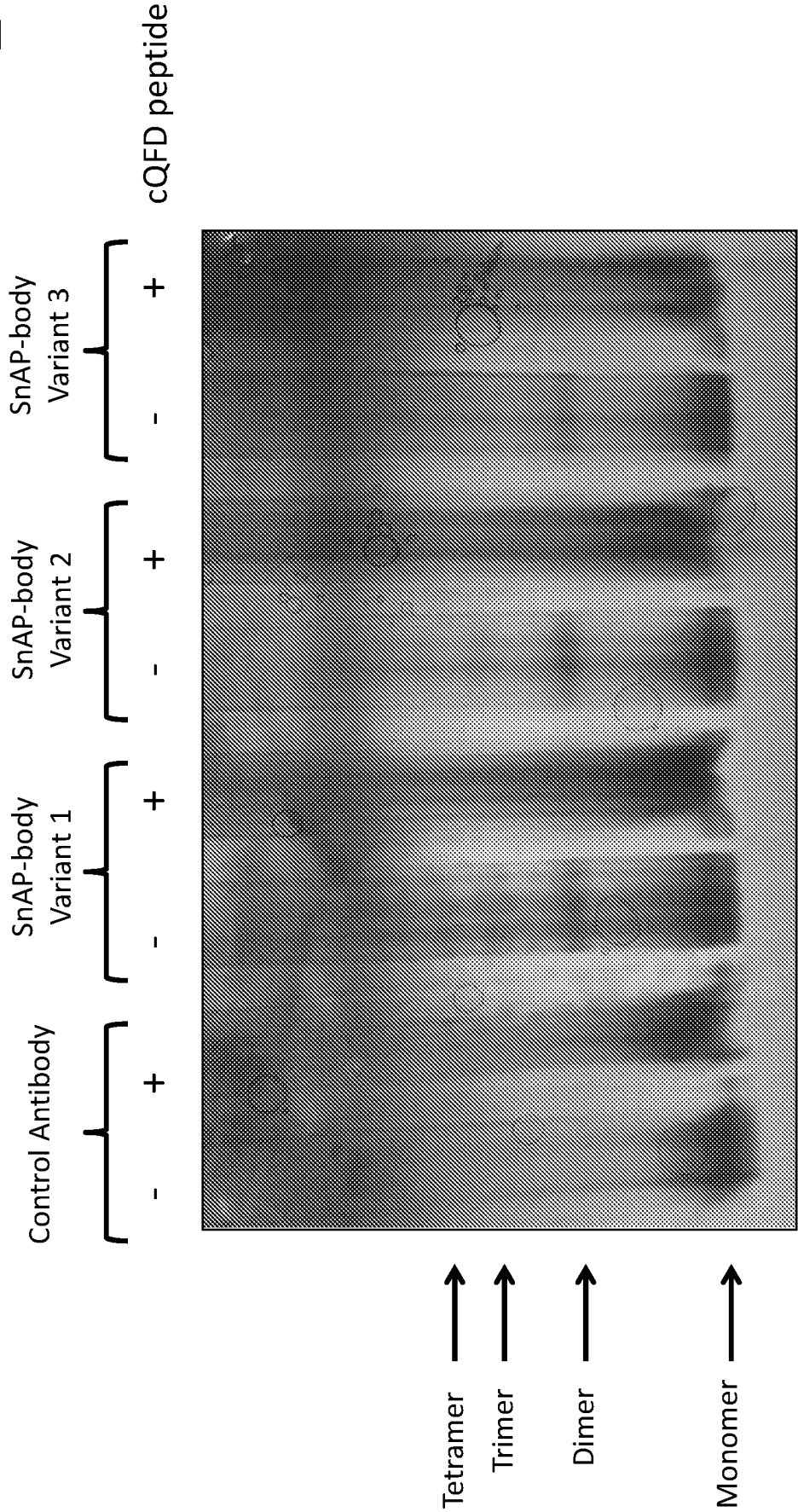
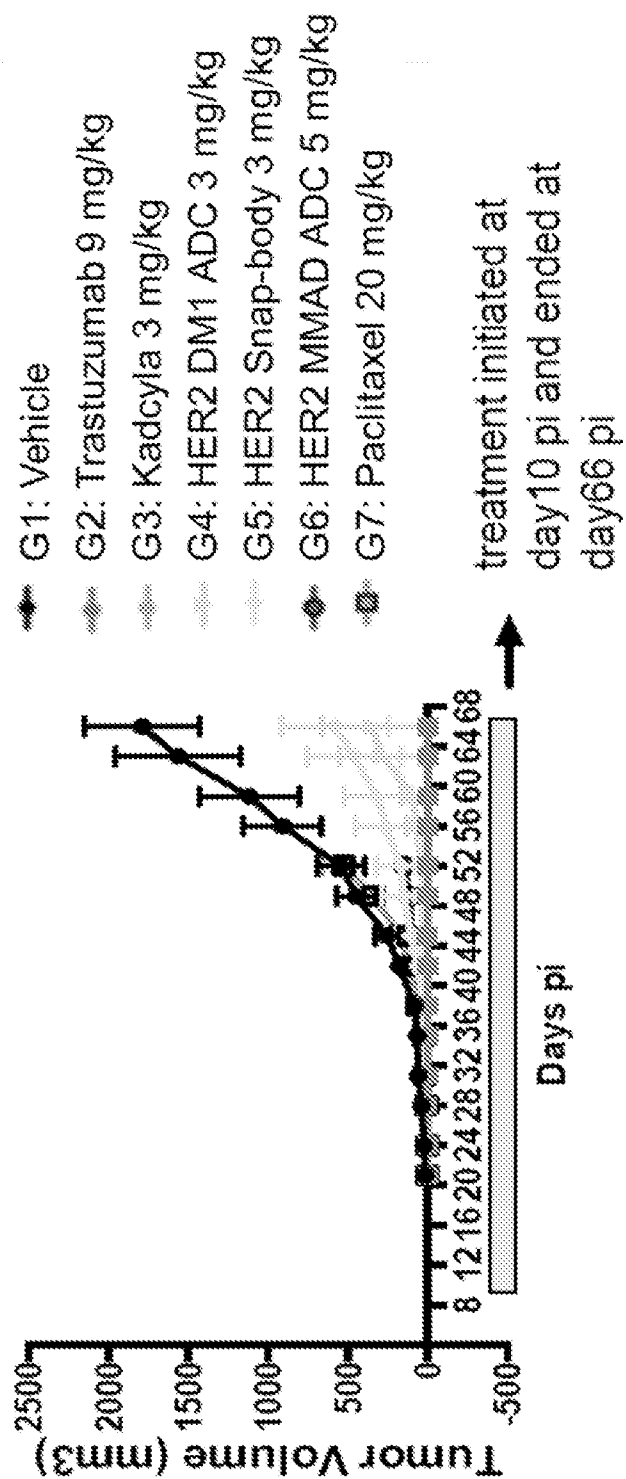


Fig. 11



13/14

Fig. 12



49JV_227262_WO_SEQ
SEQUENCE LISTING

<110> MEDITOPE BIOSCIENCES, INC.

<120> SELF-CROSSLINKING ANTIBODIES

<130> 49JV-227262-WO

<150> 62/276,803

<151> 2016-01-08

<150> 62/317,342

<151> 2016-04-01

<160> 306

<170> PatentIn version 3.5

<210> 1

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 1

Cys	Gln	Phe	Asp	Leu	Ser	Thr	Arg	Arg	Leu	Lys	Cys
1				5					10		

<210> 2

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 2

Cys	Gln	Tyr	Asn	Leu	Ser	Ser	Arg	Ala	Leu	Lys	Cys
1				5					10		

<210> 3

<211> 786

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic polynucleotide for peptide-Fc fusion protein

<400> 3

tgccagtttg acctgtcaac tcggcgactg aaatgcggtg ggggctccgg ttcaggctcg 60

ggcggttcat cgggaggagg gggaggggaa cctaagtcac gcgataagac gcacacctgt 120

cctccatgcc cagccccga gttgcttggt gggccctcag tattcctctt ccctccaaaa 180

cccaaagaca ccttgatgat ttcccgcacg ccggaagtca cgtgtgtggt cgtggatgtg 240

49JV_227262_W0_SEQ

agccatgagg atcccgaggt gaagttcaat tggtagctgg atggagtaga ggtacacaac 300
gcgaaaacga agcccaggga ggaacagtac aattccacat atcgcgtagt gtccgtgctt 360
actgtgttgc atcaagactg gctgaatggg aaggagtata agtgcaaagt atcaaacaag 420
gcgctgcctg ctccaatcga aaagaccatc tcgaaggcga aaggacaacc cagagaaccc 480
caagtctaca cgcttccgcc ctgcggggat gagctcacca aaaaccaggt atccctcact 540
tgtttggtaa aaggattcta cccgtcggac attgcagtcg agtgggagtc gaatgggcag 600
ccggaataca actacaaaac aacaccgccc gtcttggact ccgatggttc gttctttctc 660
tattcgaagc tcaccgtaga caagtcgagg tggcagcagg gcaacgtctt ttcgtgctca 720
gtgatgcatg aggcccttca caatcactat acgcagaaaa gcctgagcct gtcaccgggg 780
aagtaa 786

<210> 4
<211> 261
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 4

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ser
1 5 10 15

Gly Ser Gly Ser Gly Gly Ser Ser Gly Gly Gly Gly Gly Glu Pro Lys
20 25 30

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
35 40 45

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
50 55 60

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
65 70 75 80

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
85 90 95

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
100 105 110

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
115 120 125

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
130 135 140

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
Page 2

49JV_227262_W0_SEQ

145 150 155 160

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
165 170 175

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
180 185 190

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
195 200 205

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
210 215 220

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
225 230 235 240

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
245 250 255

Leu Ser Pro Gly Lys
260

<210> 5
<211> 1410
<212> DNA
<213> Homo sapiens

<400> 5
atgaaatgct cgtgggtgat ctttttcctt atggcggttag taaccggagt aaactccgag 60
gtccagctcg tcgaatccgg tggcggtctt gtgcagccgg gtgggtcggt gcgactgtcg 120
tgcgcagcgt cgggggtttaa catcaaagac acctatatcc actgggtgag gcaatcgccc 180
ggaaaggggc tcgaatgggt agccagaatc taccctacga atgggttatac tcgatatgcg 240
gactccgtga aaggaagatt caccatcagc gcagatacgt ccaaaaacac tgcatacctc 300
cagatgaata gccttcgggc ggaggacacg gcgatctact actgtagccg gtgggggtggg 360
gacgggttct atgcgatgga ctactgggga caggggacgc ttgtaacggt cagctcggcg 420
tcaacaaagg gacctagcgt gtttccttg gtcctctcat cgaaatcaac gtccggtggg 480
acggcggcat tggggtgtct tgtcaaggac tatttccccg agcccgtagc agtctcgtgg 540
aactcgggtg cccttacaag cggcgtagat acgtttcccc cgtgctcca atcatccgga 600
ctgtattccc tttcatccgt cgtgactgtg ccgtcctcgt cactcggaac gcaaacttac 660
atttgcaatg tcaaccacaa accgtcaa atcaaaggatc ataagaagg cgagccaaag 720
tcgtgtgata agaccacac atgccctccc tgtccagcgc cggagctggt gggagggcct 780
tcagtgttcc tcttcccgcc caaaccaa gacaccctga tgattagccg cacacccgag 840
gtgacgtgtg tcgtcgtcga tgtctcacat gaggaccgg aggtaaagtt caactggtac 900
gtggatggag tcgaagtga caacgcaaaa acaaacctc gggaagagca gtacaatagc 960

49JV_227262_W0_SEQ

acgtacagag tagtcagcgt gctcaccgtg ctgcaccagg attggctcaa tggaaaggag 1020
tacaagtgtg aagtgtcgaa taaggcgctg cctgccccca tcgaaaagac aatttcctaaa 1080
gctaaagggc aaccccgcgga gccgcaagta tacaccctcc caccctcgcg cgatgaactg 1140
accaagaacc aggtgtcatt gacgtgtctc gtcaagggtt tctatccgag cgacattgca 1200
gtagaatggg aaagcaacgg acagccggaa aacaactaca agactacacc gcctgtcctt 1260
gattcggatg gttccttctt tctttactca aaacttacag tcgacaaatc gaggtggcag 1320
cagggaaatg tgttttcgtg cagcgtgatg cagaggcct tgcataatca ctatacacag 1380
aagtcgttgt cactgtcgcc gggaaagtaa 1410

<210> 6
<211> 184
<212> PRT
<213> Homo sapiens

<400> 6

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 Ser 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 Ile 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

49JV_227262_W0_SEQ

Leu Gln Ser Ser Gly Leu Tyr Ser
180

<210> 7
<211> 184
<212> PRT
<213> Homo sapiens

<400> 7

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
180

<210> 8
<211> 705
<212> DNA
<213> Homo sapiens

<400> 8

atggagacag acacgctttt gctttgggtg ttgttgttgt gggccccgg ttcgacgggg

60

49JV_227262_W0_SEQ

gatattcaga tgaccagtc accgatcctt ctctcggcga gcgtaggggga tagagtaacg	120
atcacgtgta gagcgtccca agacgtcaac acagctgtcg cgtggatatca gcagcggaca	180
aatggatcgc cgaggctcct gatctacagc gcatcatttc tctattcggg agtcccctcc	240
cgattttccg gatcgcgcag cgggtactgac ttcaccctca cgatttcctc ctttcaaccg	300
gaagatatcg ctgattacta ctgtcagcag cactatacaa cacctcccac tttcggagca	360
gggacaaaag tggagattaa gcgcactgta gcagccccct cgggtctttat cttccctcct	420
agcgacgaac aattgaagtc agggaccgcc tcggtgggat gcctgcttaa caacttttac	480
ccacgggaag ccaaagtaca gtggaaggtg gataatgcgc tccagagcgg aaactcccaa	540
gagagcgtga cagaacagga ctcgaaggat tcgacgtact cactcagctc aacgctgacc	600
ctgtcgaaag cggactatga gaaacacaag gtctacgcgt gcgaggtgac ccatcagggc	660
ctgagctccc ccgtaactaa gtcattcaac cggggtgaat gctaa	705

<210> 9
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 9

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ile	Leu	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	Arg	Thr	Asn	Gly	Ser	Pro	Arg	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	Ile	Ala	Asp	Tyr	Tyr	Cys	Gln	Gln	His	Tyr	Thr	Thr	Pro	Pro
				85					90					95	

Thr	Phe	Gly	Ala	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

49JV_227262_W0_SEQ

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
210

<210> 10
<211> 214
<212> PRT
<213> Homo sapiens

<400> 10

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

49JV_227262_W0_SEQ

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
210

<210> 11
<211> 1440
<212> DNA
<213> Homo sapiens

<400> 11
tcactatagg ggaagcttgc cgccaccatg aaatgctcgt gggatgatctt tttccttatg 60
gcggtagtaa ccggaggtta ctccgaggtc cagctcgtcg aatccgggtg cggcttggtg 120
cagccgggtg ggtcgttgcg actgtcgtgc gcagcgtcgg ggtttaacat caaagacacc 180
tatatccact gggtaggca agcggccgga aaggggctcg aatgggtagc cagaatctac 240
cctacgaatg gttatactcg atatgaggac tccgtgaaag gaagattcac catcagcgca 300
gatacgtcca aaaacactgc atacctccag atgaatagcc ttcggggcgga ggacacggcg 360
gtctactact gtagccggtg gggtaggggac gggttctatg cgatggacta ctggggacag 420
gggacgcttg taacggctag ctcggctagc acaaagggac ctacgctgtt tcccttggtc 480
ccctcatcga aatcaacgtc cggtagggac gcggcattgg ggtgtcttgt caaggactat 540
ttccccgagc ccgtgacagt ctcgtggaac tcgggtgccc ttacaagcgg cgtacatacg 600
tttcccgcg tgctccaatc atccggactg tattcccttt catccgtcgt gactgtgccg 660
tcctcgtcac tcggaacgca aacttacatt tgcaatgtca accacaaacc gtcaaataca 720
aaggtcgata agaaggtcga gccaaagtcg tgtgataaga cccacacatg ccctccctgt 780
ccagcgccgg agctgttggg agggccttca gtgttctctt tcccgcccaa acccaaggac 840
accctgatga ttagccgcac acccgaggtg acgtgtgtcg tcgtcgatgt ctcacatgag 900
gacccggagg taaagttcaa ctggtacgtg gatggagtcg aagtgcacaa cgcaaaaaca 960
aaacctcggg aagagcagta caatagcacg tacagagtag tcagcgtgct caccgtgctg 1020
caccaggatt ggctcaatgg aaaggagtac aagtgtaaag tgtcgaataa ggcgctgcct 1080
gccccatcg aaaagacaat ttccaaagct aaagggaac cccgcgagcc gcaagtatac 1140
accctccac ctcgcgcga tgaactgacc aagaaccagg tgtcattgac gtgtctcgtc 1200
aagggcttct atccgagcga cattgcagta gaatgggaaa gcaacggaca gccggaaaac 1260
aactacaaga ctacaccgcc tgtccttgat tcggatgggt ccttctttct ttactcaaaa 1320
cttacagtcg acaaatcgag gtggcagcag ggaaatgtgt tttcgtgcag cgtgatgcac 1380
gaggccttgc ataactacta tacacagaag tcgttgtcac tgtcgccggg aaagtaatga 1440

49JV_227262_W0_SEQ

<210> 12
 <211> 477
 <212> PRT
 <213> Homo sapiens

<400> 12

Ser Leu Gly Lys Leu Ala Ala Thr Met Lys Cys Ser Trp Val Ile Phe
 1 5 10 15

Phe Leu Met Ala Val Val Thr Gly Val Asn Ser Glu Val Gln Leu Val
 20 25 30

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
 35 40 45

Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val
 50 55 60

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro
 65 70 75 80

Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
 85 90 95

Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser
 100 105 110

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly
 115 120 125

Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
 130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
 145 150 155 160

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
 165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
 180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
 195 200 205

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
 210 215 220

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
 225 230 235 240

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys

49JV_227262_W0_SEQ

245

250

255

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
260 265 270

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
275 280 285

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
290 295 300

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
305 310 315 320

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
325 330 335

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
340 345 350

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
355 360 365

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
370 375 380

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
385 390 395 400

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
405 410 415

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
420 425 430

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
435 440 445

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
450 455 460

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 13

<211> 730

<212> DNA

<213> Homo sapiens

<400> 13

ataggggaag cttgccgcca ccatggagac agacacgctt ttgctttggg tgttggtgtt 60

gtgggtcccc ggttcgaccg gtgatattca gatgaccag tcaccgtcat ccctttcggc 120

49JV_227262_W0_SEQ

gagcgtgggg gatagagtaa cgatcacgtg tagagcgtcc caagacgtca acacagctgt 180
 cgcgtggtat cagcagaagc caggaaaagc gccgaagctc ctgatctaca gcgcatcatt 240
 tctctattcg ggagtcccct cccgattttc cggatcgcg agcggtactg acttcaccct 300
 cacgatttcc tcccttcaac cggaagattt tgctacttac tactgtcagc agcactatac 360
 aacacctccc actttcggac aggggacaaa agtggagatt aagcggaccg tagcagcccc 420
 ctcggtcttt atcttccctc ctagcgacga acaattgaag tcagggaccg cctcggtggt 480
 atgcctgctt aacaactttt acccacggga agccaaagta cagtggaagg tggataatgc 540
 gctccagagc ggaaactccc aagagagcgt gacagaacag gactcgaagg attcgacgta 600
 ctcactcagc tcaacgctga ccctgtcgaa agcggactat gagaaacaca aggtctacgc 660
 gtgcgaggtg acccatcagg gcctgagctc ccccgtaact aagtcattca accggggtga 720
 atgctaata 730

<210> 14
 <211> 240
 <212> PRT
 <213> Homo sapiens

<400> 14

Gly Lys Leu Ala Ala Thr Met Glu Thr Asp Thr Leu Leu Leu Trp Val
 1 5 10 15

Leu Leu Leu Trp Val Pro Gly Ser Thr Gly Asp Ile Gln Met Thr Gln
 20 25 30

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
 35 40 45

Cys Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ala Trp Tyr Gln Gln
 50 55 60

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Phe Leu
 65 70 75 80

Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp
 85 90 95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
 100 105 110

Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr
 115 120 125

Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
 130 135 140

Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys

49JV_227262_W0_SEQ

145 150 155 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
165 170 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
180 185 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
195 200 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
210 215 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235 240

<210> 15
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> misc_feature
<223> Residue at position 2 is D-glutamine

<400> 15

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 16
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 16

Cys Gln Tyr Asp Leu Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 17
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> VARIANT
<222> (3)..(3)

<223> Xaa is beta-beta-di-phenyl-Ala

<400> 17

Cys Gln Xaa Asp Leu Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 18

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (5)..(5)

<223> Xaa is beta-beta-di-phenyl-Ala

<400> 18

Cys Gln Phe Asp Xaa Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 19

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (9)..(9)

<223> Xaa is citrulline

<400> 19

Cys Gln Phe Asp Phe Ser Thr Arg Xaa Leu Lys Cys
1 5 10

<210> 20

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 20

Cys Gln Phe Asp Phe Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 21

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 21

Cys Gln Phe Asp Glu Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 22

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 22

Cys Gln Phe Asp Tyr Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 23

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 23

Cys Gln Phe Asp Leu Ser Thr Arg Arg Gln Lys Cys
1 5 10

<210> 24

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 24

Cys Gln Phe Asp Leu Ser Thr Arg Gln Leu Lys Cys
1 5 10

<210> 25

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 25

Cys Gln Tyr Asn Leu Ser Thr Ala Arg Leu Lys Cys
1 5 10

<210> 26

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 26

Cys Gln Ala Asp Leu Ser Thr Arg Arg Leu Lys Cys
 1 5 10

<210> 27

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 27

Cys Gln Phe Asp Ala Ser Thr Arg Arg Leu Lys Cys
 1 5 10

<210> 28

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 28

Cys Gln Phe Asp Leu Ser Thr Ala Arg Leu Lys Cys
 1 5 10

<210> 29

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 29

Cys Gln Phe Asp Leu Ser Thr Arg Arg Ala Lys Cys
 1 5 10

<210> 30

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 30

Cys Gln Phe Asp Leu Ser Thr Arg Arg Glu Lys Cys
 1 5 10

<210> 31

<211> 17

49JV_227262_W0_SEQ

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Acetylation

<400> 31

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Gly Ser
1 5 10 15

Lys

<210> 32
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 32

Gly Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Gly
1 5 10

<210> 33
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 33

Gly Gln His Asp Leu Ser Thr Arg Arg Leu Lys Gly
1 5 10

<210> 34
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 34

Gly Gln Asn Asp Leu Ser Thr Arg Arg Leu Lys Gly
1 5 10

<210> 35
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
 <223> Synthetic polypeptide
 <400> 35

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

<210> 36
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> VARIANT
 <222> (3)..(3)
 <223> Xaa is 2-bromo-L-phenylalanine

<400> 36

Gly Gln Xaa Asp Leu Ser Thr Arg Arg Leu Lys Gly
 1 5 10

<210> 37
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> VARIANT
 <222> (3)..(3)
 <223> Xaa is 3-bromo-L-phenylalanine

<400> 37

Gly Gln Xaa Asp Leu Ser Thr Arg Arg Leu Lys Gly
 1 5 10

<210> 38
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> VARIANT
 <222> (3)..(3)
 <223> Xaa is 4-bromo-L-phenylalanine

<400> 38

Gly Gln Xaa Asp Leu Ser Thr Arg Arg Leu Lys Gly
 1 5 10

<210> 39
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> VARIANT
 <222> (9)..(9)
 <223> Xaa is citrulline

<400> 39

Gly Gln Phe Asp Leu Ser Thr Arg Xaa Leu Lys Gly
 1 5 10

<210> 40
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> VARIANT
 <222> (8)..(9)
 <223> Xaa is citrulline

<400> 40

Gly Gln Phe Asp Leu Ser Thr Xaa Xaa Leu Lys Gly
 1 5 10

<210> 41
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> VARIANT
 <222> (8)..(8)
 <223> Xaa is citrulline

<400> 41

Gly Gln Phe Asp Leu Ser Thr Xaa Arg Leu Lys Gly
 1 5 10

<210> 42
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (11)..(11)

<223> Xaa is 7-aminoheptanoic acid

<400> 42

Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
1 5 10

<210> 43

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (1)..(12)

<223> Xaa is is beta-alanine

<220>

<221> MOD_RES

<222> (12)..(12)

<223> bAla

<400> 43

Xaa Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
1 5 10

<210> 44

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> MOD_RES

<222> (1)..(1)

<223> Dpr

<220>

<221> VARIANT

<222> (12)..(12)

