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(71) Applicant: **LYVGEN BIOPHARMA CO., LTD.** [CN/CN]; 67 Li Bing Road, Building#4, Pudong Zhangjiang Hi-tech Park, Shanghai, 201203 (CN).

(72) Inventor; and
(71) Applicant: **WANG, Jieyi** [US/US]; 2317 Hastings Drive, Belmont, CA 94002 (US).

(72) Inventor: **WU, Yi**; Room 207, 67 Li Bing Road, Building 4, Pudong Zhangjiang Hi-tech Park, Shanghai, 201203 (CN).

(74) Agent: **CHEN, Yahua**; Polsinelli Pc, One International Place, Suite 3900, Boston, MA 02110 (US).

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(54) Title: ANTI-CD40 BINDING MOLECULES HAVING ENGINEERED FC DOMAINS AND THERAPEUTIC USES THEREOF

(57) Abstract: The disclosure provides CD40-binding molecules comprising engineered human IgG domains, for example, human IgG1, IgG2, and IgG4 variants having mutations in the hinge domain, which exhibit altered binding activity to one or more Fey receptors. Also described herein are methods for selectively activating or inhibiting immune responses in a subject using the CD40-binding molecules.

Anti-CD40 Binding Molecules Having Engineered Fc Domains and Therapeutic Uses Thereof

RELATED APPLICATION

This application claims the benefit of International Patent Application No. PCT/CN2018/0108285, filed on September 28, 2018, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

Cluster of differentiation 40 (CD40) is an antigen-presenting cell (APC) costimulatory protein required for APC activation. CD40 is a member of the tumor necrosis factor (TNF)-receptor superfamily and is essential for various immune and inflammatory responses, including T cell-dependent immunoglobulin class switching, memory B cell development, and germinal center formation. Additionally, CD40 is found on the surface of tumor cells, such as B-lymphomas and about 70% of all solid tumors. Its activation has been shown to reverse tolerance to tumor-specific antigens, leading to antigen-specific antitumor immunity.

Fc receptors (FcR) are a family of immune cell surface proteins capable of binding to the Fc portion of antibodies. There are several different types of Fc receptors, including Fcγ receptors, Fcα receptors, Fcε receptors, and neonatal Fc receptors (FcRn), which have different binding activities to IgG, IgA, IgE, and IgG antibodies, respectively. The Fcγ receptor subfamily includes FcγRI (CD64), FcγRIIA (CD32a), FcγRIIB (CD32b), FcγRIIB (CD32c), FcγRIIIA (CD16a), and FcγRIIIB (CD16b). FcγRI has high binding affinity to IgG1 and IgG3 antibodies, while the other FcγRs have low binding affinity to IgG antibodies.

Different types of Fc receptors play different roles in the immune system. For example, FcγRIII receptors, expressed on NK cells and macrophages, bind to antibodies that are attached to infected cells or invading pathogens and trigger antibody-mediated phagocytosis (ADCP) or antibody-dependent cell-mediated cytotoxicity (ADCC) of the immune cells, thereby leading to elimination of the infected cells or invading pathogens. On the other hand, FcγRIIB receptors, expressed on B cells and dendritic cells, can down regulate the activity of the immune cells when binding to IgG antibodies.

Therapies involving activated immune cells are promising approaches for eliminating diseased cells such as cancer cells. However, such therapeutic approaches often raise safety

concerns. For example, overly activated immune cells would lead to undesired cytotoxicity, causing tissue damage. It is therefore of great interest to develop new immune therapies that are effective and safe.

SUMMARY OF THE INVENTION

The present disclosure is based, at least in part, on the design of CD40-binding molecules (*e.g.*, CD40 agonists or CD40 antagonists) comprising an engineered (variant) Fc region (*e.g.*, an engineered Fc region of IgG1, IgG2, or IgG4 molecules) that exhibit desired hinge flexibility and preferred Fc receptor binding activity and/or selectivity, *e.g.*, enhanced binding affinity and/or selected to FcγRIIB or substantially reduced binding affinity to one or more FcγR receptors. Such CD40-binding molecules can be used for modulating immune responses (*e.g.*, selectively enhancing or selectively inhibiting an immune response) in subject in need of the treatment.

Accordingly, one aspect of the present disclosure provides a CD40-binding molecule (*e.g.*, a CD40 agonist or a CD40 antagonist) comprising a CD40 binding moiety and an antibody heavy chain constant region comprising an engineered Fc region, which comprises at least one mutation at any of positions 220-331, for example, any of positions 228-329, as compared to the wild-type Fc region counterpart. The numbering system is according to the EU index.