<223> Xaa is iso-aspartic acid

<400> 44

Xaa Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
1 5 10

<210> 45

<211> 12

<212> PRT

<213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> MOD_RES
 <222> (1)..(1)
 <223> bAla

<220>
 <221> VARIANT
 <222> (12)..(12)
 <223> Xaa is iso-aspartic acid

<400> 45

Xaa Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
 1 5 10

<210> 46
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> MOD_RES
 <222> (1)..(1)
 <223> Xaa is Dpr

<220>
 <221> MOD_RES
 <222> (12)..(12)
 <223> Xaa is bAla

<400> 46

Xaa Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
 1 5 10

<210> 47
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 47

Phe Asp Leu Ser Thr Arg Arg Leu Lys
 1 5

<210> 48
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 48

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys
 1 5 10

<210> 49

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (11)..(11)

<223> Xaa is 7-aminoheptanoic acid

<400> 49

Gln Tyr Asp Leu Ser Thr Arg Arg Leu Lys Xaa
 1 5 10

<210> 50

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (1)..(1)

<223> Xaa is beta-azidoalanine

<220>

<221> VARIANT

<222> (12)..(12)

<223> Xaa is propargylglycine

<400> 50

Xaa Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
 1 5 10

<210> 51

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (2)..(2)

<223> Xaa is beta-beta-di-phenyl-Ala

<220>

<221> VARIANT

<222> (11)..(11)

<223> Xaa is 7-aminoheptanoic acid

<400> 51

Gln Xaa Asp Leu Ser Thr Arg Arg Leu Lys Xaa
1 5 10

<210> 52

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> misc_feature

<223> Residue is D-glutamine

<220>

<221> VARIANT

<222> (11)..(11)

<223> Xaa is 7-aminoheptanoic acid

<400> 52

Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Xaa
1 5 10

<210> 53

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (2)..(4)

<223> Xaa is beta-beta-di-phenyl-Ala

<220>

<221> VARIANT

<222> (11)..(11)

<223> Xaa is 7-aminoheptanoic acid

<400> 53

Gln Xaa Asp Xaa Ser Thr Arg Arg Leu Lys Xaa
1 5 10

<210> 54

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> MOD_RES

49JV_227262_W0_SEQ

<222> (7)..(7)
<223> Xaa is n-butyl-arginine

<220>
<221> VARIANT
<222> (11)..(11)
<223> Xaa is 7-aminoheptanoic acid

<400> 54

Gln Phe Asp Leu Ser Thr Xaa Arg Leu Lys Xaa
1 5 10

<210> 55
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 55

Ser Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Ser
1 5 10

<210> 56
<211> 594
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 56
catcatcatc atcatcacag cagcggcctg gtgccgcgcg gcagccatat ggctagcatg 60
tcggactcag aagtcaatca agaagctaag ccagaggtca agccagaagt caagcctgag 120
actcacatca atttaaaggt gtccgatgga tcttcagaga tcttcttcaa gatcaaaaag 180
accactcctt taagaaggct gatggaagcg ttcgctaaaa gacagggtaa ggaaatggac 240
tccttaagat tcttgtacga cggtattaga attcaagctg atcagacccc tgaagatttg 300
gacatggagg ataacgatat tattgaggct cacagagaac agattggtgg atcctgccag 360
tttgatctga gcacccgccg tctgaaatgc ggtggcgggtg gatccgaagt taccatcaaa 420
gtcaacctga ttttcgcaga cggcaaaatc cagacggctg aatttaaagg cacgttcgaa 480
gaagctacgg cggaagcata tcgttacgcg gccctgctgg cgaaagtga cggcgaatac 540
acggcagacc tggaagacgg cggcaatcac atgaacatca aattcgctgg ctaa 594

<210> 57
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 57

49JV_227262_W0_SEQ

Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Ser
 1 5 10 15
 Arg Ser Gly Gly Thr Ser Gly Gly Gly Ser Val Pro Gly Ser Gly Ser
 20 25 30
 Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Ser Gly Gln
 35 40 45
 Ala Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
 50 55 60
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 65 70 75 80
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 85 90 95
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 100 105 110
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 115 120 125
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 130 135 140
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 145 150 155 160
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 165 170 175
 Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
 180 185 190
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 195 200 205
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 210 215 220
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 225 230 235 240
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
 245 250 255
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 260 265 270

49JV_227262_W0_SEQ

Pro Gly Lys
275

<210> 58
<211> 320
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> misc_feature
<223> tetravalent-meditope-Fc

<400> 58

Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Ser
1 5 10 15

Arg Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly Ser Gly Ser
20 25 30

Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Ser Gly Gln
35 40 45

Ala Ser Lys Gly Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
50 55 60

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
65 70 75 80

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
85 90 95

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
100 105 110

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
115 120 125

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
130 135 140

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
145 150 155 160

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
165 170 175

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
180 185 190

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala

195

200

205

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
 210 215 220

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
 225 230 235 240

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
 245 250 255

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
 260 265 270

Leu Ser Pro Gly Lys Gly Gly Ser Arg Ser Gly Gly Thr Ser Ser Ser
 275 280 285

Ser Ser Gly Ser Gly Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly
 290 295 300

Ser Ser Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly
 305 310 315 320

<210> 59

<211> 210

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 59

Gly Pro Gly Gly Ser Asp Pro Gly Cys Gln Phe Asp Leu Ser Thr Arg
 1 5 10 15

Arg Leu Arg Cys Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Thr Gly
 20 25 30

Ser Thr Ser Gly Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys
 35 40 45

Ser Ser Glu Gly Ser Gly Gln Ala Ser Lys Ala Lys Gly Gln Pro Arg
 50 55 60

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 65 70 75 80

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 85 90 95

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 100 105 110

49JV_227262_W0_SEQ

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
115 120 125

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
130 135 140

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
145 150 155 160

Leu Ser Leu Ser Pro Gly Lys Gly Gly Ser Arg Ser Gly Gly Thr Ser
165 170 175

Ser Ser Ser Ser Gly Ser Gly Ser Gly Ser Ser Gly Ser Thr Ser Gly
180 185 190

Ser Gly Ser Ser Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg
195 200 205

Cys Gly
210

<210> 60
<211> 726
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 60
aagcttgccg ccaccatgga gacagacacg cttttgcttt ggggtgttgtt gttgtgggtc 60
cccggttcga ccggtaccgg tgacatcttg ttgacgcagt ccccggtcat tctgagcgtg 120
tccccggag agcgggtatc gttttcctgc cgagcctcgc aagatatcaa cactgcgatt 180
gcatggtatc aacagcgcac aaacgggtcg ccgagactgc tcattctactc agcctcgttc 240
ctttatagcg gtgtgccttc gaggttctcg ggatcacggt caggaacgga ttttacactc 300
agcatcaatt ccgtggaatc agaggacatt gcggactact attgtcagca gcactacacc 360
acaccaccga ccttcggcgc tgggacgaaa gtcgaaatca agcggaccgt agcagcccc 420
tcggtcttta tcttcctcc tagcgacgaa caattgaagt cagggaccgc ctcggtggta 480
tgcttgctta acaactttta ccacgggaa gccaaagtac agtggaaggt ggataatgcg 540
ctccagagcg gaaactcca agagagcgtg acagaacagg actcgaagga ttcgacgtac 600
tcactcagct caacgtgac cctgtcgaaa gcggactatg agaaacacaa ggtctacgcg 660
tgcgaggtga cccatcaggg cctgagctcc cccgtaacta agtcattcaa ccgggggtgaa 720
tgctaa 726

<210> 61
<211> 241
<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 61

Lys Leu Ala Ala Thr Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu
 1 5 10 15

Leu Leu Trp Val Pro Gly Ser Thr Gly Thr Gly Asp Ile Leu Leu Thr
 20 25 30

Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly Glu Arg Val Ser Phe
 35 40 45

Ser Cys Arg Ala Ser Gln Asp Ile Asn Thr Ala Ile Ala Trp Tyr Gln
 50 55 60

Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile Tyr Ser Ala Ser Phe
 65 70 75 80

Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr
 85 90 95

Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser Glu Asp Ile Ala Asp
 100 105 110

Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Ala Gly
 115 120 125

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile
 130 135 140

Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val
 145 150 155 160

Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys
 165 170 175

Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu
 180 185 190

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu
 195 200 205

Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr
 210 215 220

His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu
 225 230 235 240

Cys

49JV_227262_W0_SEQ

<210> 62
 <211> 1425
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 62
 aagcttgccg ccaccatgaa atgctcgtgg gtgatctttt tccttatggc ggtagtaacc 60
 ggagttaact cccaagtaca gcttaagcag tcgggtccgg ggctgggtgca gccatcgag 120
 tcgttgtcaa tcacatgcac ggtgtcggga ttcaacatta aagacaccta tatccactgg 180
 gtccgacaat cccctggtaa agggctggag tggctcggtc ggatctaccc cacgaacgga 240
 tacaccaggt ataacacgcc ctttacatcg agactttcaa ttaacgcgga taatagcaag 300
 aatcaggtgt tcttcaagat gaatagcctc cagtcaaagtg aactgcaat ctactactgt 360
 gcccgtggg gaggggatgg cttttatgcg atggactatt gggggcaggg aactttggtc 420
 acagtaagct ccgctagcac aaaggacact agcgtgtttc ccttggtctc ctcacgaaa 480
 tcaacgtccg gtgggacggc ggcatggggg tgtcttgtca aggactatct ccccgagccc 540
 gtgacagtct cgtggaactc gggtgccctt acaagcggcg tacatacgtt tcccgccgtg 600
 ctccaatcat ccggactgta ttccctttca tccgtcgtga ctgtgccgtc ctcgtcactc 660
 ggaacgcaaa cttacatttg caatgtcaac cacaacacgt caaatacaaa ggtagataag 720
 aaggctcgagc caaagtcgtg tgataagacc cacacatgcc ctccctgtcc agcgccggag 780
 ctgttggggag ggccttcagt gttcctcttc ccgcccacac ccaaggacac cctgatgatt 840
 agccgcacac ccgaggtgac gtgtgtcgtc gtcgatgtct cacatgagga cccggaggta 900
 aagttcaact ggtacgtgga tggagtcgaa gtgcacaacg caaaaacaaa acctcgggaa 960
 gagcagtaca atagcacgta cagagtagtc agcgtgctca ccgtgctgca ccaggattgg 1020
 ctcaatggaa aggagtacaa gtgtaaagtg tcgaataagg cgctgcctgc ccccatcgaa 1080
 aagacaattt ccaaagctaa agggcaaccc cgcgagccgc aagtatacac cctcccaccc 1140
 tcgcgcgatg aactgacaa gaaccaggtg tcattgacgt gtctcgtcaa gggcttctat 1200
 ccgagcgaca ttgcagtaga atgggaaagc aacggacagc cggaaaacaa ctacaagact 1260
 acaccgcctg tccttgattc ggatggttcc ttctttcttt actcaaaact tacagtcgac 1320
 aaatcgaggt ggcagcaggg aaatgtgttt tcgtgcagcg tgatgcacga ggccttgcac 1380
 aatcactata cacagaagtc gttgtcactg tcgccgggaa agtaa 1425

<210> 63
 <211> 460
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

49JV_227262_W0_SEQ

<400> 63

Lys Leu Ala Ala Thr Met Lys Cys Ser Trp Val Ile Phe Phe Leu Met
1 5 10 15

Ala Val Val Thr Gly Val Asn Ser Gln Val Gln Leu Lys Gln Ser Gly
20 25 30

Pro Gly Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val
35 40 45

Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ser
50 55 60

Pro Gly Lys Gly Leu Glu Trp Leu Gly Arg Ile Tyr Pro Thr Asn Gly
65 70 75 80

Tyr Thr Arg Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Ala
85 90 95

Asp Asn Ser Lys Asn Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser
100 105 110

Asn Asp Thr Ala Ile Tyr Tyr Cys Ala Arg Trp Gly Gly Asp Gly Phe
115 120 125

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
145 150 155 160

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
165 170 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
180 185 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
195 200 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
210 215 220

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
225 230 235 240

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
245 250 255

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
Page 30

49JV_227262_W0_SEQ

260

265

270

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
275 280 285

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
290 295 300

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
305 310 315 320

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
325 330 335

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
340 345 350

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
355 360 365

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
370 375 380

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
385 390 395 400

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
405 410 415

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
420 425 430

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
435 440 445

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
450 455 460

<210> 64

<211> 167

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 64

Gly Pro Gly Gly Ser Asp Pro Gly Cys Gln Phe Asp Leu Ser Thr Arg
1 5 10 15

Arg Leu Arg Cys Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Thr Gly
20 25 30

49JV_227262_W0_SEQ

Ser Thr Ser Gly Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys
35 40 45

Ser Ser Glu Gly Ser Gly Gln Ala Ser Lys Ala Lys Gly Gln Pro Arg
50 55 60

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
65 70 75 80

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
85 90 95

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
100 105 110

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
115 120 125

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
130 135 140

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
145 150 155 160

Leu Ser Leu Ser Pro Gly Lys
165

<210> 65
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> misc_feature
<223> Moxetumomab light chain variable (VL) region sequence

<400> 65

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Ile Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

49JV_227262_W0_SEQ

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

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

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

<210> 66

<211> 476

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> misc_feature

<223> Moxetumomab heavy chain sequence

<400> 66

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

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile
20 25 30

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

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

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

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

Cys Ala Arg His Ser Gly Tyr Gly Thr His Trp Gly Val Leu Phe Ala
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Lys Ala Ser Gly
115 120 125

Gly Pro Glu Gly Gly Ser Leu Ala Ala Leu Thr Ala His Gln Ala Cys
130 135 140

His Leu Pro Leu Glu Thr Phe Thr Arg His Arg Gln Pro Arg Gly Trp
145 150 155 160

Glu Gln Leu Glu Gln Cys Gly Tyr Pro Val Gln Arg Leu Val Ala Leu

49JV_227262_W0_SEQ

165

170

175

Tyr Leu Ala Ala Arg Leu Ser Trp Asn Gln Val Asp Gln Val Ile Arg
 180 185 190

Asn Ala Leu Ala Ser Pro Gly Ser Gly Gly Asp Leu Gly Glu Ala Ile
 195 200 205

Arg Glu Gln Pro Glu Gln Ala Arg Leu Ala Leu Thr Leu Ala Ala Ala
 210 215 220

Glu Ser Glu Arg Phe Val Arg Gln Gly Thr Gly Asn Asp Glu Ala Gly
 225 230 235 240

Ala Ala Asn Gly Pro Ala Asp Ser Gly Asp Ala Leu Leu Glu Arg Asn
 245 250 255

Tyr Pro Thr Gly Ala Glu Phe Leu Gly Asp Gly Gly Asp Val Ser Phe
 260 265 270

Ser Thr Arg Gly Thr Gln Asn Trp Thr Val Glu Arg Leu Leu Gln Ala
 275 280 285

His Arg Gln Leu Glu Glu Arg Gly Tyr Val Phe Val Gly Tyr His Gly
 290 295 300

Thr Phe Leu Glu Ala Ala Gln Ser Ile Val Phe Gly Gly Val Arg Ala
 305 310 315 320

Arg Ser Gln Asp Leu Asp Ala Ile Trp Arg Gly Phe Tyr Ile Ala Gly
 325 330 335

Asp Pro Ala Leu Ala Tyr Gly Tyr Ala Gln Asp Gln Glu Pro Asp Ala
 340 345 350

Arg Gly Arg Ile Arg Asn Gly Ala Leu Leu Arg Val Tyr Val Pro Arg
 355 360 365

Ser Ser Leu Pro Gly Phe Tyr Arg Thr Ser Leu Thr Leu Ala Ala Pro
 370 375 380

Glu Ala Ala Gly Glu Val Glu Arg Leu Ile Gly His Pro Leu Pro Leu
 385 390 395 400

Arg Leu Asp Ala Ile Thr Gly Pro Glu Glu Glu Gly Gly Arg Leu Glu
 405 410 415

Thr Ile Leu Gly Trp Pro Leu Ala Glu Arg Thr Val Val Ile Pro Ser
 420 425 430

Ala Ile Pro Thr Asp Pro Arg Asn Val Gly Gly Asp Leu Asp Pro Ser

435 49JV_227262_W0_SEQ 440 445

Ser Ile Pro Asp Lys Glu Gln Ala Ile Ser Ala Leu Pro Asp Tyr Ala
450 455 460

Ser Gln Pro Gly Lys Pro Pro Arg Glu Asp Leu Lys
465 470 475

<210> 67
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> misc_feature
<223> Moxetumomab heavy chain variable (VH) region sequence

<400> 67

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

Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Ser Ile
20 25 30

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

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

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

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

Cys Ala Arg His Ser Gly Tyr Gly Thr His Trp Gly Val Leu Phe Ala
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
115 120

<210> 68
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 68

49JV_227262_W0_SEQ

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Ile Gln Leu Thr Gln Ser Pro Val Ile Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Glu Ser
35 40 45

Val Asp Ile Phe Gly Val Gly Phe Leu His Trp Tyr Gln Gln Lys Thr
50 55 60

Asn Gly Ser Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser
65 70 75 80

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Asp Tyr Tyr Cys
100 105 110

Gln Gln Thr Asn Glu Asp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val
115 120 125

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
130 135 140

Ser Asp Glu Gln Leu Lys Ser Gly Ala Ala Ser Val Val Cys Leu Leu
145 150 155 160

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
180 185 190

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 69

<211> 238

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

49JV_227262_W0_SEQ

<400> 69

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Glu Ser
35 40 45

Val Asp Ile Phe Gly Val Gly Phe Leu His Trp Tyr Gln Gln Lys Pro
50 55 60

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser
65 70 75 80

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
100 105 110

Gln Gln Thr Asn Glu Asp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val
115 120 125

Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
130 135 140

Ser Asp Glu Gln Leu Lys Ser Gly Ala Ala Ser Val Val Cys Leu Leu
145 150 155 160

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
180 185 190

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 70

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 70

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 Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Arg Ile Asp Pro Ala Asn Gly Asn Ser Lys 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
 Ala Pro Phe Gly Tyr Tyr Val Ser Asp Tyr Ala Met Ala Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu 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
 Asp Lys Thr His Thr 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

49JV_227262_W0_SEQ

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 Thr Cys Leu 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 Tyr 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 Lys
450

<210> 71
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 71

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

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
20 25 30

49JV_227262_W0_SEQ

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

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

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

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
85 90 95

Thr Phe Gly Ala 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 Ala
210

<210> 72
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 72

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

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

49JV_227262_W0_SEQ

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

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

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

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

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

Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

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

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
290 295 300

49JV_227262_W0_SEQ

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

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

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
355 360 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

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

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

<210> 73
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 73

Asp Ile Gln Met Thr Gln Ser Pro Ile Leu 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 Arg Thr Asn Gly Ser Pro Arg 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

49JV_227262_W0_SEQ

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

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro
115 120

<210> 74
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 74

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 Ser 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 Ile 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
115 120

<210> 75
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 75

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

49JV_227262_W0_SEQ

Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Glu Ser Val Asp Ile Phe
20 25 30

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

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

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

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

Glu Asp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

Thr Val

<210> 76
<211> 110
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide
<400> 76

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

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

Ile Ala Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg 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 Ser Ile Asn Ser Val Glu Ser
65 70 75 80

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

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val
100 105 110

49JV_227262_W0_SEQ

<210> 77
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 77

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

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

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

Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Asn Thr Pro Phe
 50 55 60

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

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

Ala 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
 115 120

<210> 78
 <211> 443
 <212> PRT
 <213> Mus musculus

<220>
 <221> VARIANT
 <222> (4)..(165)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (176)..(176)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (180)..(180)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (183)..(183)
 <223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (216)..(216)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (227)..(227)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (238)..(238)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (247)..(247)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (249)..(249)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (251)..(251)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (262)..(262)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (302)..(302)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (304)..(304)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (310)..(310)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (328)..(328)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (332)..(332)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (347)..(347)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (361)..(361)

49JV_227262_WO_SEQ

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (365)..(365)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (373)..(373)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (393)..(393)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (406)..(406)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (424)..(424)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (428)..(428)

<223> Xaa can be any naturally occurring amino acid

<220>

<221> misc_feature

<222> (437)..(437)

<223> Xaa can be any naturally occurring amino acid

<400> 78

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

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

Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Xaa Asp Trp Xaa
35 40 45

Gly Ala Xaa Tyr Pro Gly Asp Gly Asn Thr Arg Tyr Thr Gln Lys Phe
50 55 60

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

Met Gln Xaa Ser Ser Xaa Ala Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Glu Gly Asn Tyr Ala Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Xaa Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr

49JV_227262_W0_SEQ

115

120

125

Pro Xaa Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Xaa
 130 135 140

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

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

Gln Ser Asp Xaa Tyr Thr Xaa Ser Ser Ser Val Thr Val Pro Ser Ser
 180 185 190

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

Ser Thr Lys Val Asp Lys Lys Xaa Val Pro Arg Asp Cys Gly Cys Lys
 210 215 220

Pro Cys Xaa Cys Thr Val Pro Glu Val Ser Ser Val Phe Xaa Phe Pro
 225 230 235 240

Pro Lys Pro Lys Asp Val Xaa Thr Xaa Thr Xaa Thr Pro Lys Val Thr
 245 250 255

Cys Val Val Val Asp Xaa Ser Lys Asp Asp Pro Glu Val Gln Phe Ser
 260 265 270

Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg
 275 280 285

Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Xaa Pro Xaa
 290 295 300

Met His Gln Asp Trp Xaa Asn Gly Lys Glu Phe Lys Cys Arg Val Asn
 305 310 315 320

Ser Ala Ala Phe Pro Ala Pro Xaa Glu Lys Thr Xaa Ser Lys Thr Lys
 325 330 335

Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Xaa Pro Pro Pro Lys Glu
 340 345 350

Gln Met Ala Lys Asp Lys Val Ser Xaa Thr Cys Asn Xaa Thr Asp Phe
 355 360 365

Phe Pro Glu Asp Xaa Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala
 370 375 380

Glu Asn Tyr Lys Asn Thr Gln Pro Xaa Met Asp Thr Asp Gly Ser Tyr
 Page 48

49JV_227262_WO_SEQ															
385				390				395				400			
Phe	Val	Tyr	Ser	Lys 405	Xaa	Asn	Val	Gln	Lys 410	Ser	Asn	Trp	Glu	Ala 415	Gly
Asn	Thr	Phe	Thr 420	Cys	Ser	Val	Xaa	His 425	Glu	Gly	Xaa	His	Asn 430	His	His
Thr	Glu	Lys 435	Ser	Xaa	Ser	His	Ser 440	Pro	Gly	Lys					
<210>		79													
<211>		450													
<212>		PRT													
<213>		Artificial Sequence													
<220>															
<223>		Synthetic polypeptide													
<400>		79													
Glu 1	Val	Gln	Leu	Gln 5	Gln	Ser	Gly	Ala	Glu 10	Leu	Val	Lys	Pro	Gly 15	Ala
Ser	Val	Lys	Leu 20	Ser	Cys	Thr	Ala	Ser 25	Gly	Phe	Asn	Ile	Lys 30	Asp	Thr
Tyr	Val	His 35	Trp	Val	Lys	Gln	Arg 40	Pro	Glu	Gln	Gly	Leu 45	Glu	Trp	Ile
Gly	Arg 50	Ile	Asp	Pro	Ala	Asn 55	Gly	Tyr	Thr	Lys	Tyr 60	Asp	Pro	Lys	Phe
Gln 65	Gly	Lys	Ala	Thr	Ile 70	Thr	Ala	Asp	Thr	Ser 75	Ser	Asn	Thr	Ala	Tyr 80
Leu	Gln	Leu	Ser	Ser 85	Leu	Thr	Ser	Glu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Val	Arg	Pro	Leu 100	Tyr	Asp	Tyr	Tyr	Ala 105	Met	Asp	Tyr	Trp	Gly 110	Gln	Gly
Thr	Ser	Val 115	Thr	Val	Ser	Ser	Ala 120	Lys	Thr	Thr	Ala	Pro 125	Ser	Val	Tyr
Pro	Leu 130	Ala	Pro	Val	Cys	Gly 135	Asp	Thr	Thr	Gly	Ser 140	Ser	Val	Thr	Leu
Gly 145	Cys	Leu	Val	Lys	Gly 150	Tyr	Phe	Pro	Glu	Pro 155	Val	Thr	Leu	Thr	Trp 160
Asn	Ser	Gly	Ser	Leu 165	Ser	Ser	Gly	Val	His 170	Thr	Phe	Pro	Ala	Val 175	Leu

49JV_227262_W0_SEQ

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

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

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

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

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

49JV_227262_W0_SEQ

Gly Lys
450

<210> 80
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 80

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Pro Lys Ser Cys Asp

49JV_227262_W0_SEQ

210

215

220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

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

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 81
<211> 451
<212> PRT
<213> Homo sapiens

49JV_227262_W0_SEQ

<400> 81

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
 50 55 60
 Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
 100 105 110
 Gln Gly Thr Leu 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
 Asp Lys Thr His Thr 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

49JV_227262_W0_SEQ

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 Thr Cys Leu 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 Tyr 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 Lys
450

<210> 82
<211> 451
<212> PRT
<213> Homo sapiens

<400> 82

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Thr Phe Thr Asp Phe
20 25 30

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

49JV_227262_W0_SEQ

Gly Phe Ile Arg Asp Lys Ala Lys Gly Tyr Thr Thr Glu Tyr Asn Pro
 50 55 60
 Ser Val Lys Gly Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln
 65 70 75 80
 Phe Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Ala Arg Glu Gly His Thr Ala Ala Pro Phe Asp Tyr Trp Gly
 100 105 110
 Gln Gly Ser Leu 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
 Asp Lys Thr His Thr 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

49JV_227262_W0_SEQ

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 Thr Cys Leu 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 Tyr 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 Lys
450

<210> 83
<211> 442
<212> PRT
<213> Mus musculus

<400> 83

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

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

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

Gly Phe Ile Gly Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
50 55 60

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

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

49JV_227262_W0_SEQ

Tyr Cys Thr Arg₁₀₀ Asp Arg Gly Leu Arg₁₀₅ Phe Tyr Phe Asp Tyr₁₁₀ Trp Gly
 Gln Gly Thr₁₁₅ Thr Leu Thr Val Ser₁₂₀ Ser Ala Lys Thr Thr₁₂₅ Pro Pro Ser
 Val Tyr₁₃₀ Pro Leu Ala Pro Gly₁₃₅ Ser Ala Ala Gln Thr₁₄₀ Asn Ser Met Val
 Thr₁₄₅ Leu Gly Cys Leu Val₁₅₀ Lys Gly Tyr Phe Pro₁₅₅ Glu Pro Val Thr Val₁₆₀
 Thr Trp Asn Ser Gly₁₆₅ Ser Leu Ser Ser Gly₁₇₀ Val His Thr Phe Pro₁₇₅ Ala
 Val Leu Gln Ser₁₈₀ Asp Leu Tyr Thr Leu₁₈₅ Ser Ser Ser Val Thr₁₉₀ Val Pro
 Ser Ser Pro₁₉₅ Arg Pro Ser Glu Thr₂₀₀ Val Thr Cys Asn Val₂₀₅ Ala His Pro
 Ala Ser₂₁₀ Ser Thr Lys Val Asp₂₁₅ Lys Lys Ile Val Pro₂₂₀ Arg Asp Cys Pro
 Pro₂₂₅ Cys Lys Cys Pro Ala₂₃₀ Pro Asn Leu Leu Gly₂₃₅ Gly Pro Ser Val Phe₂₄₀
 Ile Phe Pro Pro Lys₂₄₅ Ile Lys Asp Val Leu₂₅₀ Met Ile Ser Leu Ser₂₅₅ Pro
 Ile Val Thr Cys₂₆₀ Val Val Val Asp Val₂₆₅ Ser Glu Asp Asp Pro₂₇₀ Asp Val
 Gln Ile Ser₂₇₅ Trp Phe Val Asn Asn₂₈₀ Val Glu Val His Thr₂₈₅ Ala Gln Thr
 Gln Thr₂₉₀ His Arg Glu Asp Tyr₂₉₅ Asn Ser Thr Leu Arg₃₀₀ Val Val Ser Ala
 Leu₃₀₅ Pro Ile Gln His Gln₃₁₀ Asp Trp Met Ser Gly₃₁₅ Lys Glu Phe Lys Cys₃₂₀
 Lys Val Asn Asn Lys₃₂₅ Asp Leu Pro Ala Pro₃₃₀ Ile Glu Arg Thr Ile₃₃₅ Ser
 Lys Pro Lys Gly₃₄₀ Ser Val Arg Ala Pro₃₄₅ Gln Val Tyr Val Leu₃₅₀ Pro Pro
 Pro Glu Glu₃₅₅ Glu Met Thr Lys Lys₃₆₀ Gln Val Thr Leu Thr₃₆₅ Cys Met Val

49JV_227262_W0_SEQ

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

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

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

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

Asn His His Thr Thr Lys Ser Phe Ser Arg
435 440

<210> 84
<211> 442
<212> PRT
<213> Mus musculus

<400> 84

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

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

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

Gly Phe Ile Gly Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala
50 55 60

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

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

Tyr Cys Thr Arg Asp Arg Gly Leu Arg Phe Tyr Phe Asp Tyr Trp Gly
100 105 110

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

Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
130 135 140

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

Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala

49JV_227262_W0_SEQ

165

170

175

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

Ser Ser Pro Arg Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
195 200 205

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Asn His His Thr Thr Lys Ser Phe Ser Arg

49JV_227262_W0_SEQ

435

440

<210> 85
 <211> 453
 <212> PRT
 <213> Homo sapiens

<400> 85

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

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

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

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

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

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

Ala Lys Tyr Pro His Tyr Tyr Gly Ser Ser His Trp Tyr Phe Asp Val
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
 130 135 140

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

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

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
 195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
 210 215 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
 225 230 235 240

49JV_227262_W0_SEQ

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 Glu Glu Met Thr Lys Asn Gln
355 360 365

Val Ser Leu Thr 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 Lys
450

<210> 86
<211> 448
<212> PRT
<213> Homo sapiens

<400> 86

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

49JV_227262_W0_SEQ

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

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

Ala Ile Ile Trp Tyr Asp Gly Asp Asn Gln Tyr Tyr Ala Asp Ser Val
50 55 60

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

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

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

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

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

49JV_227262_W0_SEQ

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

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

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 87
<211> 229
<212> PRT
<213> Homo sapiens

<400> 87

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

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

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

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

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

49JV_227262_W0_SEQ

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

Ala Arg Gly Tyr Arg Ser Tyr Ala Met 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 Asp Lys Thr
210 215 220

His Thr Cys Ala Ala
225

<210> 88
<211> 449
<212> PRT
<213> Homo sapiens

<400> 88

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

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

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

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

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

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys

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

Thr Leu Val Ile Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

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

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Ser Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Glu Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

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

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
Page 65

49JV_227262_W0_SEQ

355

360

365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

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

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415

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

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445

Lys

<210> 89
 <211> 446
 <212> PRT
 <213> Homo sapiens

<400> 89

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

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

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

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

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

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

Ala Arg Gly Gly Gly Val Phe Asp Tyr 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

49JV_227262_W0_SEQ

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 Thr His Thr
210 215 220

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

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

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

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

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

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

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

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

49JV_227262_W0_SEQ

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 90
<211> 448
<212> PRT
<213> Homo sapiens
<400> 90

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

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

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

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

Ala Lys Asp Pro Gly Thr Thr Val Ile Met Ser Trp Phe Asp Pro Trp
100 105 110

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

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

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
195 200 205

49JV_227262_W0_SEQ

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
210 215 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225 230 235 240

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

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

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
290 295 300

Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 91
<211> 448
<212> PRT
<213> Homo sapiens

<220>

49JV_227262_W0_SEQ

<221> VARIANT

<222> (1)..(1)

<223> Xaa can be any naturally occurring amino acid

<400> 91

Xaa 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 Ile Phe Ser Asn Tyr
20 25 30

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

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

Lys Asp 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 Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
100 105 110

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

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
130 135 140

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

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
210 215 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225 230 235 240

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

49JV_227262_W0_SEQ

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

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
325 330 335

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

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

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 92
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 92

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ser Phe Thr Gly His
20 25 30

49JV_227262_W0_SEQ

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

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

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

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

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

Gln Gly Thr Leu 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

Asp Lys Thr His Thr 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

49JV_227262_W0_SEQ

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 Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu 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 Tyr 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 Lys
450

<210> 93
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 93

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

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

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

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

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

49JV_227262_W0_SEQ

Met Glu Leu Ser Ser₈₅ Leu Arg Ser Glu Asp₉₀ Thr Ala Val Tyr Tyr₉₅ Cys

Ala Arg Gly Phe₁₀₀ Leu Pro Trp Phe Ala₁₀₅ Asp Trp Gly Gln Gly₁₁₀ Thr Leu

Val Thr Val₁₁₅ Ser Ser Ala Ser Thr₁₂₀ Lys Gly Pro Ser Val₁₂₅ Phe Pro Leu

Ala Pro₁₃₀ Ser Ser Lys Ser Thr₁₃₅ Ser Gly Gly Thr Ala₁₄₀ Ala Leu Gly Cys

Leu₁₄₅ Val Lys Asp Tyr Phe₁₅₀ Pro Glu Pro Val Thr₁₅₅ Val Ser Trp Asn Ser₁₆₀

Gly Ala Leu Thr Ser₁₆₅ Gly Val His Thr Phe₁₇₀ Pro Ala Val Leu Gln Ser₁₇₅

Ser Gly Leu Tyr₁₈₀ Ser Leu Ser Ser Val₁₈₅ Val Thr Val Pro Ser₁₉₀ Ser Ser

Leu Gly Thr₁₉₅ Gln Thr Tyr Ile Cys₂₀₀ Asn Val Asn His Lys₂₀₅ Pro Ser Asn

Thr Lys₂₁₀ Val Asp Lys Lys Val₂₁₅ Glu Pro Lys Ser Cys₂₂₀ Asp Lys Thr His

Thr₂₂₅ Cys Pro Pro Cys Pro₂₃₀ Ala Pro Glu Leu Leu₂₃₅ Gly Gly Pro Ser Val₂₄₀

Phe Leu Phe Pro Pro₂₄₅ Lys Pro Lys Asp Thr₂₅₀ Leu Met Ile Ser Arg₂₅₅ Thr

Pro Glu Val Thr₂₆₀ Cys Val Val Val Asp₂₆₅ Val Ser His Glu Asp₂₇₀ Pro Glu

Val Lys Phe₂₇₅ Asn Trp Tyr Val Asp₂₈₀ Gly Val Glu Val His₂₈₅ Asn Ala Lys

Thr Lys₂₉₀ Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr₃₀₀ Arg Val Val Ser

Val₃₀₅ Leu Thr Val Leu His₃₁₀ Gln Asp Trp Leu Asn₃₁₅ Gly Lys Glu Tyr Lys₃₂₀

Cys Lys Val Ser Asn₃₂₅ Lys Ala Leu Pro Ala₃₃₀ Pro Ile Glu Lys Thr₃₃₅ Ile

Ser Lys Ala Lys₃₄₀ Gly Gln Pro Arg Glu₃₄₅ Pro Gln Val Tyr Thr₃₅₀ Leu Pro

49JV_227262_W0_SEQ

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

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

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

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 94
<211> 449
<212> PRT
<213> Mus musculus

<400> 94

Asp Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Leu Gly Gly
1 5 10 15

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

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

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

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

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

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

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

49JV_227262_W0_SEQ

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160
 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175
 Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190
 Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205
 Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
 210 215 220
 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 225 230 235 240
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 260 265 270
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 290 295 300
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 325 330 335
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350
 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415

49JV_227262_W0_SEQ

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 95
<211> 443
<212> PRT
<213> Mus musculus

<400> 95

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

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

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

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

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

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

Ala Arg Val Val Tyr Tyr Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp
100 105 110

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

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

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

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

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

49JV_227262_W0_SEQ

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

His Asn His His Thr Thr Lys Ser Phe Ser Arg
435 440

<210> 96
<211> 443
<212> PRT
<213> Mus musculus

49JV_227262_W0_SEQ

<400> 96

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

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

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

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

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

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

Ala Arg Val Val Tyr Tyr Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp
100 105 110

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

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

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

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

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

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

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

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

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

Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp

49JV_227262_W0_SEQ

260

265

270

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

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

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

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

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

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

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

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

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

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

His Asn His His Thr Thr Lys Ser Phe Ser Arg
435 440

<210> 97
<211> 448
<212> PRT
<213> Homo sapiens

<400> 97

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

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

49JV_227262_W0_SEQ

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95
 Ala Arg Thr Gly Trp Leu Gly Pro 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 Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
 210 215 220
 His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
 225 230 235 240
 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 245 250 255
 Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
 260 265 270
 Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 275 280 285
 Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
 290 295 300
 Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320
 Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
 325 330 335

49JV_227262_W0_SEQ

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

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 98

<211> 399

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 98

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

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

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

Gly Val Ile Trp Ala Ser Gly Gly Thr Asp Tyr Asn Ser Ala Leu Met
50 55 60

Ser Arg Leu Ser Ile Ser Lys Asp Thr Ser Arg Asn Gln Val Val Leu
65 70 75 80

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Asp Pro Pro Ser Ser Leu Leu Arg Leu Asp Tyr Trp Gly Arg Gly
100 105 110

49JV_227262_W0_SEQ

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

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Asp Thr Leu Met Ile Ser Arg Thr
195 200 205

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
210 215 220

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
225 230 235 240

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
245 250 255

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
260 265 270

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
275 280 285

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
290 295 300

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
305 310 315 320

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
325 330 335

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
340 345 350

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
355 360 365

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
370 375 380

49JV_227262_W0_SEQ

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
385 390 395

<210> 99
<211> 450
<212> PRT
<213> Mus musculus

<400> 99

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

49JV_227262_W0_SEQ

225 230 235 240

Pro Ser Val Phe Leu₂₄₅ Phe Pro Pro Lys Pro₂₅₀ Lys Asp Thr Leu Met₂₅₅ Ile

Ser Arg Thr Pro₂₆₀ Glu Val Thr Cys Val₂₆₅ Val Val Asp Val Ser₂₇₀ His Glu

Asp Pro Glu₂₇₅ Val Lys Phe Asn Trp₂₈₀ Tyr Val Asp Gly Val₂₈₅ Glu Val His

Asn Ala₂₉₀ Lys Thr Lys Pro Arg₂₉₅ Glu Glu Gln Tyr Asn₃₀₀ Ser Thr Tyr Arg

Val Val Ser Val Leu Thr₃₁₀ Val Leu His Gln Asp₃₁₅ Trp Leu Asn Gly Lys₃₂₀

Glu Tyr Lys Cys Lys₃₂₅ Val Ser Asn Lys Ala₃₃₀ Leu Pro Ala Pro Ile₃₃₅ Glu

Lys Thr Ile Ser₃₄₀ Lys Ala Lys Gly Gln₃₄₅ Pro Arg Glu Pro Gln₃₅₀ Val Tyr

Thr Leu Pro₃₅₅ Pro Ser Arg Asp Glu₃₆₀ Leu Thr Lys Asn Gln₃₆₅ Val Ser Leu

Thr Cys₃₇₀ Leu Val Lys Gly Phe₃₇₅ Tyr Pro Ser Asp Ile₃₈₀ Ala Val Glu Trp

Glu Ser Asn Gly Gln Pro₃₉₀ Glu Asn Asn Tyr Lys₃₉₅ Thr Thr Pro Pro Val₄₀₀

Leu Asp Ser Asp Gly₄₀₅ Ser Phe Phe Leu Tyr₄₁₀ Ser Lys Leu Thr Val₄₁₅ Asp

Lys Ser Arg Trp₄₂₀ Gln Gln Gly Asn Val₄₂₅ Phe Ser Cys Ser Val₄₃₀ Met His

Glu Ala Leu₄₃₅ His Asn His Tyr Thr₄₄₀ Gln Lys Ser Leu Ser₄₄₅ Leu Ser Pro

Gly Lys₄₅₀

<210> 100
<211> 450
<212> PRT
<213> Mus musculus

<400> 100

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

49JV_227262_W0_SEQ

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp Tyr Trp Gly Gln Gly
100 105 110

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

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

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

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

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

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

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

49JV_227262_W0_SEQ

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

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

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
435 440 445

Gly Lys
450

<210> 101
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 101

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

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

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

49JV_227262_W0_SEQ

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

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

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

Ala Arg Glu Gly Tyr Tyr Gly Asn Tyr Gly Val Tyr Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser
130 135 140

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

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

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys
210 215 220

Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro Glu Phe Leu Gly Gly
225 230 235 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu
260 265 270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

49JV_227262_W0_SEQ

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu
325 330 335

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

Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu
355 360 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
370 375 380

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp
405 410 415

Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His
420 425 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu
435 440 445

Gly Lys
450

<210> 102

<211> 452

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 102

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

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

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

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

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

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

49JV_227262_W0_SEQ

Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130 135 140

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

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

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180 185 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195 200 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
210 215 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225 230 235 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
245 250 255

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

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
290 295 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
325 330 335

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

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

49JV_227262_W0_SEQ

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
370 375 380

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

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

<210> 103
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<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 Val Ser Gly Tyr Ser Ile Thr Ser Gly
20 25 30

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

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

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

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

Ala Arg Gly Ser His Tyr Phe Gly His Trp His Phe Ala Val Trp Gly
100 105 110

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

49JV_227262_W0_SEQ

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

Asp Lys Thr His Thr 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 Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu 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

49JV_227262_W0_SEQ

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr 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 Lys
450

<210> 104
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 104

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 105
<211> 435
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 105

49JV_227262_W0_SEQ

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Val Ser Ser Gly
20 25 30

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

Trp Ile Gly His Ile Tyr Tyr Ser Gly Asn Thr Asn Tyr Asn Pro Ser
50 55 60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Ile Tyr Tyr
85 90 95

Cys Val Arg Asp Arg Val Thr Gly Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Glu Arg Lys Cys Cys Val Glu Cys Pro Ala
210 215 220

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
225 230 235 240

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
245 250 255

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
260 265 270

49JV_227262_W0_SEQ

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
275 280 285

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
290 295 300

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
305 310 315 320

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
325 330 335

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
340 345 350

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
355 360 365

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
370 375 380

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
385 390 395 400

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
405 410 415

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
420 425 430

Pro Gly Lys
435

<210> 106
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 106

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

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

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

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

49JV_227262_W0_SEQ

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

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

Ala Lys Tyr Pro Tyr Tyr Tyr Gly Thr Ser His Trp Tyr Phe Asp Val
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
130 135 140

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

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

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
210 215 220

Ser Cys Asp Lys Thr His Leu
225 230

<210> 107
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 107

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

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

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

49JV_227262_W0_SEQ

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

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

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

Ala Arg Ser Thr Tyr Tyr Gly Gly Asp Trp Tyr Phe Asn Val Trp Gly
100 105 110

Ala Gly Thr Thr Val Thr Val Ser Ala 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

Asp Lys Thr His Thr 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

49JV_227262_W0_SEQ

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 Thr Cys Leu 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 Tyr 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 Lys
450

<210> 108
<211> 432
<212> PRT
<213> Mus musculus

<400> 108

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

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

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

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

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

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

Lys Arg Ser Tyr Tyr Gly His Trp Gly Gln Gly Thr Thr Leu Thr Val
Page 98

49JV_227262_W0_SEQ

100

105

110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
 115 120 125

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
 130 135 140

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

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

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

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
 195 200 205

Asp Lys Arg Val Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu
 210 215 220

Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu
 225 230 235 240

Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser
 245 250 255

Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu
 260 265 270

Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr
 275 280 285

Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser
 290 295 300

Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro
 305 310 315 320

Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln
 325 330 335

Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val
 340 345 350

Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val
 355 360 365

Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu

49JV_227262_W0_SEQ

370

375

380

Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg
 385 390 395 400

Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val
 405 410 415

Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg
 420 425 430

<210> 109
 <211> 432
 <212> PRT
 <213> Mus musculus

<400> 109

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

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

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

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

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

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

Lys Arg Ser Tyr Tyr Gly His Trp Gly Gln Gly Thr Thr Leu Thr Val
 100 105 110

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys
 115 120 125

Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys
 130 135 140

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

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

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

49JV_227262_W0_SEQ

Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val
195 200 205

Asp Lys Arg Val Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu
210 215 220

Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu
225 230 235 240

Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser
245 250 255

Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu
260 265 270

Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr
275 280 285

Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser
290 295 300

Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro
305 310 315 320

Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln
325 330 335

Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val
340 345 350

Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val
355 360 365

Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu
370 375 380

Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg
385 390 395 400

Val Glu Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val
405 410 415

Val His Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg
420 425 430

<210> 110
<211> 448
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> VARIANT

<222> (1)..(1)

<223> Xaa can be any naturally occurring amino acid

<400> 110

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Ser Asp
20 25 30

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

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

Lys Ser Arg Val Thr Met Leu Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

49JV_227262_W0_SEQ

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

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

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

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

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

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 111
<211> 447
<212> PRT
<213> Mus musculus

<400> 111

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

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

49JV_227262_W0_SEQ

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

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

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

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

 Ala Arg Val Val Tyr Tyr Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp
 100 105 110

 Gly Thr Gly Thr Thr Val Thr Val Ser Gly Pro Ser Val Phe Pro Leu
 115 120 125

 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140

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

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

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

 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205

 Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
 210 215 220

 Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
 225 230 235 240

 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 245 250 255

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

 Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 275 280 285

 Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 290 295 300

49JV_227262_W0_SEQ

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

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

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

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

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

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

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 112
<211> 447
<212> PRT
<213> Mus musculus

<400> 112

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

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

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

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

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

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

49JV_227262_W0_SEQ

Ala Arg Val Val Tyr Tyr Ser Asn Ser Tyr Trp Tyr Phe Asp Val Trp
100 105 110

Gly Thr Gly Thr Thr Val Thr Val Ser Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

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

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

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

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Ala Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

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

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

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

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

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

49JV_227262_W0_SEQ

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

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

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

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 113

<211> 451

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 113

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

49JV_227262_W0_SEQ

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 Pro Lys Ser Cys
 210 215 220
 Asp Lys Thr His Thr 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 Thr Cys Leu 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 Tyr 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

49JV_227262_W0_SEQ

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly Lys
450

<210> 114
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 114

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

Ser Leu Arg Leu Ser Cys Ala 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

49JV_227262_W0_SEQ

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 Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr 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 Thr Cys Leu 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 Tyr 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 Lys
450

49JV_227262_W0_SEQ

<210> 115
 <211> 449
 <212> PRT
 <213> Homo sapiens

<400> 115

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Thr Tyr
 20 25 30

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

Gly Ile Met Ser Pro Val Asp Ser Asp Ile Arg Tyr Ser Pro Ser Phe
 50 55 60

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

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

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

Thr Leu Val Thr Val Ser Ser Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
 210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 Page 111

49JV_227262_W0_SEQ

245

250

255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

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

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

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

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> 116
<211> 455
<212> PRT
<213> Homo sapiens

<400> 116

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

49JV_227262_W0_SEQ

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ala Val Ile Trp Asp Asp Gly Ser Tyr Lys Tyr Tyr Gly Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Asp Gly Ile Thr Met Val Arg Gly Val Met Lys Asp Tyr Phe
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
 115 120 125
 Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 130 135 140
 Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 145 150 155 160
 Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 165 170 175
 Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 180 185 190
 Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 195 200 205
 Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
 210 215 220
 Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 225 230 235 240
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 245 250 255
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 260 265 270
 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 275 280 285
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 290 295 300

49JV_227262_W0_SEQ

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
325 330 335

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

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

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 117
<211> 448
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 117

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ile Ser Tyr
20 25 30

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

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

49JV_227262_W0_SEQ

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

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

Arg Leu Asp Gly Tyr Tyr Phe Gly Phe Ala 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 Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser
225 230 235 240

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

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

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

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

49JV_227262_W0_SEQ

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

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

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 118

<211> 448

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 118

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

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

49JV_227262_W0_SEQ

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

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

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

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

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

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

49JV_227262_W0_SEQ

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 119

<211> 447

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 119

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Gly Gly
20 25 30

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

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

Lys Asp Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

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

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

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

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

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

49JV_227262_W0_SEQ

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

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
210 215 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225 230 235 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
245 250 255

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

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
275 280 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
290 295 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305 310 315 320

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

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

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

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

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

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

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

49JV_227262_W0_SEQ

<210> 120
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 120

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

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser
115

<210> 121
<211> 447
<212> PRT
<213> Homo sapiens

<400> 121

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 Val Ser Gly Tyr Thr Leu Thr Glu Leu
20 25 30

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

Gly Gly Phe Asp Pro Glu Glu Asn Glu Ile Val Tyr Ala Gln Arg Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