In some embodiments, the CD40 binding moiety is the extracellular domain of a CD40L, which may comprise the amino acid sequence of SEQ ID NO:140. A CD40-binding molecule comprising such a CD40-binding moiety may be a CD40 agonist.

In other embodiments, the CD40 binding moiety can be an anti-CD40 antibody fragment. In one embodiment, the anti-CD40 antibody fragment comprises a heavy chain that comprises a heavy chain variable region, which is linked to any of the engineered Fc regions described herein, and a light chain that comprises a light chain variable region, and a light chain constant region.

In some instances, the variant Fc region may have an enhanced binding affinity and/or selectivity to FcγRIIB relative to the wild-type counterpart. In other instances, the variant Fc region may have substantially reduced binding affinity to one or more FcγR receptors. In some examples, the variant Fc region has low or no binding activity to all FcγR receptors.

In some embodiments, the CD40-binding molecule may comprise a variant Fc region of an IgG1 molecule (*e.g.*, a human IgG1 molecule), which may comprise a mutation comprising one or more of the following: (a) an amino acid substitution or deletion within positions 233-238 (*e.g.*, 234-238); (b) a substitution at position 265; (c) a substitution at position 267; (d) a substitution at position 297; (e) a substitution at position 328, a substitution at position 329; or a combination thereof. Alternatively or in addition, the Fc variant of an IgG1 molecule may comprise one or more mutations at positions 220, 226, 229, 238, 273, 327, 330, and/or 331. In one example, the mutation comprises substitutions at any of positions 233-236, a deletion at one or more of positions 236-238, or a combination thereof. For example, the substitutions at positions 233-235 may comprise E233P, L234V, L234F, L234A, L235A, and/or L235E. In one example, the mutation comprises a deletion at one or more of positions 236-238. In another example, the substitution at position 238 can be P238S, the substation at position 265 can be D265A, or a combination thereof. In yet another example, the substitution is at position 267 and is S267E. In a further example, the substitution is at position 329 and is P329G. In an additional example, the mutation may comprise a substitution at position 265, a substitution at position 297, or a combination thereof. For example, the substitution at position 265 may be D265A and the substitution at position 297 may be N297A. Further, the one or more substitutions at positions 220, 226, 229, 327, 330, and 331 can be C220S, C226S, C229S, A327G, A330S, and P331S. Exemplary variant Fc regions derived from human IgG1 may be one of G1m1, G1m2, G1m17, G1m27, G1mAA, G1mAAG, G1N297A, G1m240, and G1m40.

In other embodiments, the CD40-binding molecule may comprise an Fc region of an IgG2 molecule (*e.g.*, a human IgG2 molecule), which may comprise a mutation comprising one or more of the following: (a) a deletion of one or more of positions 237 and 238; (b) a substitution at position 265; (b) a substitution at position 267; (c) a substitution at position 297; (d) a substitution at position 328; or a combination thereof. In some examples, the deletion is at position 237 or at both positions 237 and 238. Alternatively or in addition, the Fc variant of an IgG2 molecule may comprise at least one mutation comprising a substitution at one or more of positions 233-235, 237, 238, 268, 273, 330, and 331. For example, the substitution at one or more of positions 233-235, 237, 238, 268, 273, 330, and 331 can be

P233E, V234A, V234L, A235L, A235S, G237A, P238S, H268A, H268Q, V273E, A330S, and P331S. In one example, the substitution is at position 267 and is S267E. In another example, the substitution is at position 328 and is L328F. In an additional example, the mutation may comprise a substitution at position 265, a substitution as position 297, or a combination thereof. For example, the substitution at position 265 may be D265A and the substitution at position 297 may be N297A. In some particular examples, the variant Fc region derived from IgG2 can be one of G2m1, G2m17, G2m18, G2m19, G2m20, G2m27, G2m28, G2m29, G2m2040, G2m43, G2G4, G2mAA, and G2m40.