49JV_227262_W0_SEQ

Met Glu Leu Ser Ser₈₅ Leu Arg Ser Glu Asp₉₀ Thr Ala Val Tyr Tyr₉₅ Cys

Ala Ile Val Gly₁₀₀ Ser Phe Ser Pro Leu₁₀₅ Thr Leu Gly Leu Trp₁₁₀ Gly Gln

Gly Thr Met₁₁₅ Val Thr Val Ser Ser₁₂₀ Ala Ser Thr Lys Gly₁₂₅ Pro Ser Val

Phe Pro₁₃₀ Leu Ala Pro Cys Ser₁₃₅ Arg Ser Thr Ser Glu₁₄₀ Ser Thr Ala Ala

Leu Gly Cys Leu Val Lys₁₅₀ Asp Tyr Phe Pro Glu₁₅₅ Pro Val Thr Val Ser₁₆₀

Trp Asn Ser Gly Ala₁₆₅ Leu Thr Ser Gly Val₁₇₀ His Thr Phe Pro Ala Val₁₇₅

Leu Gln Ser Ser₁₈₀ Gly Leu Tyr Ser Leu₁₈₅ Ser Ser Val Val Thr₁₉₀ Val Pro

Ser Ser Ser₁₉₅ Leu Gly Thr Lys Thr₂₀₀ Tyr Thr Cys Asn Val₂₀₅ Asp His Lys

Pro Ser₂₁₀ Asn Thr Lys Val Asp₂₁₅ Lys Arg Val Glu Ser₂₂₀ Lys Tyr Gly Pro

Pro Cys Pro Ser Cys Pro₂₃₀ Ala Pro Glu Phe Leu₂₃₅ Gly Gly Pro Ser Val₂₄₀

Phe Leu Phe Pro Pro₂₄₅ Lys Pro Lys Asp Thr₂₅₀ Leu Met Ile Ser Arg₂₅₅ Thr

Pro Glu Val Thr₂₆₀ Cys Val Val Val Asp₂₆₅ Val Ser Gln Glu Asp₂₇₀ Pro Glu

Val Gln Phe Asn Trp Tyr Val Asp₂₈₀ Gly Val Glu Val His₂₈₅ Asn Ala Lys

Thr Lys₂₉₀ Pro Arg Glu Glu Gln₂₉₅ Phe Asn Ser Thr Tyr₃₀₀ Arg Val Val Ser

Val Leu Thr Val Leu His₃₁₀ Gln Asp Trp Leu Asn₃₁₅ Gly Lys Glu Tyr Lys₃₂₀

Cys Lys Val Ser Asn₃₂₅ Lys Gly Leu Pro Ser₃₃₀ Ser Ile Glu Lys Thr₃₃₅ Ile

Ser Lys Ala Lys₃₄₀ Gly Gln Pro Arg Glu₃₄₅ Pro Gln Val Tyr Thr₃₅₀ Leu Pro

49JV_227262_W0_SEQ

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

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

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

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

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
435 440 445

<210> 122
<211> 451
<212> PRT
<213> Homo sapiens

<400> 122

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Asp Pro Arg Gly Ala Thr Leu Tyr Tyr Tyr Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
115 120 125

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
130 135 140

49JV_227262_W0_SEQ

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 145 150 155 160
 Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 165 170 175
 Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 180 185 190
 Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
 195 200 205
 Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
 210 215 220
 Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
 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 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 275 280 285
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
 290 295 300
 Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
 305 310 315 320
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
 325 330 335
 Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
 340 345 350
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 355 360 365
 Leu Thr Cys Leu 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
 Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 405 410 415

49JV_227262_W0_SEQ

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 Lys
450

<210> 123
<211> 448
<212> PRT
<213> Homo sapiens

<400> 123

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

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

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

Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu
50 55 60

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

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

Arg Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser 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 Lys Thr Tyr Thr Cys Asn Val Asp His
Page 124

49JV_227262_W0_SEQ

195

200

205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
 210 215 220
 Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
 225 230 235 240
 Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
 245 250 255
 Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
 260 265 270
 Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
 275 280 285
 Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
 290 295 300
 Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
 305 310 315 320
 Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
 325 330 335
 Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
 340 345 350
 Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
 355 360 365
 Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
 370 375 380
 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
 385 390 395 400
 Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
 405 410 415
 Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
 420 425 430
 Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
 435 440 445

<210> 124
 <211> 451
 <212> PRT
 <213> Homo sapiens

49JV_227262_W0_SEQ

<400> 124

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

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

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asp Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Val Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Val Ser Ile Phe Gly Val Gly Thr Phe Asp Tyr Trp Gly
100 105 110

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

Val Leu 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 Arg Val Glu Pro Lys Ser Cys
210 215 220

Asp Lys Thr His Thr 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

49JV_227262_W0_SEQ

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 Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu 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 Tyr 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 Lys
450

<210> 125
<211> 214
<212> PRT
<213> Mus musculus

<220>
<221> VARIANT
<222> (21)..(117)
<223> Xaa is isoleucine or leucine

<220>
<221> misc_feature
<222> (125)..(125)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature

49JV_227262_W0_SEQ

<222> (136)..(136)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (144)..(144)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (150)..(150)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (160)..(160)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (179)..(179)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (181)..(181)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (205)..(205)
<223> Xaa can be any naturally occurring amino acid

<400> 125

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

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

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

Tyr Asn Ala Lys Thr Xaa Ala Gly Gly Val Ser Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr His Phe Ser Xaa Lys Xaa Lys Ser Xaa Gln Pro
65 70 75 80

Glu Asp Phe Gly Xaa Tyr Tyr Cys Gln His His Tyr Gly Xaa Phe Pro
85 90 95

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

Pro Thr Val Ser Xaa Phe Pro Pro Ser Ser Glu Gln Xaa Thr Ser Gly
115 120 125

Gly Ala Ser Val Val Cys Phe Xaa Asn Asn Phe Tyr Pro Lys Asp Xaa
Page 128

49JV_227262_W0_SEQ

130

135

140

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

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

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

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

Phe Asn Arg Asn Glu Cys
210

<210> 126

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 126

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

Asp Thr Val Ser Ile Thr Cys His Ala Ser Gln Gly Ile Ser Ser Asn
20 25 30

Ile Gly Trp Leu Gln Gln Lys Pro Gly Lys Ser Phe Met Gly Leu Ile
35 40 45

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

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

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

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

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

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

49JV_227262_W0_SEQ

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

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

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

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

Phe Asn Arg Asn Glu Cys
210

<210> 127

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 127

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

Asp Thr Val Ser Ile Thr Cys His Ala Ser Gln Gly Ile Ser Ser Asn
20 25 30

Ile Gly Trp Leu Gln Gln Lys Pro Gly Lys Ser Phe Met Gly Leu Ile
35 40 45

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

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

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

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

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

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

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
Page 130

49JV_227262_W0_SEQ

145 150 155 160

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

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

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

Phe Asn Arg Asn Glu Cys
210

<210> 128
<211> 214
<212> PRT
<213> Homo sapiens

<400> 128

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 Gly Ile Arg Asn Tyr
20 25 30

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

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

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

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr
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

49JV_227262_W0_SEQ

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
210

<210> 129

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 129

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

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

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

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

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

Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln His Ile Ser Arg Pro Arg
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

49JV_227262_W0_SEQ

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
210

<210> 130
<211> 213
<212> PRT
<213> Mus musculus

<400> 130

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Thr Tyr Ile
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Ser Trp Ile Tyr
35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln His Trp Ser Ser Lys Pro Pro Thr
85 90 95

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

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

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

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

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

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

Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe
Page 133

195

200

205

Asn Arg Asn Glu Cys
210

<210> 131
<211> 213
<212> PRT
<213> Mus musculus

<400> 131

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Thr Tyr Ile
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Ser Trp Ile Tyr
35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln His Trp Ser Ser Lys Pro Pro Thr
85 90 95

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

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

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

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

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

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

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

Asn Arg Asn Glu Cys
210

49JV_227262_W0_SEQ

<210> 132
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 132

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 Ser Ala Ser Gln Asp Ile Ser Asn Tyr
 20 25 30

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Val Pro Trp
 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
 210

49JV_227262_W0_SEQ

<210> 133
 <211> 394
 <212> PRT
 <213> Homo sapiens

<400> 133

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

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

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

Ala Ile Ile Trp Tyr Asp Gly Asp Asn Gln Tyr Tyr Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Leu Arg Thr Gly Pro 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 Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser
 180 185 190

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

Ile Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro
 210 215 220

Lys Leu Leu Ile Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser
 225 230 235 240

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
 Page 136

49JV_227262_W0_SEQ

245

250

255

Ser Leu Glu Ala Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser
 260 265 270

Ser Leu Pro Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
 275 280 285

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 290 295 300

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 305 310 315 320

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
 325 330 335

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
 340 345 350

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 355 360 365

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 370 375 380

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 385 390

<210> 134
 <211> 214
 <212> PRT
 <213> Homo sapiens

<400> 134

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

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

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

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

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

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

49JV_227262_W0_SEQ

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
210

<210> 135
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 135

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

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
20 25 30

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

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

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

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
85 90 95

49JV_227262_W0_SEQ

Thr Phe Gly Ala 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 Ala
210

<210> 136
<211> 215
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 136

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Ser
20 25 30

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

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

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

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

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

49JV_227262_W0_SEQ

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

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

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Pro Arg Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 137
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 137

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

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

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

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

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

Asp Phe Ala Thr Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg Thr Val Ala Ala Pro
100 105 110

49JV_227262_W0_SEQ

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 138
<211> 215
<212> PRT
<213> Homo sapiens

<400> 138

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 Arg Gly Arg
20 25 30

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

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

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

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

Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
Page 141

49JV_227262_W0_SEQ

130

135

140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 139

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 139

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 Gly Ala Ser Glu Asn Ile Tyr Gly Ala
20 25 30

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Val Leu Asn Thr Pro Leu
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

49JV_227262_W0_SEQ

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
210

<210> 140
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 140

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 Lys Thr Ile Ser Lys Tyr
20 25 30

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Asn Glu Tyr Pro Leu
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
Page 143

145 150 155 160

Phe Asn Arg Gly Glu Cys
210

<210>	141
<211>	214
<212>	PRT
<213>	Homo sapiens

<400> 141

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

49JV_227262_W0_SEQ

Ser Thr Leu Thr 180 Leu Ser Lys Ala Asp 185 Tyr Glu Lys His Lys 190 Val Tyr

Ala Cys Glu 195 Val Thr His Gln 200 Gly Leu Ser Ser Pro 205 Val Thr Lys Ser

Phe Asn Arg Gly Glu Cys 210

<210> 142

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 142

Asp Ile Val Met Thr 5 Gln Ser Gln Arg Phe 10 Met Ser Thr Thr 15 Val Gly

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

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

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

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

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

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

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

Thr Ala 130 Ser Val Val Cys 135 Leu Leu Asn Asn Phe Tyr 140 Pro Arg Glu Ala

Lys Val Gln Trp 145 Lys Val 150 Asp Asn Ala Leu 155 Gln Ser Gly Asn Ser 160 Gln

Glu Ser Val Thr 165 Glu Gln Asp Ser Lys 170 Asp Ser Thr Tyr Ser 175 Leu Ser

49JV_227262_W0_SEQ

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
210

<210> 143
<211> 209
<212> PRT
<213> Mus musculus

<400> 143

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
85 90 95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
Page 146

195 49JV_227262_W0_SEQ 200 205

Asn

<210> 144
 <211> 209
 <212> PRT
 <213> Mus musculus

<400> 144

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
 35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
 65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
 85 90 95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
 130 135 140

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 195 200 205

Asn

49JV_227262_W0_SEQ

<210> 145
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 145

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 Gly Ser Ser
 20 25 30

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

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

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

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

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
 100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205

Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 146
 <211> 220
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 146

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
 20 25 30

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

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

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

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

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

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

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

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 145 150 155 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 210 215 220

<210> 147

<211> 213

<212> PRT

<213> Mus musculus

49JV_227262_W0_SEQ

<400> 147

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

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

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

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
85 90 95

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

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

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

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

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

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

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

Asn Arg Asn Glu Cys
210

<210> 148

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 148

49JV_227262_W0_SEQ

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

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

Met Ala Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro Arg Leu Leu Ile
35 40 45

His Tyr Thr Ser Ala Leu Gln Pro Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 149
<211> 214
<212> PRT
<213> Homo sapiens

<400> 149

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
Page 151

49JV_227262_W0_SEQ

20

25

30

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

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

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

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

Thr Phe Gly Gln Gly Thr Arg Leu 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
210

<210> 150
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 150

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

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

49JV_227262_W0_SEQ

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

Lys Leu Leu Ile Tyr Ala Ala Ser Tyr Leu Glu Ser Gly Val Pro Ser
50 55 60

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

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

Glu Asp Pro Tyr Thr Phe Gly Gln 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
210 215

<210> 151
<211> 214
<212> PRT
<213> Homo sapiens

<400> 151

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

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

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

49JV_227262_W0_SEQ

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

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

Glu Asp Ile Ala Thr Tyr Phe Cys Gln His Phe Asp His Leu Pro Leu
85 90 95

Ala Phe Gly Gly 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
210

<210> 152
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 152

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

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

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

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

49JV_227262_W0_SEQ

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Thr Val Pro Trp
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
210

<210> 153
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 153

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Ile
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

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

49JV_227262_W0_SEQ

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Thr Ser Asn Pro Pro Thr
85 90 95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 154
<211> 210
<212> PRT
<213> Mus musculus

<400> 154

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

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

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

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

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

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Tyr
Page 156

49JV_227262_W0_SEQ

85

90

95

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

Pro Thr 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
 210

<210> 155
 <211> 210
 <212> PRT
 <213> Mus musculus

<400> 155

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

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

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

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

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

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Tyr
 85 90 95

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

49JV_227262_W0_SEQ

Pro Thr 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
210

<210> 156
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 156

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

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

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

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

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

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

49JV_227262_W0_SEQ

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
210

<210> 157
<211> 210
<212> PRT
<213> Mus musculus

<400> 157

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
85 90 95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
Page 159

49JV_227262_W0_SEQ

130

135

140

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

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
 165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
 180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
 195 200 205

Asn Arg
 210

<210> 158
 <211> 210
 <212> PRT
 <213> Mus musculus

<400> 158

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Val Ser Tyr Met
 20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
 35 40 45

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

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Val Glu Ala Glu
 65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Phe Asn Pro Pro Thr
 85 90 95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
 130 135 140

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

49JV_227262_W0_SEQ

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg
210

<210> 159
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 159

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

Asp Arg Val Thr Ile Thr Cys 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

49JV_227262_W0_SEQ

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
210

<210> 160

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 160

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

49JV_227262_W0_SEQ

Ser Thr Leu Thr 180 Leu Ser Lys Ala Asp 185 Tyr Glu Lys His Lys 190 Val Tyr

Ala Cys Glu 195 Val Thr His Gln Gly 200 Leu Ser Ser Pro Val 205 Thr Lys Ser

Phe Asn Arg Gly Glu Cys
210

<210> 161
<211> 214
<212> PRT
<213> Homo sapiens

<400> 161

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

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

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

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

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

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

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

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

Thr Ala 130 Ser Val Val Cys Leu 135 Leu Asn Asn Phe Tyr 140 Pro Arg Glu Ala

Lys Val 145 Gln Trp Lys Val 150 Asp Asn Ala Leu Gln 155 Ser Gly Asn Ser Gln 160

Glu Ser Val Thr 165 Glu Gln Asp Ser Lys Asp 170 Ser Thr Tyr Ser Leu 175 Ser

Ser Thr Leu Thr 180 Leu Ser Lys Ala Asp 185 Tyr Glu Lys His Lys 190 Val Tyr

49JV_227262_W0_SEQ

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
210

<210> 162
<211> 214
<212> PRT
<213> Homo sapiens
<400> 162

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

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

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

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

Ser Glu 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 Phe Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly 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

49JV_227262_W0_SEQ

Phe Asn Arg Gly Glu Cys
210

<210> 163
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 163

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

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

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

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

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

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

Glu Asp Pro Trp 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
210 215

49JV_227262_W0_SEQ

<210> 164
 <211> 219
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 164

Asp Val 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 Lys Ser Ser Gln Ser Leu Leu Asp Ser
 20 25 30

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

Pro Gln Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp 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 Trp Gln Gly
 85 90 95

Thr His Phe Pro Arg Thr Phe Gly Gln 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
 210 215

49JV_227262_W0_SEQ

<210> 165
 <211> 219
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 165

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 Ile Val His Ser
 20 25 30

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

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Tyr 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 Gly
 85 90 95

Ser His Val Pro Trp Thr Phe Gly Gln 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
 210 215

<210> 166
 <211> 111

49JV_227262_W0_SEQ

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 166

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

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

Gly Ile Ser Phe Met Lys Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val 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

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

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 167
<211> 217
<212> PRT
<213> Homo sapiens

<400> 167

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

Arg Val Thr Ile Ser Cys Thr Gly Ser Gly Ser Asn Ile Gly Ala Pro
20 25 30

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

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

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Val Glu Ala Gly
85 90 95

Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
Page 168

49JV_227262_W0_SEQ

100

105

110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145 150 155 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
165 170 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 168
<211> 214
<212> PRT
<213> Homo sapiens

<400> 168

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 Ser Ile Asn Ser Tyr
20 25 30

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

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

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

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

Thr Phe Gly Pro 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

49JV_227262_W0_SEQ

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
210

<210> 169
<211> 216
<212> PRT
<213> Homo sapiens

<400> 169

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

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

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
115 120 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

49JV_227262_W0_SEQ

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

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
165 170 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
180 185 190

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 170
<211> 214
<212> PRT
<213> Homo sapiens

<400> 170

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Ala 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

49JV_227262_W0_SEQ

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
210

<210> 171
<211> 221
<212> PRT
<213> Homo sapiens
<400> 171

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

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

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

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

Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe
65 70 75 80

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

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

Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

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

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

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
Page 172

49JV_227262_W0_SEQ

180

185

190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
 210 215 220

<210> 172
 <211> 321
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CD23 protein sequence

<400> 172

Met Glu Glu Gly Gln Tyr Ser Glu Ile Glu Glu Leu Pro Arg Arg Arg
 1 5 10 15

Cys Cys Arg Arg Gly Thr Gln Ile Val Leu Leu Gly Leu Val Thr Ala
 20 25 30

Ala Leu Trp Ala Gly Leu Leu Thr Leu Leu Leu Leu Trp His Trp Asp
 35 40 45

Thr Thr Gln Ser Leu Lys Gln Leu Glu Glu Arg Ala Ala Arg Asn Val
 50 55 60

Ser Gln Val Ser Lys Asn Leu Glu Ser His His Gly Asp Gln Met Ala
 65 70 75 80

Gln Lys Ser Gln Ser Thr Gln Ile Ser Gln Glu Leu Glu Glu Leu Arg
 85 90 95

Ala Glu Gln Gln Arg Leu Lys Ser Gln Asp Leu Glu Leu Ser Trp Asn
 100 105 110

Leu Asn Gly Leu Gln Ala Asp Leu Ser Ser Phe Lys Ser Gln Glu Leu
 115 120 125

Asn Glu Arg Asn Glu Ala Ser Asp Leu Leu Glu Arg Leu Arg Glu Glu
 130 135 140

Val Thr Lys Leu Arg Met Glu Leu Gln Val Ser Ser Gly Phe Val Cys
 145 150 155 160

Asn Thr Cys Pro Glu Lys Trp Ile Asn Phe Gln Arg Lys Cys Tyr Tyr
 165 170 175

Phe Gly Lys Gly Thr Lys Gln Trp Val His Ala Arg Tyr Ala Cys Asp
 Page 173

49JV_227262_W0_SEQ

180

185

190

Asp Met Glu Gly Gln Leu Val Ser Ile His Ser Pro Glu Glu Gln Asp
195 200 205

Phe Leu Thr Lys His Ala Ser His Thr Gly Ser Trp Ile Gly Leu Arg
210 215 220

Asn Leu Asp Leu Lys Gly Glu Phe Ile Trp Val Asp Gly Ser His Val
225 230 235 240

Asp Tyr Ser Asn Trp Ala Pro Gly Glu Pro Thr Ser Arg Ser Gln Gly
245 250 255

Glu Asp Cys Val Met Met Arg Gly Ser Gly Arg Trp Asn Asp Ala Phe
260 265 270

Cys Asp Arg Lys Leu Gly Ala Trp Val Cys Asp Arg Leu Ala Thr Cys
275 280 285

Thr Pro Pro Ala Ser Glu Gly Ser Ala Glu Ser Met Gly Pro Asp Ser
290 295 300

Arg Pro Asp Pro Asp Gly Arg Leu Pro Thr Pro Ser Ala Pro Leu His
305 310 315 320

Ser

<210> 173
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 173

Gly Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Gly
1 5 10

<210> 174
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 174

Gly Lys Leu Arg Arg Thr Ser Leu Asp Phe Gln Gly
1 5 10

<210> 175

49JV_227262_W0_SEQ

<211> 847
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> CD22 protein sequence

<400> 175

Met His Leu Leu Gly Pro Trp Leu Leu Leu Leu Val Leu Glu Tyr Leu
1 5 10 15

Ala Phe Ser Asp Ser Ser Lys Trp Val Phe Glu His Pro Glu Thr Leu
20 25 30

Tyr Ala Trp Glu Gly Ala Cys Val Trp Ile Pro Cys Thr Tyr Arg Ala
35 40 45

Leu Asp Gly Asp Leu Glu Ser Phe Ile Leu Phe His Asn Pro Glu Tyr
50 55 60

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

Lys Asp Gly Lys Val Pro Ser Glu Gln Lys Arg Val Gln Phe Leu Gly
85 90 95

Asp Lys Asn Lys Asn Cys Thr Leu Ser Ile His Pro Val His Leu Asn
100 105 110

Asp Ser Gly Gln Leu Gly Leu Arg Met Glu Ser Lys Thr Glu Lys Trp
115 120 125

Met Glu Arg Ile His Leu Asn Val Ser Glu Arg Pro Phe Pro Pro His
130 135 140

Ile Gln Leu Pro Pro Glu Ile Gln Glu Ser Gln Glu Val Thr Leu Thr
145 150 155 160

Cys Leu Leu Asn Phe Ser Cys Tyr Gly Tyr Pro Ile Gln Leu Gln Trp
165 170 175

Leu Leu Glu Gly Val Pro Met Arg Gln Ala Ala Val Thr Ser Thr Ser
180 185 190

Leu Thr Ile Lys Ser Val Phe Thr Arg Ser Glu Leu Lys Phe Ser Pro
195 200 205

Gln Trp Ser His His Gly Lys Ile Val Thr Cys Gln Leu Gln Asp Ala
210 215 220

Asp Gly Lys Phe Leu Ser Asn Asp Thr Val Gln Leu Asn Val Lys His
Page 175

49JV_227262_W0_SEQ

225 230 235 240
 Thr Pro Lys Leu Glu Ile Lys Val Thr Pro Ser Asp Ala Ile Val Arg
 245 250 255
 Glu Gly Asp Ser Val Thr Met Thr Cys Glu Val Ser Ser Ser Asn Pro
 260 265 270
 Glu Tyr Thr Thr Val Ser Trp Leu Lys Asp Gly Thr Ser Leu Lys Lys
 275 280 285
 Gln Asn Thr Phe Thr Leu Asn Leu Arg Glu Val Thr Lys Asp Gln Ser
 290 295 300
 Gly Lys Tyr Cys Cys Gln Val Ser Asn Asp Val Gly Pro Gly Arg Ser
 305 310 315 320
 Glu Glu Val Phe Leu Gln Val Gln Tyr Ala Pro Glu Pro Ser Thr Val
 325 330 335
 Gln Ile Leu His Ser Pro Ala Val Glu Gly Ser Gln Val Glu Phe Leu
 340 345 350
 Cys Met Ser Leu Ala Asn Pro Leu Pro Thr Asn Tyr Thr Trp Tyr His
 355 360 365
 Asn Gly Lys Glu Met Gln Gly Arg Thr Glu Glu Lys Val His Ile Pro
 370 375 380
 Lys Ile Leu Pro Trp His Ala Gly Thr Tyr Ser Cys Val Ala Glu Asn
 385 390 395 400
 Ile Leu Gly Thr Gly Gln Arg Gly Pro Gly Ala Glu Leu Asp Val Gln
 405 410 415
 Tyr Pro Pro Lys Lys Val Thr Thr Val Ile Gln Asn Pro Met Pro Ile
 420 425 430
 Arg Glu Gly Asp Thr Val Thr Leu Ser Cys Asn Tyr Asn Ser Ser Asn
 435 440 445
 Pro Ser Val Thr Arg Tyr Glu Trp Lys Pro His Gly Ala Trp Glu Glu
 450 455 460
 Pro Ser Leu Gly Val Leu Lys Ile Gln Asn Val Gly Trp Asp Asn Thr
 465 470 475 480
 Thr Ile Ala Cys Ala Ala Cys Asn Ser Trp Cys Ser Trp Ala Ser Pro
 485 490 495
 Val Ala Leu Asn Val Gln Tyr Ala Pro Arg Asp Val Arg Val Arg Lys
 Page 176

510

Glu Met Asn Ile Pro Arg Thr Gly Asp Ala Glu Ser Ser Glu Met Gln
Page 177

49JV_227262_W0_SEQ

770

775

780

Arg Pro Pro Pro Asp Cys Asp Asp Thr Val Thr Tyr Ser Ala Leu His
 785 790 795 800

Lys Arg Gln Val Gly Asp Tyr Glu Asn Val Ile Pro Asp Phe Pro Glu
 805 810 815

Asp Glu Gly Ile His Tyr Ser Glu Leu Ile Gln Phe Gly Val Gly Glu
 820 825 830

Arg Pro Gln Ala Gln Glu Asn Val Asp Tyr Val Ile Leu Lys His
 835 840 845

<210> 176
 <211> 3300
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CD22 nucleotide sequence