In yet other embodiments, the CD40-binding molecule may comprise an Fc region of an IgG4 molecule (*e.g.*, a human IgG4 molecule), which may comprise (a) an amino acid residue substitution at position 228; (b) a substitution or deletion at any one positions 235-238; (c) a substitution at position 265; (d) a substitution at position 267; (e) a substitution at position 297; (e) a substitution at position 328; or a combination thereof. In one example, the substitution at position 228 is S228P. In another example, the deletion is at one or more of positions 236, 237, and 238 (*e.g.*, at both positions 236 and 237). Alternatively or in addition, the Fc variant of an IgG4 molecule may comprise a substitution at one or more of positions 233-235, 237, and 273. For example, the substitution at one or more positions 233-235, 237, and 273 may be E233P, F234V, F234A, L235S, L235E, L235A, G237A, and V273E. In another example, the substitution at position 267 is S267E. In a further example, the substitution at position 328 is L328F. In an additional example, the mutation may comprise a substitution at position 265, a substitution at position 297, or a combination thereof. For example, the substitution at position 265 may be D265A and the substitution at position 297 may be N297A. In some particular examples, the variant Fc region is one of G4m1, G4m2, G4m20, G4m28, G4m30, G4m41, G4m42, G4m46, G4mPE, G4mAA, and G4m40.

Any of the variant Fc regions described herein may exhibit an enhanced binding activity and/or an enhanced selectivity to FcγRIIB as compared with the wild-type Fc region. Alternatively, the variant Fc regions described herein may have low or no binding activity to any of the FcγR receptors. In some instances, the variant Fc region may exhibit a decreased binding affinity to FcγRIIB. Alternatively or in addition, the variant Fc region binds FcRn.

The anti-CD40 antibody fragment in any of the CD40-binding molecules described herein may be of a human antibody or a humanized antibody. In some embodiments, the anti-CD40 antibody is an agonist antibody. In some examples, the anti-CD40 antibody may comprise the same heavy chain complementary determining regions (HC CDRs) as those in SEQ ID NO: 128 or as those in any one of 19G6D6, 36G7B8, 13F1A7, 9F12D9, and 17C5C2, and/or the same light chain complementary determining regions (LC CDRs) as those in SEQ ID NO: 129 or those in any one of 19G6D6, 36G7B8, 13F1A7, 9F12D9, and 17C5C2. In one example, the antibody fragment may comprise a heavy chain variable region of SEQ ID NO: 128 and/or a light chain variable region of SEQ ID NO: 129. In other examples, the antibody fragment may comprise the same heavy chain variable region and/or the same light chain variable region as one of 19G6D6, 36G7B8, 13F1A7, 9F12D9, and 17C5C2.

Additionally, provided herein is a pharmaceutical composition, comprising any of the CD40-binding molecules described herein and a pharmaceutically acceptable carrier. Such a pharmaceutical composition may be used to selectively modulate (*e.g.*, selectively activate or selectively inhibit) an immune response in a subject.

In yet another aspect, the present disclosure provides a method for selectively modulating (*e.g.*, selectively activating or selectively inhibiting) an immune response in a subject, the method comprising administering to a subject in need thereof an effective amount of a CD40-binding molecule as described herein.

In any of the methods described herein, the subject can be a human patient having or suspected of having a cancer and the CD40-binding molecule may be a CD40 agonist. Exemplary cancers include lung cancer, stomach cancer, liver cancer, breast cancer, skin cancer, pancreatic cancer, brain cancer, prostate cancer, bladder cancer, colorectal cancer, sarcoma, bone cancer, lymphoma and a hematological cancer.

Alternatively, the subject can be a human patient having or suspected of having an immune-related disorder and the CD40-binding molecule may be a CD40 antagonist. Exemplary immune disorders include autoimmune diseases, immune-deficiencies, or allergies. In some embodiments, the target disease for treatment is an autoimmune disease.

In yet another aspect, the disclosure provides an isolated anti-CD40 antibody, which binds to the same epitope of CD40 as a reference antibody selected from the group consisting

of: 19G6D6, 36G7B8, 13F1A7, 9F12D9, and 17C5C2 or competes against the reference antibody from binding to the epitope.

In some embodiments, the antibody comprises a heavy chain complementary determining region 1 (CDR1), a heavy chain complementary determining region 2 (CDR2), and a heavy chain complementary determining region 3 (CDR3), which collectively are at least 85% identical to the respective heavy chain CDRs of the reference antibody; and/or wherein the antibody comprises a light chain CDR1, a light chain CDR2, and a light chain CDR3, which collectively are at least 85% identical to the respective light chain CDRs of the reference antibody.

In another embodiment, the heavy chain CDR1, heavy chain CDR2, and heavy chain CDR3 collectively comprise 10 or fewer amino acid mutations relative to the respective heavy chain CDRs of the reference antibody; and/or wherein the light chain CDR1, light chain CDR2, and light chain CDR3 collectively comprise 10 or fewer amino acid mutations relative to the respective light chain CDRs of the reference antibody.