<400> 176
 acttctcctt ttgctctcag atgctgccag ggtccctgaa gagggaagac acgcggaaac 60
 aggcttgacac ccagacacga caccatgcat ctctctggcc cctggctcct gctcctgggtt 120
 ctagaatact tggctttctc tgactcaagt aaatgggttt ttgagcacc ctaaaccctc 180
 tacgcctggg agggggcctg cgtctggatc ccctgcacct acagagccct agatggtgac 240
 ctggaaagct tcatcctgtt ccacaatcct gagtataaca agaacacctc gaagtttgat 300
 gggacaagac tctatgaaag cacaaggat gggaagggtt cttctgagca gaaaagggtg 360
 caattcctgg gagacaagaa taagaactgc aactgagta tccaccgggt gcacctcaat 420
 gacagtgggtc agctggggct gaggatggag tccaagactg agaaatggat ggaacgaata 480
 cacctcaatg tctctgaaag gccttttcca cctcatatcc agctccctcc agaaattcaa 540
 gagtcccagg aagtcactct gacctgcttg ctgaatttct cctgctatgg gtatccgac 600
 caattgcagt ggctcctaga gggggttcca atgaggcagg ctgctgtcac ctgcacctcc 660
 ttgaccatca agtctgtctt caccgggagc gagctcaagt tctccccaca gtggagtcac 720
 catgggaaga ttgtgacctg ccagcttcag gatgcagatg ggaagttcct ctccaatgac 780
 acggtgcagc tgaacgtgaa gcacaccccg aagttggaga tcaaggtcac tcccagtgat 840
 gccatagtga gggaggggga ctctgtgacc atgacctgcg aggtcagcag cagcaaccgg 900
 gagtacacga cggtatcctg gctcaaggat gggacctcgc tgaagaagca gaatacatc 960
 acgctaaacc tgcgcgaagt gaccaaggac cagagtggga agtactgctg tcagggtctcc 1020
 aatgacgtgg gcccggaag gtcggaagaa gtgttctctgc aagtgcagta tgccccggaa 1080
 ccttcacagg ttcagatcct ccactcaccg gctgtggagg gaagtcaagt cgagtttctt 1140

49JV_227262_W0_SEQ

tgcatgtcac	tggccaatcc	tcttccaaca	aattacacgt	ggtaccacaa	tgggaaagaa	1200
atgcagggaa	ggacagagga	gaaagtccac	atcccaaaga	tcctcccctg	gcacgctggg	1260
acttattcct	gtgtggcaga	aaacattctt	ggtactggac	agagggggccc	gggagctgag	1320
ctggatgtcc	agtatcctcc	caagaaggtg	accacagtga	ttcaaaaccc	catgccgatt	1380
cgagaaggag	acacagtgc	cctttcctgt	aactacaatt	ccagtaaccc	cagtgttacc	1440
cggtatgaat	ggaaacccca	tggcgcctgg	gaggagccat	cgcttggggg	gctgaagatc	1500
caaaacgttg	gctgggacaa	cacaaccatc	gcctgcgcag	cttgtaatag	ttggtgctcg	1560
tgggcctccc	ctgtcgcctt	gaatgtccag	tatgcccccc	gagacgtgag	ggtccggaaa	1620
atcaagcccc	tttccgagat	tcactctgga	aactcgggtc	gcctccaatg	tgactttctc	1680
agcagccacc	ccaaagaagt	ccagttcttc	tgggagaaaa	atggcagggt	tctggggaaa	1740
gaaagccagc	tgaattttga	ctccatctcc	ccagaagatg	ctgggagtta	cagctgctgg	1800
gtgaacaact	ccataggaca	gacagcgtcc	aaggcctgga	cacttgaagt	gctgtatgca	1860
cccaggaggc	tgcgtgtgtc	catgagcccc	ggggaccaag	tgatggaggg	gaagagtgc	1920
accctgacct	gtgagagcga	cgccaaccct	ccgtctctcc	actacacctg	gtttgactgg	1980
aataaccaa	gcctccccta	ccacagccag	aagctgagat	tggagccggg	gaaggtccag	2040
cactcgggtg	cctactgggt	ccaggggacc	aacagtgtgg	gcaagggccg	ttcgcctctc	2100
agcaccttca	ccgtctacta	tagcccggag	accatcggca	ggcgagtggc	tgtgggactc	2160
gggtcctgcc	tcgccatcct	catcctggca	atctgtgggc	tcaagctcca	gcgacgttgg	2220
aagaggacac	agagccagca	ggggcttcag	gagaattcca	gcggccagag	cttctttgtg	2280
aggaataaaa	aggttagaag	ggccccctc	tctgaaggcc	cccactccct	gggatgctac	2340
aatccaatga	tggaagatgg	cattagctac	accaccctgc	gctttcccga	gatgaacata	2400
ccacgaactg	gagatgcaga	gtcctcagag	atgcagagac	ctccccgga	ctgcgatgac	2460
acggtcactt	attcagcatt	gcacaagcgc	caagtgggcg	actatgagaa	cgtcattcca	2520
gattttccag	aagatgaggg	gattcattac	tcagagctga	tccagtttgg	ggtcggggag	2580
cggcctcagg	cacaagaaaa	tgtggactat	gtgatcctca	aacattgaca	ctggatgggc	2640
tgcagcagag	gcactggggg	cagcgggggc	caggaagtc	cccagagttc	cccagacacc	2700
gccacatggc	ttcctcctgc	gcgcatgtgc	gcacacacac	acacacacgc	acacacacac	2760
acacacactc	actgcggaga	acctgtgtcc	tggctcagag	ccagtctttt	tggtgagggg	2820
aaccccaaac	ctccaaaact	cctgcccctg	ttctcttcca	ctctccttgc	taccagaaaa	2880
tccatctaaa	tacctgccct	gacatgcaca	cctccccctg	ccccaccac	ggccactggc	2940
catctccacc	cccagctgct	tgtgtccctc	ctgggatctg	ctcgtcatca	tttttccttc	3000
ccttctccat	ctctctggcc	ctctaccctt	gatctgacat	cccactcac	gaatattatg	3060
cccagtttct	gcctctgagg	gaaagcccag	aaaaggacag	aaacgaagta	gaaagggggc	3120
cagtcctggc	ctggcttctc	ctttggaagt	gaggcattgc	acggggagac	gtacgtatca	3180

49JV_227262_W0_SEQ

gcggccctt gactctgggg actccgggtt tgagatggac acactggtgt ggattaaacct 3240
gccagggaga cagagctcac aataaaaatg gctcagatgc cacttcaaag aaaaaaaaaa 3300

<210> 177
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> misc_feature
<223> Epratuzumab light chain sequence

<400> 177

Met Lys Leu Pro Val Arg Leu Leu Val Leu Leu Leu Phe Trp Ile Pro
1 5 10 15

Ala Ser Arg Gly Asp Val Gln Val Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser
35 40 45

Leu Ala Asn Ser Tyr Gly Asn Thr Phe Leu Ser Trp Tyr Leu His Lys
50 55 60

Pro Gly Lys Ala Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
100 105 110

Cys Leu Gln Gly Thr His Gln Pro Tyr Thr Phe Gly Gln Gly Thr Lys
115 120 125

Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
130 135 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145 150 155 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

49JV_227262_W0_SEQ

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 178

<211> 467

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> misc_feature

<223> Epratuzumab heavy chain sequence

<400> 178

Met Asp Phe Gly Phe Ser Leu Val Phe Leu Ala Leu Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe
35 40 45

Thr Asn Tyr Trp Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Ile Gly Gly Ile Asn Pro Gly Asn Asn Tyr Ala Thr Tyr Arg
65 70 75 80

Arg Lys Phe Gln Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Thr Arg Glu Gly Tyr Gly Asn Tyr Gly Ala Trp Phe Ala
115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
130 135 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145 150 155 160

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
Page 181

49JV_227262_W0_SEQ

165

170

175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
 180 185 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 195 200 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
 210 215 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
 225 230 235 240

Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
 245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
 275 280 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
 305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
 340 345 350

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 355 360 365

Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
 370 375 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
 420 425 430

Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
 Page 182

435 49JV_227262_W0_SEQ 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Leu Gly Lys
465

<210> 179
<211> 135
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<220>
<221> misc_feature
<223> Epratuzumab light chain variable (VL) region sequence

<400> 179

Met Lys Leu Pro Val Arg Leu Leu Val Leu Leu Leu Phe Trp Ile Pro
1 5 10 15

Ala Ser Arg Gly Asp Val Gln Val Thr Gln Ser Pro Ser Ser Leu Ser
20 25 30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser
35 40 45

Leu Ala Asn Ser Tyr Gly Asn Thr Phe Leu Ser Trp Tyr Leu His Lys
50 55 60

Pro Gly Lys Ala Pro Gln Leu Leu Ile Tyr Gly Ile Ser Asn Arg Phe
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
100 105 110

Cys Leu Gln Gly Thr His Gln Pro Tyr Thr Phe Gly Gln Gly Thr Lys
115 120 125

Val Glu Ile Lys Arg Thr Val
130 135

<210> 180
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> MOD_RES

<222> (5)..(5)

<223> Ala(diphenyl)

<400> 180

Cys Gln Phe Asp Ala Ser Arg Arg Arg Leu Lys Cys
1 5 10

<210> 181

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> MOD_RES

<222> (3)..(3)

<223> Ala(diphenyl)

<400> 181

Cys Gln Ala Asp Leu Ser Thr Arg Arg Leu Lys Cys
1 5 10

<210> 182

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 182

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Gly Ser
1 5 10 15

<210> 183

<211> 140

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<220>

<221> misc_feature

<223> Epratuzumab heavy chain variable (VH) region sequence

<400> 183

Met Asp Phe Gly Phe Ser Leu Val Phe Leu Ala Leu Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Arg Phe
 35 40 45

Thr Asn Tyr Trp Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
 50 55 60

Glu Trp Ile Gly Gly Ile Asn Pro Gly Asn Asn Tyr Ala Thr Tyr Arg
 65 70 75 80

Arg Lys Phe Gln Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser
 85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
 100 105 110

Tyr Tyr Cys Thr Arg Glu Gly Tyr Gly Asn Tyr Gly Ala Trp Phe Ala
 115 120 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 130 135 140

<210> 184
 <211> 1488
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CD23 gene sequence

<400> 184
 aacggcttca gctagggagc ggggagccca atagagtcag aggccaaata gaacaggaac 60
 ttggaacaag cagaatttag cataatgaat cctccaagcc aggagatcga ggagcttccc 120
 aggaggcggg gttgcaggcg tgggactcag atcgtgctgc tggggctggg gaccgccgct 180
 ctgtgggctg ggctgctgac tctgcttctc ctgtggcact gggacaccac acagagtcta 240
 aaacagctgg aagagagggc tgcccgggaa gtctctcaag tttccaagaa cttggaaagc 300
 caccacggtg accagatggc gcagaaatcc cagtccacgc agatttcaca ggaactggag 360
 gaacttcgag ctgaacagca gagattgaaa tctcaggact tggagctgtc ctggaacctg 420
 aacgggcttc aagcagatct gagcagcttc aagtcccagg aattgaacga gaggaacgaa 480
 gcttcagatt tgctggaaag actccgggag gaggtgacaa agctaaggat ggagttgcag 540
 gtgtccagcg gctttgtgtg caacacgtgc cctgaaaagt ggatcaattt ccaacggaag 600
 tgctactact tcggcaaggg caccaagcag tgggtccacg cccggtatgc ctgtgacgac 660
 atggaagggc agctggtcag catccacagc ccggaggagc aggacttcct gaccaagcat 720
 gccagccaca ccggctcctg gattggcctt cggaacttgg acctgaaggg ggagtttatc 780

49JV_227262_W0_SEQ

```

tgggtggatg ggagccacgt ggactacagc aactgggctc caggggagcc caccagccgg      840
agccagggcg aggactgcgt gatgatgcgg ggctccggtc gctggaacga cgccttctgc      900
gaccgtaagc tgggcgcctg ggtgtgcgac cggctggcca catgcacgcc gccagccagc      960
gaaggttccg cggagtccat gggacctgat tcaagaccag accctgacgg cgcctgccc     1020
accccctctg cccctctcca ctcttgagca tggatacagc caggcccaga gcaagaccct     1080
gaagaccccc aaccacggcc taaaagcctc tttgtggctg aaaggtcctt gtgacatttt     1140
ctgccacca aacggaggca gctgacacat ctcccgtcc tctatggccc ctgccttccc     1200
aggagtacac cccaacagca ccctctccag atgggagtgc cccaacagc accctctcca     1260
gatgagagta caccacaaca gcaccctctc cagatgagag tacaccccaa cagcaccctc     1320
tccagatgag agtacacccc aacagcacc tctccagatg cagccccatc tcctcagcac     1380
cccaggacct gagtatcccc agctcaggtg gtgagtcctc ctgtccagcc tgcataata     1440
aaatggggca gtgatggcct cccacatttg tccccttctt ggaaaaaa                1488

```

<210> 185
 <211> 129
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<220>
 <221> misc_feature
 <223> Lumiliximab light chain variable (VL) region sequence plus leader
 <400> 185

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
 1 5 10 15

Leu Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 35 40 45

Gln Asp Ile Arg Tyr Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60

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

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
 85 90 95

Val Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
 100 105 110

49JV_227262_W0_SEQ

Val Tyr Ser Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
 115 120 125

Lys

<210> 186
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<400> 186

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys
 1 5 10

<210> 187
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<400> 187

Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys
 1 5 10

<210> 188
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<400> 188

Gly Pro Gly Gly Ser Asp Pro Gly Cys Gln Phe Asp Leu Ser Thr Arg
 1 5 10 15

Arg Leu Arg Cys
 20

49JV_227262_W0_SEQ

<210> 189
 <211> 13
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<400> 189

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly
 1 5 10

<210> 190
 <211> 137
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> Lumiliximab heavy chain variable (VH) region sequence plus leader

<400> 190

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

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ala Lys
 20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Arg Phe
 35 40 45

Thr Phe Asn Asn Tyr Tyr Met Asp Trp Val Arg Gln Ala Pro Gly Gln
 50 55 60

Gly Leu Glu Trp Val Ser Arg Ile Ser Ser Ser Gly Asp Pro Thr Trp
 65 70 75 80

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala
 85 90 95

Asn Asn Thr Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
 100 105 110

Ala Val Tyr Tyr Cys Ala Ser Leu Thr Thr Gly Ser Asp Ser Trp Gly

115

120

125

Gln Gly Val Leu Val Thr Val Ser Ser
 130 135

<210> 191
 <211> 279
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CD37 protein sequence

<400> 191

Met Ser Ala Gln Glu Ser Cys Leu Ser Leu Ile Lys Tyr Phe Leu Phe
 1 5 10 15

Val Phe Asn Leu Phe Phe Phe Val Leu Gly Ser Leu Ile Phe Cys Phe
 20 25 30

Gly Ile Trp Ile Leu Ile Asp Lys Thr Ser Phe Val Ser Phe Val Gly
 35 40 45

Leu Ala Phe Val Pro Leu Gln Ile Trp Ser Lys Val Leu Ala Ile Ser
 50 55 60

Gly Ile Phe Thr Met Gly Ile Ala Leu Leu Gly Cys Val Gly Ala Leu
 65 70 75 80

Lys Glu Leu Arg Cys Leu Leu Gly Leu Tyr Phe Gly Met Leu Leu Leu
 85 90 95

Leu Phe Ala Thr Gln Ile Thr Leu Gly Ile Leu Ile Ser Thr Gln Arg
 100 105 110

Ala Gln Leu Glu Arg Ser Leu Arg Asp Val Val Glu Lys Thr Ile Gln
 115 120 125

Lys Tyr Gly Thr Asn Pro Glu Glu Thr Ala Ala Glu Glu Ser Trp Asp
 130 135 140

Tyr Val Gln Phe Gln Leu Arg Cys Cys Gly Trp His Tyr Pro Gln Asp
 145 150 155 160

Trp Phe Gln Val Leu Ile Leu Arg Gly Asn Gly Ser Glu Ala His Arg
 165 170 175

Val Pro Cys Ser Cys Tyr Asn Leu Ser Ala Thr Asn Asp Ser Thr Ile
 180 185 190

Leu Asp Lys Val Ile Leu Pro Gln Leu Ser Arg Leu Gly His Leu Ala
 Page 189

195

200

205

Arg Ser Arg His Ser Ala Asp Ile Cys Ala Val Pro Ala Glu Ser His
 210 215 220

Ile Tyr Arg Glu Gly Cys Ala Gln Gly Leu Gln Lys Trp Leu His Asn
 225 230 235 240

Leu Ile Ser Ile Val Gly Ile Cys Leu Gly Val Gly Leu Leu Glu Leu
 245 250 255

Gly Phe Met Thr Leu Ser Ile Phe Leu Cys Arg Asn Leu Asp His Val
 260 265 270

Tyr Asn Arg Leu Ala Tyr Arg
 275

<210> 192
 <211> 1263
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> CD37 gene sequence

<400> 192
 ttcttttctc ttcagctct ccgtctctct ttctctctca gcctctttct ttctccctgt 60
 ctccccact gtcagcacct cttctgtgtg gtgagtggac cgcttacccc actaggtgaa 120
 gatgtcagcc caggagagct gcctcagcct catcaagtac ttctctttcg ttttcaacct 180
 cttcttcttc gtcctcggca gcctgatctt ctgcttcggc atctggatcc tcattgacaa 240
 gaccagcttc gtgtcctttg tgggcttggc cttcgtgcct ctgcagatct ggtccaaagt 300
 cctggccatc tcaggaatct tcacatggg catcgccctc ctgggttgtg tgggggccct 360
 caaggagctc cgctgcctcc tgggcctgta ttttgggatg ctgctgctcc tgtttgccac 420
 acagatcacc ctgggaatcc tcattctcac tcagcgggcc cagctggagc gaagcttgcg 480
 ggacgtcgta gagaaaacca tccaaaagta cggcaccaac cccgaggaga ccgcggccga 540
 ggagagctgg gactatgtgc agttccagct gcgctgctgc ggctggcact acccgagga 600
 ctggttccaa gtcctcatcc tgagaggtaa cgggtcggag gcgcaccgcg tgccctgctc 660
 ctgctacaac ttgtcggcga ccaacgactc cacaatccta gataaggtga tcttgcccca 720
 gctcagcagg cttggacacc tggcgcggtc cagacacagt gcagacatct gcgctgtccc 780
 tgagagagc cacatctacc gcgagggctg cgcgcagggc ctccagaagt ggctgcacaa 840
 caaccttatt tccatagtgg gcatttgcct gggcgtcggc ctactcgagc tcgggttcat 900
 gacgctctcg atattcctgt gcagaaacct ggaccacgtc tacaaccggc tcgctcgata 960
 ccgttaggcc ccgccctccc caaagtcccg ccccgccccc gtcacgtgcg ctgggcactt 1020

49JV_227262_W0_SEQ

ccctgctgcc tgtaaattatt tgtttaatcc ccagttcgcc tggagccctc cgccttcaca 1080
 ttcccctggg gaccacgtg gctgctgcc cctgctgctg tcacctctcc cacgggacct 1140
 ggggctttcg tccacagctt cctgtcccca tctgtcggcc taccaccacc cacaagatta 1200
 tttttcacc aaacctcaaa taaatcccct gcgttttttg taaaaaaaaa aaaaaaaaaa 1260
 aaa 1263

<210> 193
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> Otlertuzumab light chain variable (VL) region sequence

<400> 193

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

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

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

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

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 194
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>

49JV_227262_W0_SEQ

<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> Otlertuzumab heavy chain variable (VH) region sequence

<400> 194

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

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

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

Lys 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 Ser Val Gly Pro Phe Asp Ser Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Gly
115

<210> 195
<211> 255
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Mucin-1 protein sequence

<400> 195

Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Thr
1 5 10 15

Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly
20 25 30

Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
35 40 45

Thr Glu Lys Asn Ala Phe Asn Ser Ser Leu Glu Asp Pro Ser Thr Asp
50 55 60

49JV_227262_W0_SEQ

Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met Phe Leu Gln Ile
65 70 75 80

Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile Lys Phe Arg Pro
85 90 95

Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg Glu Gly Thr Ile
100 105 110

Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr Lys Thr Glu Ala
115 120 125

Ala Ser Arg Tyr Asn Leu Thr Ile Ser Asp Val Ser Val Ser Asp Val
130 135 140

Pro Phe Pro Phe Ser Ala Gln Ser Gly Ala Gly Val Pro Gly Trp Gly
145 150 155 160

Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala Leu Ala Ile Val
165 170 175

Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg Lys Asn Tyr Gly
180 185 190

Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His Pro Met Ser Glu
195 200 205

Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro Pro Ser Ser Thr
210 215 220

Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn Gly Gly Ser Ser
225 230 235 240

Leu Ser Tyr Thr Asn Pro Ala Val Ala Ala Thr Ser Ala Asn Leu
245 250 255

<210> 196
<211> 768
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Mucin-1 gene sequence

<400> 196
atgacaccgg gcaccagtc tcctttcttc ctgctgctgc tcctcacagt gcttacagtt 60
gttacaggtt ctggtcatgc aagctctacc ccaggtggag aaaaggagac ttcggctacc 120
cagagaagtt cagtgccag ctctactgag aagaatgctt ttaattcctc tctggaagat 180
cccagcaccg actactacca agagctgcag agagacattt ctgaaatgtt tttgcagatt 240

49JV_227262_W0_SEQ

tataaacaag gggggttttct gggcctctcc aatattaagt tcaggccagg atctgtggtg 300
 gtacaattga ctctggcctt ccgagaaggt accatcaatg tccacgacgt ggagacacag 360
 ttcaatcagt ataaaacgga agcagcctct cgatataacc tgacgatctc agacgtcagc 420
 gtgagtgatg tgccatttcc tttctctgcc cagtctgggg ctgggggtgcc aggctggggc 480
 atcgcgctgc tgggtgctggt ctgtgttctg gttgcgctgg ccattgtcta tctcattgcc 540
 ttggctgtct gtcagtgccg ccgaaagaac tacgggcagc tggacatctt tccagcccgg 600
 gataacctacc atcctatgag cgagtacccc acctaccaca cccatgggcg ctatgtgccc 660
 cctagcagta ccgatcgtag cccctatgag aagggttctg caggtaatgg tggcagcagc 720
 ctctcttaca caaaccagc agtggcagcc acttctgcc acttgtag 768

<210> 197
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> hPAM4-Cide light chain variable (VL) region sequence

<400> 197

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Ser Ser
 20 25 30

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

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

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

Pro Glu Asp Ser Ala Ser Tyr Phe Cys His Trp Asn Arg Tyr Pro Tyr
 85 90 95

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

<210> 198
 <211> 120

49JV_227262_W0_SEQ

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> hPAM4-Cide heavy chain variable (VH) region sequence

<400> 198

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

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

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

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

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

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

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

Thr Leu Val Thr Val Ser Ser Ala
115 120

<210> 199
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 199

Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Gly Gly Ser Val Pro Gly
1 5 10 15

49JV_227262_W0_SEQ

Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly
20 25 30

Ser Gly Gln Ala Ser
35

<210> 200
<211> 39
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 200

Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly
1 5 10 15

Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly
20 25 30

Ser Gly Gln Ala Ser Lys Gly
35

<210> 201
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 201

Gly Gly Ser Arg Ser Gly Gly Thr Ser Ser Ser Ser Ser Gly Ser Gly
1 5 10 15

Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Ser Ser Gly
20 25 30

<210> 202
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>

49JV_227262_W0_SEQ

<221> misc_feature
<223> Synthetic construct

<400> 202

Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly
1 5 10 15

Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly
20 25 30

Ser Gly Gln Ala
35

<210> 203
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 203

Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Gly Gly Ser Val Pro Gly
1 5 10 15

Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser
20 25 30

<210> 204
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 204

Gly Gly Ser Arg Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly
1 5 10 15

Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser
20 25 30

<210> 205
<211> 111
<212> PRT
<213> Artificial Sequence

49JV_227262_W0_SEQ

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic construct

<400> 205

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

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
20 25 30

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
35 40 45

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
50 55 60

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

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
85 90 95

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
100 105 110

<210> 206

<211> 225

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic construct

<400> 206

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
1 5 10 15

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
20 25 30

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
35 40 45

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
50 55 60

49JV_227262_W0_SEQ

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
65 70 75 80

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
85 90 95

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
100 105 110

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
115 120 125

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
130 135 140

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
145 150 155 160

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
165 170 175

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
180 185 190

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
195 200 205

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
210 215 220

Lys
225

<210> 207
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 207

Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly
1 5 10

<210> 208
<211> 112
<212> PRT
<213> Artificial Sequence

49JV_227262_W0_SEQ

<220>
<223> 002-H08 light chain variable (VL) region sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 208

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

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

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

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

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

Ser Gly Ser Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 209
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> 002-H08 heavy chain variable (VH) region sequence

<400> 209

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

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

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

49JV_227262_W0_SEQ

Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Ser Pro Leu Glu Ser Pro Val Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Ile Val Ser Ser
115

<210> 210
<211> 310
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> SDC-1 protein sequence

<400> 210

Met Arg Arg Ala Ala Leu Trp Leu Trp Leu Cys Ala Leu Ala Leu Ser
1 5 10 15

Leu Gln Pro Ala Leu Pro Gln Ile Val Ala Thr Asn Leu Pro Pro Glu
20 25 30

Asp Gln Asp Gly Ser Gly Asp Asp Ser Asp Asn Phe Ser Gly Ser Gly
35 40 45

Ala Gly Ala Leu Gln Asp Ile Thr Leu Ser Gln Gln Thr Pro Ser Thr
50 55 60

Trp Lys Asp Thr Gln Leu Leu Thr Ala Ile Pro Thr Ser Pro Glu Pro
65 70 75 80

Thr Gly Leu Glu Ala Thr Ala Ala Ser Thr Ser Thr Leu Pro Ala Gly
85 90 95

Glu Gly Pro Lys Glu Gly Glu Ala Val Val Leu Pro Glu Val Glu Pro
100 105 110

Gly Leu Thr Ala Arg Glu Gln Glu Ala Thr Pro Arg Pro Arg Glu Thr
115 120 125

Thr Gln Leu Pro Thr Thr His Gln Ala Ser Thr Thr Thr Ala Thr Thr
130 135 140

49JV_227262_W0_SEQ

Ala Gln Glu Pro Ala Thr Ser His Pro His Arg Asp Met Gln Pro Gly
145 150 155 160

His His Glu Thr Ser Thr Pro Ala Gly Pro Ser Gln Ala Asp Leu His
165 170 175

Thr Pro His Thr Glu Asp Gly Gly Pro Ser Ala Thr Glu Arg Ala Ala
180 185 190

Glu Asp Gly Ala Ser Ser Gln Leu Pro Ala Ala Glu Gly Ser Gly Glu
195 200 205

Gln Asp Phe Thr Phe Glu Thr Ser Gly Glu Asn Thr Ala Val Val Ala
210 215 220

Val Glu Pro Asp Arg Arg Asn Gln Ser Pro Val Asp Gln Gly Ala Thr
225 230 235 240

Gly Ala Ser Gln Gly Leu Leu Asp Arg Lys Glu Val Leu Gly Gly Val
245 250 255

Ile Ala Gly Gly Leu Val Gly Leu Ile Phe Ala Val Cys Leu Val Gly
260 265 270

Phe Met Leu Tyr Arg Met Lys Lys Lys Asp Glu Gly Ser Tyr Ser Leu
275 280 285

Glu Glu Pro Lys Gln Ala Asn Gly Gly Ala Tyr Gln Lys Pro Thr Lys
290 295 300

Gln Glu Glu Phe Tyr Ala
305 310

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

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> Indatuximab rvtansine light chain variable (VL) region sequence

<400> 211

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

49JV_227262_W0_SEQ

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

Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Glu Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Pro
65 70 75 80

Glu Asp Ile Gly Thr Tyr Tyr Cys Gln Gln Tyr Ser Lys Leu Pro Arg
85 90 95

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

<210> 212
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> Indatuximab rvtansine heavy chain variable (VH) region sequence

<400> 212

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

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

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

Gly Glu Ile Leu Pro Gly Thr Gly Arg Thr Ile Tyr Asn Glu Lys Phe
50 55 60

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

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

49JV_227262_W0_SEQ

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

Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala
115 120

<210> 213
<211> 1210
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> EGFR protein sequence
<400> 213

Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
1 5 10 15

Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
20 25 30

Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
35 40 45

Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
50 55 60

Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys
65 70 75 80

Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
85 90 95

Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
100 105 110

Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
115 120 125

Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
130 135 140

His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
145 150 155 160

Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
165 170 175

Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
180 185 190

49JV_227262_W0_SEQ

Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
195 200 205

Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
210 215 220

Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
225 230 235 240

Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
245 250 255

Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
260 265 270

Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
275 280 285

Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
290 295 300

Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
305 310 315 320

Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val
325 330 335

Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
340 345 350

Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
355 360 365

Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr
370 375 380

Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu
385 390 395 400

Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
405 410 415

Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln
420 425 430

His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
435 440 445

Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
450 455 460

49JV_227262_W0_SEQ

Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
465 470 475 480

Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
485 490 495

Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
500 505 510

Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
515 520 525

Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
530 535 540

Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro
545 550 555 560

Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
565 570 575

Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
580 585 590

Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
595 600 605

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
610 615 620

Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
625 630 635 640

Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
645 650 655

Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
660 665 670

Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
675 680 685

Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
690 695 700

Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
705 710 715 720

Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
725 730 735

49JV_227262_W0_SEQ

Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
740 745 750

Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
755 760 765

Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
770 775 780

Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
785 790 795 800

Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
805 810 815

Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
820 825 830

Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro
835 840 845

Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala
850 855 860

Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
865 870 875 880

Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
885 890 895

Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
900 905 910

Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
915 920 925

Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
930 935 940

Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
945 950 955 960

Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
965 970 975

Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
980 985 990

Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
995 1000 1005

49JV_227262_W0_SEQ

Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe
 1010 1015 1020

Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu
 1025 1030 1035

Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn
 1040 1045 1050

Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg
 1055 1060 1065

Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
 1070 1075 1080

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro
 1085 1090 1095

Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
 1100 1105 1110

Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro
 1115 1120 1125

His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln
 1130 1135 1140

Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala
 1145 1150 1155

Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln
 1160 1165 1170

Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys
 1175 1180 1185

Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val Ala Pro Gln
 1190 1195 1200

Ser Ser Glu Phe Ile Gly Ala
 1205 1210

<210> 214
 <211> 5616
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> EGFR gene sequence

<400> 214
 ccccggcgca ggcggccgc agcagcctcc gcccccgca cgggtgtgagc gcccgacgcg

49JV_227262_W0_SEQ

gccgaggcgg	ccggagtccc	gagctagccc	cggcggccgc	cgccgcccag	accggacgac	120
aggccacctc	gtcggcgctc	gcccgagtcc	ccgcctcgcc	gccaacgcca	caaccaccgc	180
gcacggcccc	ctgactccgt	ccagtattga	tcgggagagc	cggagcgagc	tcttcgggga	240
gcagcgatgc	gaccctccgg	gacggccggg	gcagcgctcc	tggcgctgct	ggctgcgctc	300
tgccccggcg	gtcgggctct	ggaggaaaag	aaagtttgcc	aaggcacgag	taacaagctc	360
acgcagttgg	gcacttttga	agatcatttt	ctcagcctcc	agaggatggt	caataactgt	420
gaggtggtcc	ttgggaattt	ggaaattacc	tatgtgcaga	ggaattatga	tctttccttc	480
ttaaagacca	tccaggaggt	ggctgggtat	gtcctcattg	ccctcaacac	agtggagcga	540
attccttttg	aaaacctgca	gatcatcaga	ggaaatatgt	actacgaaaa	ttcctatgcc	600
ttagcagtct	tatctaacta	tgatgcaa	aaaaccggac	tgaaggagct	gcccattgaga	660
aatttacagg	aaatcctgca	tggcgccgtg	cggttcagca	acaaccctgc	cctgtgcaac	720
gtggagagca	tccagtggcg	ggacatagtc	agcagtgact	ttctcagcaa	catgtcgatg	780
gacttccaga	accacctggg	cagctgccaa	aagtgtgatc	caagctgtcc	caatgggagc	840
tgctgggggtg	caggagagga	gaactgccag	aaactgacca	aatcatctg	tgcccagcag	900
tgctccgggc	gctgccgtgg	caagtcccc	agtgactgct	gccacaacca	gtgtgctgca	960
ggctgcacag	gccccggga	gagcgactgc	ctggtctgcc	gcaaattccg	agacgaagcc	1020
acgtgcaagg	acacctgccc	cccactcatg	ctctacaacc	ccaccacgta	ccagatggat	1080
gtgaaccccg	agggcaaata	cagctttggt	gccacctgcg	tgaagaagtg	tccccgtaat	1140
tatgtggtga	cagatcacgg	ctcgtgcgtc	cgagcctgtg	gggccgacag	ctatgagatg	1200
gaggaagacg	gcgtccgcaa	gtgtaagaag	tgcaagggc	cttgccgcaa	agtgtgtaac	1260
ggaataggta	ttggtgaatt	taaagactca	ctctccataa	atgctacgaa	tattaaacac	1320
ttcaaaaact	gcacctccat	cagtggcgat	ctccacatcc	tgccggtggc	atttaggggt	1380
gactccttca	cacatactcc	tcctctggat	ccacaggaac	tggatattct	gaaaaccgta	1440
aaggaaatca	cagggttttt	gctgattcag	gcttggcctg	aaaacaggac	ggacctccat	1500
gcctttgaga	acctagaaat	catacgcggc	aggaccaagc	aacatgggtca	gttttctctt	1560
gcagtcgtca	gcctgaacat	aacatccttg	ggattacgct	ccctcaagga	gataagtgat	1620
ggagatgtga	taatttcagg	aaacaaaaat	ttgtgctatg	caaatacaat	aaactggaaa	1680
aaactgtttg	ggacctccgg	tcagaaaacc	aaaattataa	gcaacagagg	tgaaaacagc	1740
tgcaaggcca	caggccaggt	ctgccatgcc	ttgtgctccc	ccgagggctg	ctggggccccg	1800
gagcccaggg	actgcgtctc	ttgccggaat	gtcagccgag	gcagggaatg	cgtggacaag	1860
tgcaaccttc	tggaggggtga	gccaagggag	tttgtggaga	actctgagtg	catacagtgc	1920
caccagagt	gcctgcctca	ggccatgaac	atcacctgca	caggacgggg	accagacaac	1980
tgtatccagt	gtgcccacta	cattgacggc	ccccactgcg	tcaagacctg	cccggcagga	2040
gtcatgggag	aaaacaacac	cctgggtctgg	aagtacgcag	acgccggcca	tgtgtgccac	2100

49JV_227262_W0_SEQ

ctgtgccatc	caaactgcac	ctacggatgc	actgggccag	gtcttgaagg	ctgtccaacg	2160
aatgggccta	agatcccgtc	catcgccact	gggatggtgg	gggccctcct	cttgctgctg	2220
gtggtggccc	tggggatcgg	cctcttcatg	cgaaggcgcc	acatcgttcg	gaagcgcacg	2280
ctgcggaggc	tgctgcagga	gaggagctt	gtggagcctc	ttacaccag	tggagaagct	2340
cccaaccaag	ctctcttgag	gatcttgaag	gaaactgaat	tcaaaaagat	caaagtgtctg	2400
ggctccggtg	cgttcggcac	ggtgtataag	ggactctgga	tcccagaagg	tgagaaagtt	2460
aaaattcccg	tcgctatcaa	ggaattaaga	gaagcaacat	ctccgaaagc	caacaaggaa	2520
atcctcgatg	aagcctacgt	gatggccagc	gtggacaacc	cccacgtgtg	ccgcctgctg	2580
ggcatctgcc	tcacctccac	cgtgcagctc	atcacgcagc	tcatgccctt	cggctgcctc	2640
ctggactatg	tccgggaaca	caaagacaat	attggctccc	agtacctgct	caactggtgt	2700
gtgcagatcg	caaagggcat	gaactacttg	gaggaccgtc	gcttggtgca	ccgcgacctg	2760
gcagccagga	acgtactggt	gaaaacaccg	cagcatgtca	agatcacaga	ttttgggctg	2820
gccaaactgc	tgggtgcgga	agagaaagaa	taccatgcag	aaggaggcaa	agtgccatc	2880
aagtggatgg	cattggaatc	aattttacac	agaatctata	cccaccagag	tgatgtctgg	2940
agctacgggg	tgaccgtttg	ggagttgatg	acctttggat	ccaagccata	tgacggaatc	3000
cctgccagcg	agatctcctc	catcctggag	aaaggagaac	gcctccctca	gccaccata	3060
tgtaccatcg	atgtctacat	gatcatggtc	aagtgtctgga	tgatagacgc	agatagtcgc	3120
ccaaagtcc	gtgagttgat	catcgaattc	tccaaaatgg	cccagagacc	ccagcgctac	3180
cttgtcattc	agggggatga	aagaatgcat	ttgccaagtc	ctacagactc	caacttctac	3240
cgtgccctga	tggatgaaga	agacatggac	gacgtggtgg	atgccgacga	gtacctcatc	3300
ccacagcagg	gcttcttcag	cagcccctcc	acgtcacgga	ctccccctcct	gagctctctg	3360
agtgcaacca	gcaacaattc	caccgtggct	tgcatgtgata	gaaatgggct	gcaaagctgt	3420
cccatcaagg	aagacagctt	cttgacgca	tacagctcag	acccacagag	cgccttgact	3480
gaggacagca	tagacgacac	cttcctccca	gtgcctgaat	acataaacca	gtccgttccc	3540
aaaaggcccc	ctggctctgt	gcagaatcct	gtctatcaca	atcagcctct	gaaccccgcg	3600
cccagcagag	accacacta	ccaggacccc	cacagcactg	cagtgggcaa	ccccgagtat	3660
ctcaacactg	tccagcccac	ctgtgtcaac	agcacattcg	acagccctgc	ccactgggcc	3720
cagaaaggca	gccaccaa	tagcctggac	aaccctgact	accagcagga	cttctttccc	3780
aaggaagcca	agccaaatgg	catctttaag	ggctccacag	ctgaaaatgc	agaataccta	3840
agggtcgcg	cacaaagcag	tgaatttatt	ggagcatgac	cacggaggat	agtatgagcc	3900
ctaaaaatcc	agactctttc	gatacccagg	accaagccac	agcaggctcct	ccatcccaac	3960
agccatgccc	gcattagctc	ttagaccac	agactggttt	tgcaacgttt	acaccgacta	4020
gccaggaagt	acttcacct	cgggcacatt	ttgggaagtt	gcattccttt	gtcttcaaac	4080
tgtgaagcat	ttacagaaac	gcacccagca	agaatattgt	ccctttgagc	agaaatttat	4140

49JV_227262_W0_SEQ

ctttcaaaga ggtatatttg aaaaaaaaaa aaagtatatg tgaggatttt tattgattgg	4200
ggatcttggg gtttttcatt gtcgctattg atttttactt caatgggctc ttccaacaag	4260
gaagaagctt gctggtagca cttgctaccc tgagttcatc caggcccaac tgtgagcaag	4320
gagcacaagc cacaagtctt ccagaggatg cttgattcca gtggttctgc ttcaaggctt	4380
ccactgcaaa acactaaaga tccaagaagg ctttcatggc cccagcaggc cggatcggtg	4440
ctgtatcaag tcatggcagg tacagtagga taagccactc tgtcccttcc tgggcaaaga	4500
agaaacggag gggatggaat tcttccttag acttactttt gtaaaaatgt cccacaggta	4560
cttactcccc actgatggac cagtgggttc cagtcatgag cgttagactg acttgtttgt	4620
cttccattcc attgttttga aactcagtat gctgcccctg tcttgctgtc atgaaatcag	4680
caagagagga tgacacatca aataataact cggattccag cccacattgg attcatcagc	4740
atttggacca atagcccaca gctgagaatg tggaatacct aaggatagca ccgcttttgt	4800
tctcgcaaaa acgtatctcc taatttgagg ctcagatgaa atgcatcagg tcctttgggg	4860
catagatcag aagactacaa aaatgaagct gctctgaaat ctccttttagc catcacccca	4920
accccccaaa attagtttgt gttacttatg gaagatagtt ttctcctttt acttcacttc	4980
aaaagctttt tactcaaaga gtatatgttc cctccaggtc agctgcccc aaaccccctc	5040
cttacgcttt gtcacacaaa aagtgtctct gccttgagtc atctattcaa gcacttacag	5100
ctctggccac aacagggcat ttacagggtg cgaatgacag tagcattatg agtagtgtgg	5160
aattcaggta gtaaatatga aactaggggt tgaaattgat aatgctttca caacatttgc	5220
agatgtttta gaaggaaaa agttccttcc taaaataatt tctctacaat tggaagattg	5280
gaagattcag ctagttagga gccaccttt tttcctaate tgtgtgtgcc ctgtaacctg	5340
actggttaac agcagtcctt tgtaaacagt gttttaaaact ctcctagtca atatccaccc	5400
catccaattt atcaaggaag aaatgggttca gaaaatatatt tcagcctaca gttatgttca	5460
gtcacacaca catacaaaat gttccttttg cttttaaaagt aatttttgac tcccagatca	5520
gtcagagccc ctacagcatt gttaagaaag tatttgattt ttgtctcaat gaaaataaaa	5580
ctatattcat ttccactcta aaaaaaaaaa aaaaaa	5616

<210> 215
 <211> 109
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> ABT-806 light chain variable (VL) region sequence

49JV_227262_W0_SEQ

<400> 215

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

Asp Thr Val Ser Ile Thr Cys His Ser Ser Gln Asp Ile Asn Ser Asn
20 25 30

Ile Gly Trp Leu Gln Gln Lys Pro Gly Lys Ser Phe Lys Gly Leu Ile
35 40 45

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

Ser Gly Ser Gly Ala Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln Tyr Ala Gln Phe Pro Trp
85 90 95

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

<210> 216

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic construct

<220>

<221> misc_feature

<223> ABT-806 heavy chain variable (VH) region sequence

<400> 216

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Phe Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Asn Thr Arg Tyr Asn Pro Ser Leu
50 55 60

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

49JV_227262_W0_SEQ

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

Val Thr Ala Gly Arg Gly Phe Pro Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala
115

<210> 217
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> ABT-806 light chain sequence

<400> 217

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

Asp Thr Val Ser Ile Thr Cys His Ser Ser Gln Asp Ile Asn Ser Asn
20 25 30

Ile Gly Trp Leu Gln Gln Lys Pro Gly Lys Ser Phe Lys Gly Leu Ile
35 40 45

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

Ser Gly Ser Gly Ala Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln Tyr Ala Gln Phe Pro Trp
85 90 95

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

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

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

49JV_227262_W0_SEQ

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

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

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

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

Phe Asn Arg Asn Glu Cys
210

<210> 218
<211> 216
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> ABT-806 heavy chain sequence

<400> 218

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

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile Thr Ser Asp
20 25 30

Phe Ala Trp Asn Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Tyr Ile Ser Tyr Ser Gly Asn Thr Arg Tyr Asn Pro Ser Leu
50 55 60

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

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

Val Thr Ala Gly Arg Gly Phe Pro Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

49JV_227262_W0_SEQ

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

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

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

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

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

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

Val Asp Lys Lys Leu Glu Pro Ser
210 215

<210> 219
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> Zatuximab light chain variable (VL) region sequence

<400> 219

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

Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

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

Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Ala Gln Asn
Page 215

49JV_227262_W0_SEQ

85

90

95

Leu Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val
115

<210> 220
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> Zatuximab heavy chain variable (VH) region sequence

<400> 220

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

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

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

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

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

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

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

Thr Ser Val Thr Val Ser Ser
115

<210> 221
<211> 219
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic construct

<220>

<221> misc_feature

<223> Zatuximab light chain sequence

<400> 221

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

Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

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

Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

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

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

Leu Glu Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu 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
210 215

49JV_227262_W0_SEQ

<210> 222
 <211> 447
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> Zatuximab heavy chain sequence

<400> 222

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

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

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

Gly Glu Ile Asn Pro Ser Ser Gly Arg Asn Asn Tyr Asn Glu Lys Phe
 50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Phe Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Val Arg Tyr Tyr Gly Tyr Asp Glu Ala Met Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190

49JV_227262_W0_SEQ

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Gly
435 440 445

<210> 223
<211> 960
<212> DNA
<213> Artificial Sequence

49JV_227262_W0_SEQ

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> tetravalent meditope-Fc (M4FC)

```

<400> 223
gggtgccagt tcgacctttc cactcgccgc ttgaggtgcg gtggttcccg tagtggaggt      60
acttctggaa caggcagcac ttcggggtcc ggatcaagcg gaagcacatc tggttccgga      120
aagtctagcg agggttccgg acaagcctcc aaggggacac acacgtgtcc tccttgtcca      180
gctcccagac tgctgggagg accatctgta tttctgttcc caccaaagcc caaagatacc      240
ctcatgattt cgcgtacccc tgaagtcaca tgcgttgtcg tcgatgtgag tcatgaggac      300
cctgaagtta agttcaattg gtacgtcgac ggagtcgaag tgcataacgc taaaacaaaa      360
ccgagagaag aacagtacaa cagcacatac agagtgggtga gcgtgctcac cgtacttcac      420
caggactggc tgaatggtaa agagtataag tgtaaagtta gcaacaaggc gttgcctgct      480
ccaatcgaga aaacctctc caaggcaaag ggccaaccca gggaacccca agtatacacc      540
ctgccccctg cgagagatga gttgactaag aaccaagtga gtcttacgtg cttgggtgaag      600
ggcttctacc catccgacat agcagttgag tgggagtcaa atggccagcc cgaaaacaac      660
tacaagacaa cccctcccggt actggactcc gatggatctt tcttcctcta ttcaaagctc      720
acggctcgaca agtctaggtg gcagcaaggc aatgtgttca gctgctcagt catgcacgag      780
gccctgcaca accactatac tcagaagtca ctttcgctct ccccgggaaa aggtgggttcg      840
cgtagtggcg gtacgagtag ctcaagcagt ggttccggta gtggatcttc cggttccacc      900
tcaggctctg gtcacatcggg atgtcagttt gatctctcaa ctaggcgttt gcgctgcggc      960

```

<210> 224
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MB-004-107 Gemtuzumab enabled antibody, light chain

<400> 224

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

49JV_227262_W0_SEQ

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 225
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>

49JV_227262_W0_SEQ

<221> misc_feature

<223> MB-004-107 Gemtuzumab enabled antibody, heavy chain

<400> 225

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Arg Met His Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
 50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Ile Tyr Tyr Cys
 85 90 95

Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
 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 Thr His Thr
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

49JV_227262_W0_SEQ

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 226
<211> 219
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MOR-208 Light chain

<400> 226

49JV_227262_W0_SEQ

Asp Ile Val Met Thr Gln Ser Pro Ala Ile Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Lys Ser Leu Gln Asn Val
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Gln Gln Lys Thr Asn Gly Ser
35 40 45

Pro Arg Leu Leu Ile Tyr Arg Met Ser Asn Leu Asn Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Glu Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Ile Gln His
85 90 95

Leu Glu Tyr Pro Ile Thr Phe Gly Ala Gly Thr Lys Leu 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
210 215

<210> 227
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

49JV_227262_W0_SEQ

<220>

<221> misc_feature

<223> MOR-208 Heavy chain

<400> 227

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Ser Ser Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Tyr Tyr Tyr Gly Thr Arg Val Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu 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

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
225 230 235 240

Gly Pro Asp Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
Page 225

49JV_227262_W0_SEQ

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 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
275 280 285

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
290 295 300

Arg Val Val Ser Val Leu Thr Val Val 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 Glu
325 330 335

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
340 345 350

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu 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

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr 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 Lys
450

<210> 228
<211> 693
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

49JV_227262_W0_SEQ

<220>
 <221> misc_feature
 <223> His6-SMT3-Bivalent mediotope (BVM) sequence (Nucleotide)
 <400> 228
 atgggcagca gccatcatca tcatcatcac agcagcggcc tgggtgccgcg cggcagccat 60
 atgggtggtg gttcgtggtc gcatccgcag tttgaaaaag gcggtggttc ggggtggtggc 120
 atgtcagact cagaagtga ttaggaagcg aaaccggaag tgaaaccgga agttaaacgg 180
 gaaaccata ttaacctgaa agtcagtgat ggcagctctg aaattttctt taaaattaag 240
 aaaaccacgc cgctgcgtcg cctgatggaa gcgtttgcc aacgtcaggg caaagaaatg 300
 gatagcctgc gtttcctgta tgacggtatt cgcattccagg cggatcaaac gccggaagac 360
 ctggatatgg aagataatga cattatcgaa gctcatcgtg aacaaatcgg tggcggcggg 420
 tcagccgctc cgtcctctgc tccgagtcg tctgccccgt gccagtttga cctgtctacc 480
 cgtcgtctga gttgtggtgg tgcgagcccg gccgcaagtc cgtccgcacc gagcagcccg 540
 gcgcccgaag ccccgagcgc agtccgagt tccgccccgt caccgagcgc gccggggcggc 600
 tgccagtttg atctgtcaac ccgtcgctg tctgtgtggcg gtgcgagccc ggccgcaagc 660
 ccgtctgcgc cgtcatcgcc ggcaccgaaa taa 693

<210> 229
 <211> 230
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> His6-SMT3-Bivalent mediotope (BVM) sequence (Amino Acid)

<400> 229
 Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15
 Arg Gly Ser His Met Gly Gly Gly Ser Trp Ser His Pro Gln Phe Glu
 20 25 30
 Lys Gly Gly Gly Ser Gly Gly Gly Met Ser Asp Ser Glu Val Asn Gln
 35 40 45
 Glu Ala Lys Pro Glu Val Lys Pro Glu Val Lys Pro Glu Thr His Ile
 50 55 60
 Asn Leu Lys Val Ser Asp Gly Ser Ser Glu Ile Phe Phe Lys Ile Lys
 65 70 75 80

49JV_227262_W0_SEQ

Lys Thr Thr Pro Leu Arg Arg Leu Met Glu Ala Phe Ala Lys Arg Gln
85 90 95

Gly Lys Glu Met Asp Ser Leu Arg Phe Leu Tyr Asp Gly Ile Arg Ile
100 105 110

Gln Ala Asp Gln Thr Pro Glu Asp Leu Asp Met Glu Asp Asn Asp Ile
115 120 125

Ile Glu Ala His Arg Glu Gln Ile Gly Gly Gly Gly Ser Ala Ala Pro
130 135 140

Ser Ser Ala Pro Ser Pro Ser Ala Pro Cys Gln Phe Asp Leu Ser Thr
145 150 155 160

Arg Arg Leu Ser Cys Gly Gly Ala Ser Pro Ala Ala Ser Pro Ser Ala
165 170 175

Pro Ser Ser Pro Ala Pro Lys Ala Pro Ser Ala Ala Pro Ser Ser Ala
180 185 190

Pro Ser Pro Ser Ala Pro Gly Gly Cys Gln Phe Asp Leu Ser Thr Arg
195 200 205

Arg Leu Ser Cys Gly Gly Ala Ser Pro Ala Ala Ser Pro Ser Ala Pro
210 215 220

Ser Ser Pro Ala Pro Lys
225 230

<210> 230
<211> 840
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> His6-SMT-Trivalent mediotope (TVM) sequence (Nucleotide)

<400> 230
atgggcagca gccatcatca tcatcatcac agcagcggcc tgggtgccgcg cggcagccat 60
atgggtggtg gttcgtggtc gcatccgcag tttgaaaaag gcggtggttc ggggtggtggc 120
atgtcagact cagaagtga tcaaggaagc aaaccggaag tgaaaccgga agttaaacgc 180
gaaaccata ttaacctgaa agtcagtgat ggcagctctg aaattttctt taaaattaag 240
aaaaccacgc cgctgcgtcg cctgatggaa gcgtttgcc aacgtcaggg caaagaaatg 300

49JV_227262_W0_SEQ

gatagcctgc gtttcctgta tgacggtatt cgcattccagg cggatcaaac gccggaagac 360
ctggatatgg aagataatga cattatcgaa gtcattcgtg aacaaatcgg tggcggcggt 420
tcagccgctc cgtcctctgc tccgagtcgg tctgccccgt gccagtttga cctgtctacc 480
cgtcgtctga gttgtggtgg tgcgagcccc gccgcaagtc cgtccgcacc gagcagcccc 540
gcgcccgaag ccccgagcgc agtcccgagt tccgccccgt caccgagcgc gccgggaggc 600
tgccagtttg atctgtcaac ccgtcgcctg tcgtgtggcg gtgcgagccc ggccgcaagc 660
ccgtctgcgc cgtcatcgcc ggcaccgaaa gcccgcctcg cagctccgag cagcgcaccg 720
agtccgtccg ctccggggcg ttgccaattc gacctgtcta cgcgtcgcct gagttgtggt 780
ggtagcccgt ctgccccgtc atcgccgtcc agcccgaaac tgccggaaac cggttgagggc 840

<210> 231
<211> 258
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> His6-SMT-Trivalent mediotope (TVM) sequence (Amino Acid)

<400> 231

Met Gly Gly Gly Ser Trp Ser His Pro Gln Phe Glu Lys Gly Gly Gly
1 5 10 15

Ser Gly Gly Gly Met Ser Asp Ser Glu Val Asn Gln Glu Ala Lys Pro
20 25 30

Glu Val Lys Pro Glu Val Lys Pro Glu Thr His Ile Asn Leu Lys Val
35 40 45

Ser Asp Gly Ser Ser Glu Ile Phe Phe Lys Ile Lys Lys Thr Thr Pro
50 55 60

Leu Arg Arg Leu Met Glu Ala Phe Ala Lys Arg Gln Gly Lys Glu Met
65 70 75 80

Asp Ser Leu Arg Phe Leu Tyr Asp Gly Ile Arg Ile Gln Ala Asp Gln
85 90 95

Thr Pro Glu Asp Leu Asp Met Glu Asp Asn Asp Ile Ile Glu Ala His
100 105 110

Arg Glu Gln Ile Gly Gly Gly Gly Ser Ala Ala Pro Ser Ser Ala Pro

49JV_227262_W0_SEQ

115

120

125

Ser Pro Ser Ala Pro Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Ser
130 135 140

Cys Gly Gly Ala Ser Pro Ala Ala Ser Pro Ser Ala Pro Ser Ser Pro
145 150 155 160

Ala Pro Lys Ala Pro Ser Ala Ala Pro Ser Ser Ala Pro Ser Pro Ser
165 170 175

Ala Pro Gly Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Ser Cys
180 185 190

Gly Gly Ala Ser Pro Ala Ala Ser Pro Ser Ala Pro Ser Ser Pro Ala
195 200 205

Pro Lys Ala Pro Ser Ala Ala Pro Ser Ser Ala Pro Ser Pro Ser Ala
210 215 220

Pro Gly Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Ser Cys Gly
225 230 235 240

Gly Ser Pro Ser Ala Pro Ser Ser Pro Ser Ser Pro Lys Leu Pro Glu
245 250 255

Thr Gly

<210> 232
<211> 474
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MPL-zHER2 nucleic acid

<400> 232
tgccagttcg atctgtccac ccgtcgtctg aaatgcggcg gcggcggctc ggaagtcacg 60
attaaagtca acctgatttt tgcggatggt aaaattcaga ccgccgaatt taaaggcacc 120
ttcgaagaag caacggctga agcgtatcgt tacgcggccc tgctggctaa agtgaacggt 180
gaatatacgg cggatctgga agacggcgggt aaccacatga atatcaaatt tgcaggggaat 240
tcgggcggtg gcagcgggtg cagcggttct ggcagtgggt gtcctcgggaa ttcaggcggt 300
gataacaaat tcaacaaaga aatgcgcaac gcctattggg aaattgcact gctgccgaat 360

49JV_227262_W0_SEQ

ctgaacaatc agcaaaaacg tgcgttcacg cgctctctgt acgatgaccc gtcccaaagc 420
gcaaattctgc tggcggaagc gaaaaaactg aacgacgcac aagccccgaa gtaa 474

<210> 233
<211> 157
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MPL-ZHER2 amino acid

<400> 233

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Gly
1 5 10 15

Ser Glu Val Thr Ile Lys Val Asn Leu Ile Phe Ala Asp Gly Lys Ile
20 25 30

Gln Thr Ala Glu Phe Lys Gly Thr Phe Glu Glu Ala Thr Ala Glu Ala
35 40 45

Tyr Arg Tyr Ala Ala Leu Leu Ala Lys Val Asn Gly Glu Tyr Thr Ala
50 55 60

Asp Leu Glu Asp Gly Gly Asn His Met Asn Ile Lys Phe Ala Gly Asn
65 70 75 80

Ser Gly Gly Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Gly Ser Gly
85 90 95

Asn Ser Gly Val Asp Asn Lys Phe Asn Lys Glu Met Arg Asn Ala Tyr
100 105 110

Trp Glu Ile Ala Leu Leu Pro Asn Leu Asn Asn Gln Gln Lys Arg Ala
115 120 125

Phe Ile Arg Ser Leu Tyr Asp Asp Pro Ser Gln Ser Ala Asn Leu Leu
130 135 140

Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro Lys
145 150 155

<210> 234
<211> 474
<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic construct

<220>

<221> misc_feature

<223> zIGF1R - MPL nucleic acid

<400> 234

```

gaggtaaaac atatgaattc cgtcgataac aaattcaaca aagagcggtta cagcgcatac      60
tatgaaatct ggcagttgcc gaacctgaac gttcgtcaga aagcagcggtt cattggtagc      120
ctgcaagatg atccgagcca aagcgccaat ctgctggctg aggcgaaaaa gctgaatgac      180
gcgcaggccc cgaagaactc gagcggtagc ggtggtggta gcggaattc cggttgccaa      240
tttgacttga gcacgcgtcg cctgaagtgt ggtggcggtg gctctgaggt tactattaag      300
gtgaacctga tttttgcaga cggtaaaatc cagaccgccg agttcaaggg caccttcgaa      360
gaagcgacgg cagaggcgta tcgctacgca gctctgctgg cgaaagtgaa tgggtgagtat      420
accgcggacc tggaagatgg cggcaaccac atgaatatca agtttgcggg ctaa          474

```

<210> 235

<211> 157

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic sequence

<220>

<221> misc_feature

<223> Synthetic construct

<220>

<221> misc_feature

<223> zIGF1R - MPL Amino Acid

<400> 235

```

Glu Val Lys His Met Asn Ser Val Asp Asn Lys Phe Asn Lys Glu Arg
1          5          10          15

```

```

Tyr Ser Ala Tyr Tyr Glu Ile Trp Gln Leu Pro Asn Leu Asn Val Arg
          20          25          30

```

```

Gln Lys Ala Ala Phe Ile Gly Ser Leu Gln Asp Asp Pro Ser Gln Ser
          35          40          45

```

```

Ala Asn Leu Leu Ala Glu Ala Lys Lys Leu Asn Asp Ala Gln Ala Pro
          50          55          60

```

```

Lys Asn Ser Ser Gly Ser Gly Gly Gly Ser Gly Asn Ser Gly Cys Gln

```

65 70 75 80

49JV_227262_W0_SEQ

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
115 120 125

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
130 135 140

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
145 150 155 160

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
165 170 175

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
180 185 190

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
195 200 205

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
210 215 220

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
225 230 235 240

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
245 250 255

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
260 265 270

Pro Gly Lys
275

<210> 237
<211> 44
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MB-002-109 bivalent meditope peptide

<400> 237

Lys Pro Thr Thr Ile Gln Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu
1 5 10 15

49JV_227262_W0_SEQ

Lys Cys Val Arg Ile Asn Phe Lys Gly Gly Tyr Ile Ser Cys Gln Phe
 20 25 30

Asp Leu Ser Thr Arg Arg Leu Lys Cys Asp Ile His
 35 40

<210> 238
 <211> 43
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> MB-002-110 bivalent mediotope peptide

<400> 238

Lys Pro Thr Thr Ile Gln Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu
 1 5 10 15

Lys Cys Arg Ile Asn Phe Lys Gly Gly Tyr Ile Ser Cys Gln Phe Asp
 20 25 30

Leu Ser Thr Arg Arg Leu Lys Cys Asp Ile His
 35 40

<210> 239
 <211> 37
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> MB-002-111 bivalent mediotope peptide

<400> 239

Thr Ile Gln Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Val
 1 5 10 15

Arg Ile Asn Lys Gly Ser Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu
 20 25 30

Lys Cys Asp Ile His

35

<210> 240
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<400> 240

Phe Lys Leu Met Val Trp Tyr
 1 5

<210> 241
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> 83E mediotope enabled antibody trastuzumab light chain

<400> 241

Asp Ile Gln Met Thr Gln Ser Pro Ile Leu 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 Arg Thr Asn Gly Ser Pro Arg 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 Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

49JV_227262_W0_SEQ

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
210

<210> 242
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> 83E meditope enabled antibody trastuzumab VL sequence

<400> 242

Asp Ile Gln Met Thr Gln Ser Pro Ile Leu 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 Arg Thr Asn Gly Ser Pro Arg 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

49JV_227262_W0_SEQ

Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro
115 120

<210> 243
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MB-004-107 Gemtuzumab enabled antibody VL

<400> 243

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val
100 105

<210> 244
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

49JV_227262_W0_SEQ

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> MB-004-107 Gemtuzumab enabled antibody VH

<400> 244

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Arg Met His Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
 50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Ile Tyr Tyr Cys
 85 90 95

Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
 100 105 110

Thr Val Ser Ser
 115

<210> 245
 <211> 115
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic sequence

<220>
 <221> misc_feature
 <223> Synthetic construct

<220>
 <221> misc_feature
 <223> MOR-208 VL

<400> 245

Asp Ile Val Met Thr Gln Ser Pro Ala Ile Leu Ser Leu Ser Pro Gly
 1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ser Ser Lys Ser Leu Gln Asn Val
 20 25 30

49JV_227262_W0_SEQ

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Gln Gln Lys Thr Asn Gly Ser
35 40 45

Pro Arg Leu Leu Ile Tyr Arg Met Ser Asn Leu Asn Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
65 70 75 80

Ser Ser Leu Glu Pro Glu Asp Glu Ala Asp Tyr Tyr Cys Ile Gln His
85 90 95

Leu Glu Tyr Pro Ile Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val
115

<210> 246
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> MOR-208 VH

<400> 246

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Val Met His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Ser Ser Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

49JV_227262_W0_SEQ

Ala Arg Gly Thr Tyr Tyr Tyr Gly Thr Arg Val Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 247
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> aldehyde tag

<400> 247

Leu Cys Thr Pro Ser Arg
1 5

<210> 248
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>
<221> misc_feature
<223> aldehyde tag

<400> 248

Leu Cys Thr Pro Ser Arg Gly Ser Leu Phe Thr Gly Arg
1 5 10

<210> 249
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<220>

49JV_227262_W0_SEQ

<221> misc_feature
<223> sortase sequence

<220>
<221> VARIANT
<222> (3)..(3)
<223> Xaa is any amino acid

<400> 249

Leu Pro Xaa Thr Gly
1 5

<210> 250
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 250

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Ser Arg
1 5 10 15

Ser Gly Gly Thr Ser Gly Gly Gly Ser Val Pro Gly Ser Gly Ser Ser
20 25 30

Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Ser Gly Gln Ala
35 40 45

Ser Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
50 55 60

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
65 70 75 80

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
85 90 95

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
100 105 110

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
115 120 125

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
130 135 140

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
145 150 155 160

49JV_227262_W0_SEQ

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
165 170 175

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
180 185 190

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
195 200 205

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
210 215 220

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
225 230 235 240

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
245 250 255

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
260 265 270

Gly Lys

<210> 251
<211> 318
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

<220>
<221> misc_feature
<223> Synthetic construct

<400> 251

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Ser Arg
1 5 10 15

Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly Ser Gly Ser Ser
20 25 30

Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Ser Gly Gln Ala
35 40 45

Ser Lys Gly Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
50 55 60

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
65 70 75 80

49JV_227262_W0_SEQ

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
85 90 95

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
100 105 110

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
115 120 125

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
130 135 140

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
145 150 155 160

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
165 170 175

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
180 185 190

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
195 200 205

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
210 215 220

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
225 230 235 240

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
245 250 255

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
260 265 270

Ser Pro Gly Lys Gly Gly Ser Arg Ser Gly Gly Thr Ser Ser Ser Ser
275 280 285

Ser Gly Ser Gly Ser Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Ser
290 295 300

Ser Gly Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys
305 310 315

<210> 252
<211> 201
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic sequence

49JV_227262_W0_SEQ

<220>

<221> misc_feature

<223> Synthetic construct

<400> 252

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Ser Arg
1 5 10 15

Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly Ser Gly Ser Ser
20 25 30

Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Ser Gly Gln Ala
35 40 45

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
50 55 60

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
65 70 75 80

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
85 90 95

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
100 105 110

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
115 120 125

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
130 135 140

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly
145 150 155 160

Gly Ser Arg Ser Gly Gly Thr Ser Ser Ser Ser Gly Ser Gly Ser
165 170 175

Gly Ser Ser Gly Ser Thr Ser Gly Ser Gly Ser Ser Gly Cys Gln Phe
180 185 190

Asp Leu Ser Thr Arg Arg Leu Arg Cys
195 200

<210> 253

<211> 159

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic sequence

49JV_227262_W0_SEQ

<220>

<221> misc_feature

<223> Synthetic construct

<400> 253

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Arg Cys Gly Gly Ser Arg
1 5 10 15

Ser Gly Gly Thr Ser Gly Thr Gly Ser Thr Ser Gly Ser Gly Ser Ser
20 25 30

Gly Ser Thr Ser Gly Ser Gly Lys Ser Ser Glu Gly Ser Gly Gln Ala
35 40 45

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
50 55 60

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
65 70 75 80

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
85 90 95

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
100 105 110

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
115 120 125

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
130 135 140

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
145 150 155

<210> 254

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Anti-CD33 Light Chain

<400> 254

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

49JV_227262_W0_SEQ

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 255
<211> 484
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-CD33 SnAP-body variant 1 heavy chain
<400> 255

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
35 40 45

Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly
50 55 60

49JV_227262_W0_SEQ

Tyr Thr Phe Thr Ser Tyr Arg Met His Trp Val Lys Gln Ser Pro Gly
 65 70 75 80
 Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr
 85 90 95
 Glu Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys
 100 105 110
 Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp
 115 120 125
 Ser Ala Ile Tyr Tyr Cys Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp
 130 135 140
 Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 145 150 155 160
 Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 165 170 175
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 180 185 190
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 195 200 205
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 210 215 220
 Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
 225 230 235 240
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
 245 250 255
 Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 260 265 270
 Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 275 280 285
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 290 295 300
 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 305 310 315 320
 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 325 330 335

49JV_227262_W0_SEQ

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340 345 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
355 360 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370 375 380

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385 390 395 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405 410 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420 425 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435 440 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450 455 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465 470 475 480

Ser Pro Gly Lys

<210> 256
<211> 476
<212> PRT
<213> Artificial Sequence

<220>
<223> Anti-CD33 SnAP-body variant 2 heavy chain

<400> 256

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Ala Ala Arg Ala Ala Ala Ala Arg Ala Ala Ala Ala Arg Ala Gln Val
20 25 30

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
35 40 45

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
50 55 60

49JV_227262_W0_SEQ

His Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
 65 70 75 80
 Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
 85 90 95
 Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
 100 105 110
 Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg
 115 120 125
 Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
 130 135 140
 Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
 145 150 155 160
 Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
 165 170 175
 Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 180 185 190
 Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 195 200 205
 Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 210 215 220
 Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
 225 230 235 240
 Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
 245 250 255
 Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
 260 265 270
 Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
 275 280 285
 Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
 290 295 300
 Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
 305 310 315 320
 Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
 325 330 335

49JV_227262_W0_SEQ

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
340 345 350

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
355 360 365

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
370 375 380

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
385 390 395 400

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
405 410 415

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
420 425 430

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
435 440 445

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
450 455 460

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 257
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Control anti-CD33 heavy chain

<400> 257

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Arg Met His Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Ile Tyr Tyr Cys
85 90 95

49JV_227262_W0_SEQ

Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
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 Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

49JV_227262_W0_SEQ

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 258
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Meditope-enabled Gemtuzumab VL

<400> 258

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Ala Ala Thr Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ser Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 259
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Meditope-enabled Gemtuzumab VL

49JV_227262_W0_SEQ

<400> 259

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Met
35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ile Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Asp Ser Lys
85 90 95

Met Phe Gly Gln Gly Thr Lys Val Glu Val Lys
100 105

<210> 260

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Meditope-enabled gemtuzumab VH

<400> 260

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Arg Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

49JV_227262_W0_SEQ

Thr Val Ser Ser
115

<210> 261
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Meditope-enabled gemtuzumab VH

<400> 261

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Arg Ser
20 25 30

Ala Ile Ile Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Val Pro Met Phe Gly Pro Pro Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Phe Tyr Phe Cys
85 90 95

Ala Gly Gly Tyr Gly Ile Tyr Ser Pro Glu Glu Tyr Asn Gly Gly Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 262
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic linker 1

<400> 262

Gly Gly Gly Ala Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys
1 5 10 15

Lys Ala Ala Glu Glu Ala Ala Lys Ala Ala
20 25

<210> 263
<211> 18
<212> PRT
<213> Artificial Sequence

49JV_227262_W0_SEQ

<220>

<223> Synthetic linker 2

<400> 263

Gly Gly Gly Ala Ala Ala Arg Ala Ala Ala Ala Arg Ala Ala Ala Ala
1 5 10 15

Arg Ala

<210> 264

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic linker 3

<400> 264

Gly Gly Gly Ser Lys Asp Glu Ile Asp Ser Ala Val Lys
1 5 10

<210> 265

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Flexible linker portion 1

<400> 265

Gly Gly Gly
1

<210> 266

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Rigid linker portion 1

<400> 266

Ala Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala
1 5 10 15

Glu Glu Ala Ala Lys Ala Ala
20

<210> 267

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Rigid linker portion 2

49JV_227262_W0_SEQ

<400> 267

Ala Ala Ala Arg Ala Ala Ala Ala Arg Ala Ala Ala Ala Arg Ala
1 5 10 15

<210> 268

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Rigid linker portion 3

<400> 268

Ser Lys Asp Glu Ile Asp Ser Ala Val Lys
1 5 10

<210> 269

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> 1GCN glucagon

<400> 269

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr
20 25

<210> 270

<211> 38

<212> PRT

<213> Artificial Sequence

<220>

<223> Leucine zipper 1C94:A

<400> 270

Cys Gly Gly Arg Glu Gly Val Leu Lys Lys Leu Arg Ala Val Glu Asn
1 5 10 15

Glu Leu His Tyr Asn Lys Ser Leu Leu Glu Glu Val Lys Asp Glu Leu
20 25 30

Gln Lys Met Arg Gln Leu
35

<210> 271

<211> 37

<212> PRT

<213> Artificial Sequence

<220>

<223> Leucine zipper 1C94:A

49JV_227262_W0_SEQ

<400> 271

Gly Gly Arg Glu Gly Val Leu Lys Lys Leu Arg Ala Val Glu Asn Glu
1 5 10 15

Leu His Tyr Asn Lys Ser Leu Leu Glu Glu Val Lys Asp Glu Leu Gln
20 25 30

Lys Met Arg Gln Leu
35

<210> 272

<211> 183

<212> PRT

<213> Artificial Sequence

<220>

<223> Four helix bundle 1FHA

<400> 272

Met Thr Thr Ala Ser Thr Ser Gln Val Arg Gln Asn Tyr His Gln Asp
1 5 10 15

Ser Glu Ala Ala Ile Asn Arg Gln Ile Asn Leu Glu Leu Tyr Ala Ser
20 25 30

Tyr Val Tyr Leu Ser Met Ser Tyr Tyr Phe Asp Arg Asp Asp Val Ala
35 40 45

Leu Lys Asn Phe Ala Lys Tyr Phe Leu His Gln Ser His Glu Glu Arg
50 55 60

Glu His Ala Glu Lys Leu Met Lys Leu Gln Asn Gln Arg Gly Gly Arg
65 70 75 80

Ile Phe Leu Gln Asp Ile Gln Lys Pro Asp Cys Asp Asp Trp Glu Ser
85 90 95

Gly Leu Asn Ala Met Glu Cys Ala Leu His Leu Glu Lys Asn Val Asn
100 105 110

Gln Ser Leu Leu Glu Leu His Lys Leu Ala Thr Asp Lys Asn Asp Pro
115 120 125

His Leu Cys Asp Phe Ile Glu Thr His Tyr Leu Asn Glu Gln Val Lys
130 135 140

Ala Ile Lys Glu Leu Gly Asp His Val Thr Asn Leu Arg Lys Met Gly
145 150 155 160

Ala Pro Glu Ser Gly Leu Ala Glu Tyr Leu Phe Asp Lys His Thr Leu
165 170 175

49JV_227262_W0_SEQ

Gly Asp Ser Asp Asn Glu Ser
180

<210> 273
<211> 153
<212> PRT
<213> Artificial Sequence

<220>
<223> Myoglobin 3RGK

<400> 273

Gly Leu Ser Asp Gly Glu Trp Gln Leu Val Leu Asn Val Trp Gly Lys
1 5 10 15

Val Glu Ala Asp Ile Pro Gly His Gly Gln Glu Val Leu Ile Arg Leu
20 25 30

Phe Lys Gly His Pro Glu Thr Leu Glu Lys Phe Asp Arg Phe Lys His
35 40 45

Leu Lys Ser Glu Asp Glu Met Lys Ala Ser Glu Asp Leu Lys Lys His
50 55 60

Gly Ala Thr Val Leu Thr Ala Leu Gly Gly Ile Leu Lys Lys Lys Gly
65 70 75 80

His His Glu Ala Glu Ile Lys Pro Leu Ala Gln Ser His Ala Thr Lys
85 90 95

His Lys Ile Pro Val Lys Tyr Leu Glu Phe Ile Ser Glu Ala Ile Ile
100 105 110

Gln Val Leu Gln Ser Lys His Pro Gly Asp Phe Gly Ala Asp Ala Gln
115 120 125

Gly Ala Met Asn Lys Ala Leu Glu Leu Phe Arg Lys Asp Met Ala Ser
130 135 140

Asn Tyr Lys Glu Leu Gly Phe Gln Gly
145 150

<210> 274
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> EK peptide

<400> 274

Tyr Ala Glu Ala Ala Lys Ala Ala Glu Ala Ala Lys Ala Ala Glu Ala
1 5 10 15

49JV_227262_W0_SEQ

Ala Lys Ala Phe
20

<210> 275
<211> 154
<212> PRT
<213> Artificial Sequence

<220>
<223> SnAP-body Variant 1 VH

<400> 275

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
35 40 45

Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly
50 55 60

Tyr Thr Phe Thr Ser Tyr Arg Met His Trp Val Lys Gln Ser Pro Gly
65 70 75 80

Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Thr Gly Tyr Thr
85 90 95

Glu Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys
100 105 110

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp
115 120 125

Ser Ala Ile Tyr Tyr Cys Ala Arg Gly Gly Gly Val Phe Asp Tyr Trp
130 135 140

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
145 150

<210> 276
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain of meditope enabled gemtuzumab

<400> 276

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

49JV_227262_W0_SEQ

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 277

<211> 484

<212> PRT

<213> Artificial Sequence

<220>

<223> cQFD meditope, variant 1 linker, fused to the heavy chain of
meditope enabled gemtuzumab

<400> 277

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
Page 261

30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
Page 262

49JV_227262_W0_SEQ

290

295

300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305 310 315 320

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325 330 335

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340 345 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
355 360 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370 375 380

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385 390 395 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405 410 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420 425 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435 440 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450 455 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465 470 475 480

Ser Pro Gly Lys

<210> 278

<211> 476

<212> PRT

<213> Artificial Sequence

<220>

<223> cQFD meditope, variant 2 linker, fused to the heavy chain of meditope enabled gemtuzumab

<400> 278

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Ala Ala Arg Ala Ala Ala Ala Arg Ala Ala Ala Ala Arg Ala Gln Val
20 25 30

49JV_227262_W0_SEQ

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
35 40 45

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
50 55 60

His Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
65 70 75 80

Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
85 90 95

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
100 105 110

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg
115 120 125

Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
145 150 155 160

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
165 170 175

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
180 185 190

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
195 200 205

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
210 215 220

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
225 230 235 240

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
245 250 255

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
260 265 270

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
275 280 285

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
290 295 300

49JV_227262_W0_SEQ

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
305 310 315 320

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
325 330 335

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
340 345 350

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
355 360 365

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
370 375 380

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
385 390 395 400

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
405 410 415

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
420 425 430

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
435 440 445

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
450 455 460

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 279
<211> 471
<212> PRT
<213> Artificial Sequence

<220>
<223> cQFD meditope, variant 3 linker, fused to the heavy chain of
meditope enabled gemtuzumab

<400> 279

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ser
1 5 10 15

Lys Asp Glu Ile Asp Ser Ala Val Lys Gln Val Gln Leu Gln Gln Ser
20 25 30

Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

49JV_227262_W0_SEQ

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met His Trp Val Lys Gln
50 55 60

Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Thr
65 70 75 80

Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr
85 90 95

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
100 105 110

Phe Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Gly Gly Gly Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

49JV_227262_W0_SEQ

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 280

<211> 487

<212> PRT

<213> Artificial Sequence

<220>

<223> cQFD meditope, variant 1 linker, fused to the heavy chain of I83E
cetuximab

<400> 280

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
35 40 45

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
50 55 60

49JV_227262_W0_SEQ

Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
 65 70 75 80
 Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Asn Thr Asp
 85 90 95
 Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser
 100 105 110
 Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser Asn Asp Thr
 115 120 125
 Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe
 130 135 140
 Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr
 145 150 155 160
 Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 165 170 175
 Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 180 185 190
 Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 195 200 205
 Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 210 215 220
 Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 225 230 235 240
 Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
 245 250 255
 Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 260 265 270
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 275 280 285
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 290 295 300
 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 305 310 315 320
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 325 330 335

49JV_227262_W0_SEQ

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
340 345 350

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
355 360 365

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
370 375 380

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
385 390 395 400

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
405 410 415

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
420 425 430

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
435 440 445

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
450 455 460

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
465 470 475 480

Leu Ser Leu Ser Pro Gly Lys
485

<210> 281
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Meditope enabled trastuzumab light chain
<400> 281

Asp Ile Gln Met Thr Gln Ser Pro Ser Ile 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 Arg Thr Asn Lys Ala Pro Arg 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

49JV_227262_W0_SEQ

Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu 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
210

<210> 282
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<223> cQFD meditope, variant 1 linker, fused to the heavy chain of
meditope enabled trastuzumab

<400> 282

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly
35 40 45

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
50 55 60

Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ser Pro Gly
65 70 75 80

49JV_227262_W0_SEQ

Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
 85 90 95
 Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr
 100 105 110
 Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
 115 120 125
 Thr Ala Ile Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
 130 135 140
 Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
 145 150 155 160
 Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
 165 170 175
 Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
 180 185 190
 Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
 195 200 205
 His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
 210 215 220
 Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
 225 230 235 240
 Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
 245 250 255
 Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 260 265 270
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 275 280 285
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 290 295 300
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 305 310 315 320
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 325 330 335
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 340 345 350

49JV_227262_W0_SEQ

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
355 360 365

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
370 375 380

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
385 390 395 400

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
405 410 415

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
420 425 430

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
435 440 445

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
450 455 460

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
465 470 475 480

Ser Leu Ser Leu Ser Pro Gly
485

<210> 283
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Lintuzumab light chain

<400> 283

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 Glu Ser Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Lys
Page 272

49JV_227262_W0_SEQ

85

90

95

Glu Val Pro Trp Thr Phe Gly Gln 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
 210 215

<210> 284

<211> 446

<212> PRT

<213> Artificial Sequence

<220>

<223> Lintuzumab heavy chain

<400> 284

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Tyr Ile Tyr Pro Tyr Asn Gly Gly Thr Gly Tyr Asn Gln Lys Phe
 50 55 60

Lys Ser Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

49JV_227262_W0_SEQ

Ala Arg Gly Arg Pro Ala Met Asp Tyr 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 Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

49JV_227262_W0_SEQ

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 285
<211> 218
<212> PRT
<213> Artificial Sequence

<220>
<223> Meditope-enabled lintuzumab light chain

<400> 285

Asp Ile Gln Met Thr Gln Ser Pro Ser Ile Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Arg Thr Asn Lys Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Asp Asp Glu Ala Asp Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Ala Gly Thr Lys Leu 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
Page 275

49JV_227262_W0_SEQ

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
210 215

<210> 286

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<223> Meditope-enabled lintuzumab light chain, variant 1

<400> 286

Asp Ile Gln Met Thr Gln Ser Pro Ser Ile Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Thr Asn Lys Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Asp Asp Glu Ala Asp Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Ala Gly Thr Lys Leu 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

49JV_227262_W0_SEQ

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
210 215

<210> 287

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<223> Meditope-enabled lintuzumab light chain, variant 2

<400> 287

Asp Ile Gln Met Thr Gln Ser Pro Ser Ile Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Arg Thr Asn Lys Ala Pro
35 40 45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Ala Gly Thr Lys Leu 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
Page 277

49JV_227262_W0_SEQ

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
210 215

<210> 288

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<223> Meditope-enabled lintuzumab light chain, variant 3

<400> 288

Asp Ile Gln Met Thr Gln Ser Pro Ser Ile Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
20 25 30

Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro
35 40 45

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Asp Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Trp Thr Phe Gly Ala Gly Thr Lys Leu 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

49JV_227262_W0_SEQ

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
210 215

<210> 289
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Meditope-enabled lintuzumab heavy chain

<400> 289

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Pro Tyr Asn Gly Gly Thr Gly Tyr Asn Gln Lys Phe
50 55 60

Lys Ser Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Pro Ala Met Asp Tyr 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
Page 279

49JV_227262_W0_SEQ

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 Thr His Thr
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
 355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
 370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
 385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
 405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
 420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 435 440 445

<210> 290

49JV_227262_W0_SEQ

<211> 484
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Meditope-enabled lintuzumab heavy chain, variant 1

<400> 290

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
 1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
 20 25 30

Glu Ala Ala Lys Ala Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu
 35 40 45

Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly
 50 55 60

Tyr Thr Phe Thr Asp Tyr Asn Met His Trp Val Arg Gln Ser Pro Gly
 65 70 75 80

Gln Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Pro Tyr Asn Gly Gly Thr
 85 90 95

Gly Tyr Asn Gln Lys Phe Lys Ser Lys Ala Thr Ile Thr Ala Asp Glu
 100 105 110

Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp
 115 120 125

Thr Ala Ile Tyr Tyr Cys Ala Arg Gly Arg Pro Ala Met Asp Tyr Trp
 130 135 140

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 145 150 155 160

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 165 170 175

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 180 185 190

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 195 200 205

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 210 215 220

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
 225 230 235 240

49JV_227262_W0_SEQ

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
245 250 255

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
260 265 270

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
275 280 285

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
290 295 300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305 310 315 320

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325 330 335

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340 345 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
355 360 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370 375 380

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385 390 395 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405 410 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420 425 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435 440 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450 455 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465 470 475 480

Ser Pro Gly Lys

<210> 291
<211> 476
<212> PRT

<213> Artificial Sequence

<220>

<223> Meditope-enabled lintuzumab heavy chain, variant 2

<400> 291

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
 1 5 10 15

Ala Ala Arg Ala Ala Ala Arg Ala Ala Ala Arg Ala Glu Val
 20 25 30

Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val
 35 40 45

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met
 50 55 60

His Trp Val Arg Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
 65 70 75 80

Ile Tyr Pro Tyr Asn Gly Gly Thr Gly Tyr Asn Gln Lys Phe Lys Ser
 85 90 95

Lys Ala Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu
 100 105 110

Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys Ala Arg
 115 120 125

Gly Arg Pro Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
 130 135 140

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
 145 150 155 160

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
 165 170 175

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
 180 185 190

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
 195 200 205

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
 210 215 220

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
 225 230 235 240

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
 Page 283

49JV_227262_W0_SEQ

245

250

255

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
260 265 270

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
275 280 285

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
290 295 300

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
305 310 315 320

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
325 330 335

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
340 345 350

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
355 360 365

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
370 375 380

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
385 390 395 400

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
405 410 415

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
420 425 430

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
435 440 445

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
450 455 460

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 292

<211> 471

<212> PRT

<213> Artificial Sequence

<220>

<223> Meditope-enabled lintuzumab heavy chain, variant 3

<400> 292

49JV_227262_W0_SEQ

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ser
 1 5 10 15
 Lys Asp Glu Ile Asp Ser Ala Val Lys Glu Val Gln Leu Val Gln Ser
 20 25 30
 Gly Ala Glu Val Lys Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys
 35 40 45
 Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Asn Met His Trp Val Arg Gln
 50 55 60
 Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Pro Tyr Asn
 65 70 75 80
 Gly Gly Thr Gly Tyr Asn Gln Lys Phe Lys Ser Lys Ala Thr Ile Thr
 85 90 95
 Ala Asp Glu Ser Thr Asn Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg
 100 105 110
 Ser Glu Asp Thr Ala Ile Tyr Tyr Cys Ala Arg Gly Arg Pro Ala Met
 115 120 125
 Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
 130 135 140
 Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 145 150 155 160
 Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 165 170 175
 Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 180 185 190
 Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 195 200 205
 Val Val Thr Val Pro Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 210 215 220
 Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
 225 230 235 240
 Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 245 250 255
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 260 265 270

49JV_227262_W0_SEQ

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
325 330 335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
450 455 460

Leu Ser Leu Ser Pro Gly Lys
465 470

<210> 293
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain of CD33-SnAPbody MB-005-101

<400> 293

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
Page 286

49JV_227262_W0_SEQ

20

25

30

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 294

<211> 484

<212> PRT

<213> Artificial Sequence

<220>

<223> Heavy chain of CD33-SnAPbody MB-005-101. The cQFD meditope (*italic and underlined*) and variant 1 linker (**bold**) are fused to the heavy chain of meditope enabled gemtuzumab

<400> 294

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
Page 287

30

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
Page 288

49JV_227262_W0_SEQ

290

295

300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305 310 315 320

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
325 330 335

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340 345 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
355 360 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370 375 380

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
385 390 395 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405 410 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420 425 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435 440 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450 455 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465 470 475 480

Ser Pro Gly Lys

<210> 295

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Light chain of CD33-SnAPbody MB-005-102

<400> 295

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

49JV_227262_W0_SEQ

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 296

<211> 476

<212> PRT

<213> Artificial Sequence

<220>

<223> Heavy chain of CD33-SnAPbody MB-005-102. The cQFD meditope
(*italic and underlined*) and variant 2 linker (**bold**) are fused to
the heavy chain of meditope enabled gemtuzumab

<400> 296

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Ala Ala Arg Ala Ala Ala Ala Arg Ala Ala Ala Ala Arg Ala Gln Val
20 25 30

49JV_227262_W0_SEQ

Gln Leu Gln Gln Ser Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val
35 40 45

Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met
50 55 60

His Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr
65 70 75 80

Ile Asn Pro Ser Thr Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp
85 90 95

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
100 105 110

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg
115 120 125

Gly Gly Gly Val Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
130 135 140

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
145 150 155 160

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
165 170 175

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
180 185 190

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
195 200 205

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
210 215 220

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
225 230 235 240

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
245 250 255

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
260 265 270

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
275 280 285

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
290 295 300

49JV_227262_W0_SEQ

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
305 310 315 320

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
325 330 335

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
340 345 350

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
355 360 365

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
370 375 380

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
385 390 395 400

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
405 410 415

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
420 425 430

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
435 440 445

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
450 455 460

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
465 470 475

<210> 297
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain of CD33-SnAPbody MB-005-103

<400> 297

Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Tyr Met
20 25 30

His Trp Phe Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Trp Ile Tyr
35 40 45

Thr Thr Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
Page 292

49JV_227262_W0_SEQ

50

55

60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Ser Thr Tyr Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 298

<211> 471

<212> PRT

<213> Artificial Sequence

<220>

<223> Heavy chain of CD33-SnAPbody MB-005-103. The cQFD meditope
(*italic and underlined*) and variant 3 linker (**bold**) are fused to
the heavy chain of meditope enabled gemtuzumab

<400> 298

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ser
1 5 10 15

Lys Asp Glu Ile Asp Ser Ala Val Lys Gln Val Gln Leu Gln Gln Ser
20 25 30

Gly Ala Glu Leu Ala Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
35 40 45

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Arg Met His Trp Val Lys Gln
Page 293

49JV_227262_W0_SEQ

50

55

60

Ser Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Thr
65 70 75 80

Gly Tyr Thr Glu Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr
85 90 95

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
100 105 110

Phe Glu Asp Ser Ala Ile Tyr Tyr Cys Ala Arg Gly Gly Gly Val Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
130 135 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
145 150 155 160

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
165 170 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
180 185 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
195 200 205

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
210 215 220

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
225 230 235 240

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
245 250 255

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
260 265 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
275 280 285

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
290 295 300

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
305 310 315 320

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
Page 294

49JV_227262_W0_SEQ

325

330

335

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
 340 345 350

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 355 360 365

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 370 375 380

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 385 390 395 400

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 405 410 415

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 420 425 430

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 435 440 445

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 450 455 460

Leu Ser Leu Ser Pro Gly Lys
 465 470

<210> 299

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Light chain of EGFR-SnAPbody MB005-104

<400> 299

Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
 1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
 20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
 35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
 65 70 75 80

49JV_227262_W0_SEQ

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
85 90 95

Thr Phe Gly Ala 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
210

<210> 300
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain of EGFR-SnAPbody MB005-104. The cQFD meditope
(*italic and underlined*) and variant 1 linker (**bold**) are fused to
the heavy chain of cetuximab

<400> 300

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
35 40 45

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
50 55 60

Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
65 70 75 80

49JV_227262_W0_SEQ

Lys Gly Leu Glu Trp₈₅ Leu Gly Val Ile Trp₉₀ Ser Gly Gly Asn Thr Asp
 Tyr Asn Thr Pro₁₀₀ Phe Thr Ser Arg Leu₁₀₅ Ser Ile Asn Lys Asp₁₁₀ Asn Ser
 Lys Ser Gln₁₁₅ Val Phe Phe Lys Met₁₂₀ Asn Ser Leu Gln Ser₁₂₅ Asn Asp Thr
 Ala Ile Tyr Tyr Cys Ala Arg₁₃₅ Ala Leu Thr Tyr Tyr₁₄₀ Asp Tyr Glu Phe
 Ala Tyr Trp Gly Gln Gly₁₅₀ Thr Leu Val Thr Val₁₅₅ Ser Ala Ala Ser Thr₁₆₀
 Lys Gly Pro Ser Val₁₆₅ Phe Pro Leu Ala Pro₁₇₀ Ser Ser Lys Ser Thr₁₇₅ Ser
 Gly Gly Thr Ala₁₈₀ Ala Leu Gly Cys Leu₁₈₅ Val Lys Asp Tyr Phe₁₉₀ Pro Glu
 Pro Val Thr₁₉₅ Val Ser Trp Asn Ser₂₀₀ Gly Ala Leu Thr Ser₂₀₅ Gly Val His
 Thr Phe Pro Ala Val Leu Gln₂₁₅ Ser Ser Gly Leu Tyr₂₂₀ Ser Leu Ser Ser
 Val Val Thr Val Pro Ser₂₃₀ Ser Ser Leu Gly Thr₂₃₅ Gln Thr Tyr Ile Cys₂₄₀
 Asn Val Asn His Lys₂₄₅ Pro Ser Asn Thr Lys₂₅₀ Val Asp Lys Arg Val₂₅₅ Glu
 Pro Lys Ser Cys₂₆₀ Asp Lys Thr His Thr₂₆₅ Cys Pro Pro Cys Pro₂₇₀ Ala Pro
 Glu Leu Leu Gly Gly Pro Ser Val₂₈₀ Phe Leu Phe Pro Pro₂₈₅ Lys Pro Lys
 Asp Thr Leu Met Ile Ser Arg₂₉₅ Thr Pro Glu Val Thr₃₀₀ Cys Val Val Val
 Asp Val Ser His Glu Asp₃₁₀ Pro Glu Val Lys Phe₃₁₅ Asn Trp Tyr Val Asp₃₂₀
 Gly Val Glu Val His₃₂₅ Asn Ala Lys Thr Lys₃₃₀ Pro Arg Glu Glu Gln Tyr₃₃₅
 Asn Ser Thr Tyr₃₄₀ Arg Val Val Ser Val₃₄₅ Leu Thr Val Leu His₃₅₀ Gln Asp

49JV_227262_W0_SEQ

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
355 360 365

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
370 375 380

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
385 390 395 400

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
405 410 415

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
420 425 430

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
435 440 445

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
450 455 460

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
465 470 475 480

Leu Ser Leu Ser Pro Gly Lys
485

<210> 301
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain of EGFR-SnAPbody MB005-105
<400> 301

Asp Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
Page 298

Thr Phe Gly Ala 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
 210

<210> 302

<211> 487

<212> PRT

<213> Artificial Sequence

<220>

<223> Heavy chain of EGFR-SnAPbody MB005-105. The cQFD meditope (*italic and underlined*) and variant 3 linker (**bold**) are fused to the heavy chain of I83E cetuximab

<400> 302

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
 1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
 20 25 30

Glu Ala Ala Lys Ala Ala Gln Val Gln Leu Lys Gln Ser Gly Pro Gly
 35 40 45

Leu Val Gln Pro Ser Gln Ser Leu Ser Ile Thr Cys Thr Val Ser Gly
 50 55 60

Phe Ser Leu Thr Asn Tyr Gly Val His Trp Val Arg Gln Ser Pro Gly
 65 70 75 80

Lys Gly Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Asn Thr Asp
 Page 299

49JV_227262_W0_SEQ

85

90

95

Tyr Asn Thr Pro Phe Thr Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser
 100 105 110

Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ser Asn Asp Thr
 115 120 125

Ala Ile Tyr Tyr Cys Ala Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe
 130 135 140

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr
 145 150 155 160

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
 165 170 175

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
 180 185 190

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
 195 200 205

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
 210 215 220

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
 225 230 235 240

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu
 245 250 255

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 260 265 270

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 275 280 285

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 290 295 300

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 305 310 315 320

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 325 330 335

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 340 345 350

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
 Page 300

49JV_227262_W0_SEQ

355

360

365

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 370 375 380

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 385 390 395 400

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 405 410 415

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 420 425 430

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 435 440 445

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 450 455 460

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 465 470 475 480

Leu Ser Leu Ser Pro Gly Lys
 485

<210> 303

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> Light chain of HER2-SnAPbody MB005-106

<400> 303

Asp Ile Gln Met Thr Gln Ser Pro Ser Ile 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 Arg Thr Asn Lys Ala Pro Arg 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 Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
 85 90 95

49JV_227262_W0_SEQ

Thr Phe Gly Ala Gly Thr Lys Leu 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
210

<210> 304
<211> 487
<212> PRT
<213> Artificial Sequence

<220>
<223> Heavy chain of HER2-SnAPbody MB005-106. The cQFD meditope
(*italic and underlined*) and variant 3 linker (**bold**) are fused to
the heavy chain of meditope enabled trastuzumab

<400> 304

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Glu Val Gln Leu Val Glu Ser Gly Gly Gly
35 40 45

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
50 55 60

Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg Gln Ser Pro Gly
65 70 75 80

Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr
85 90 95

49JV_227262_W0_SEQ

Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr
100 105 110

Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
115 120 125

Thr Ala Ile Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala
130 135 140

Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
145 150 155 160

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
165 170 175

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
180 185 190

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
195 200 205

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
210 215 220

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
225 230 235 240

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
245 250 255

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
260 265 270

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
275 280 285

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
290 295 300

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
305 310 315 320

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
325 330 335

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
340 345 350

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
355 360 365

49JV_227262_W0_SEQ

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
370 375 380

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
385 390 395 400

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
405 410 415

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
420 425 430

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
435 440 445

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
450 455 460

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
465 470 475 480

Ser Leu Ser Leu Ser Pro Gly
485

<210> 305
<211> 211
<212> PRT
<213> Artificial Sequence

<220>
<223> Light chain of CD19-SnAPbody MB005-107

<400> 305

Glu Ile Val Leu Thr Gln Ser Pro Val Ile Leu Ser Ala Ser Pro Gly
1 5 10 15

Glu Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Gly Val Asn Tyr Met
20 25 30

His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Ser Met Glu Pro Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys His Gln Arg Gly Ser Tyr Thr Phe Gly
85 90 95

Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val
Page 304

49JV_227262_W0_SEQ

100

105

110

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
115 120 125

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
130 135 140

Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145 150 155 160

Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
165 170 175

Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
180 185 190

Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
195 200 205

Gly Glu Cys
210

<210> 306

<211> 488

<212> PRT

<213> Artificial Sequence

<220>

<223> Heavy chain of CD19-SnAPbody MB005-107. The cQFD meditope (*italic and underlined*) and variant 3 linker (**bold**) are fused to the heavy chain of meditope enabled anti CD19 antibody

<400> 306

Cys Gln Phe Asp Leu Ser Thr Arg Arg Leu Lys Cys Gly Gly Gly Ala
1 5 10 15

Arg Glu Glu Ala Ala Lys Ala Ala Glu Glu Ala Lys Lys Ala Ala Glu
20 25 30

Glu Ala Ala Lys Ala Ala Gln Val Gln Leu Val Gln Pro Gly Ala Glu
35 40 45

Val Val Lys Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Thr Ser Gly
50 55 60

Tyr Thr Phe Thr Ser Asn Trp Met His Trp Val Lys Gln Ser Pro Gly
65 70 75 80

Gln Gly Leu Glu Trp Ile Gly Glu Ile Asp Pro Ser Asp Ser Tyr Thr
85 90 95

Asn Tyr Asn Gln Asn Phe Gln Gly Lys Ala Lys Leu Thr Val Asp Lys
Page 305

49JV_227262_W0_SEQ

100

105

110

Ser Thr Ser Thr Ala Tyr Met Glu Val Ser Ser Leu Arg Ser Asp Asp
 115 120 125

Thr Ala Ile Tyr Tyr Cys Ala Arg Gly Ser Asn Pro Tyr Tyr Tyr Ala
 130 135 140

Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Ser
 145 150 155 160

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
 165 170 175

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
 180 185 190

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
 195 200 205

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
 210 215 220

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
 225 230 235 240

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
 245 250 255

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 260 265 270

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 275 280 285

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 290 295 300

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 305 310 315 320

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 325 330 335

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 340 345 350

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 355 360 365

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 Page 306

49JV_227262_W0_SEQ

370

375

380

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
385 390 395 400

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
405 410 415

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
420 425 430

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
435 440 445

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
450 455 460

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
465 470 475 480

Ser Leu Ser Leu Ser Pro Gly Lys
485