In one embodiment, the antibody comprises a heavy chain variable region that is at least 85% identical to the heavy chain variable region of the reference antibody and/or a light chain variable region that is at least 85% identical to the light chain variable region of the reference antibody.

In some embodiments, the heavy chain variable region comprises 10 or fewer amino acid residue mutations relative to the heavy chain variable region of the reference antibody; and/or and a light chain variable region that comprises 10 or fewer amino acid mutations relative to the light chain variable region of the reference antibody.

In some examples, the anti-CD40 antibody disclosed herein may comprise the same heavy chain variable region CDRs as the reference antibody and/or the same light chain variable region CDRs as the reference antibody.

Any of the anti-CD40 antibodies described herein may be a human antibody or a humanized antibody. Also provided herein is a pharmaceutical composition comprising any of the anti-CD40 antibodies described herein and a pharmaceutically acceptable carrier.

Further, the instant disclosure features an isolated nucleic acid or set of nucleic acids which collectively encode any of the CD40 binding molecules or any of the anti-CD40 antibodies described herein. The nucleic acid or set of nucleic acids may be located on one or

two vectors, for example, expression vectors. Also provided herein are host cells comprising such vector(s).

The instant disclosure also features pharmaceutical compositions comprising one or more of the CD40-binding molecules described herein and/or one or more of the anti-CD40 antibodies disclosed herein for use in treating a target disorder as described herein, or uses of such CD40-binding molecules and/or anti-CD40 antibodies for manufacturing a medicament for use in treating the target disorder.

The details of one or more embodiments of the invention are set forth in the description below. Other features or advantages of the present invention will be apparent from the following drawings and detailed description of several embodiments, and also from the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1A-1D are charts showing binding activity of various anti-CD40 antibody 383 IgG variants as indicated to different types of Fcγ receptors expressed on CHO-K1 cells at the various concentrations as indicated. The concentrations of each IgG variant, from left to right, are 0.1 μg/ml, 0.3 μg/ml, 1 μg/ml, 3 μg/ml, 10 μg/ml, and 30 μg/ml. The two rightmost bars ("2nd only" and "blank") served as controls. **FIG 1A**: binding affinity to FcγRI. **FIG. 1B**: binding affinity to FcγRII. **FIG. 1C**: binding affinity to FcγRIIB. **FIG. 1D**: binding affinity to FcγRIIIA.

FIG. 2 is a chart showing stimulation of human CD40 activation in a reporter assay by a number of anti-CD40 antibody 383 IgG variants as indicated by IL8 secretion. The concentrations of each IgG variant, from left to right, correspond to: 0.003 μg/ml, 0.01 μg/ml, 0.03 μg/ml, 0.1 μg/ml, 0.3 μg/ml, 1 μg/ml, 3 μg/ml, and 10 μg/ml.

FIGs. 3A-3D are charts showing binding activity of a number of anti-CD40 antibody 383 IgG variants as indicated to different types of Fcγ receptors expressed on CHO-K1 cells. The concentrations of each anti-CD40 antibody 383 IgG variant, from left to right, are 0.3 μg/ml, 1 μg/ml, 3 μg/ml, 10 μg/ml, and 30 μg/ml. The two rightmost bars ("2nd only" and "blank") served as controls. **FIG. 3A**: binding affinity to FcγRIIB. **FIG. 3B**: binding affinity to FcγRI. **FIG. 3C**: binding affinity to FcγRIIA. **FIG. 3D**: binding affinity to FcγRIIIA.

FIGs. 4A-4F are charts showing stimulation of human CD40 activation indicated by

IL8 secretion in a reporter assay by a number of anti-CD40 antibody 383 IgG variants in solution and/or in co-culture with FcγRIIB expressing cells. The concentrations of each IgG variant, from left to right, correspond to: 0.003 μg/ml, 0.01 μg/ml, 0.03 μg/ml, 0.1 μg/ml, 0.3 μg/ml, and 1 μg/ml. Dash line indicates baseline reporter signal in each assay. **FIG 4A**: IgG variants IgG1m2, IgG2m20, IgG1m40, IgG4m40. **FIG. 4B**: IgG variants IgG1m240, IgG2m2040, IgG4m41, IgG4m42, IgG2m43, IgG2m44, and IgG4mAA . **FIG. 4C**: IgG variants IgG1 N297A, IgG2mAA, IgG2G4, IgG4mPE, and IgG1mAAG. **FIG. 4D**: IgG variants of IgG1m47, IgG1m48, IgG1m49, IgG1m50, and IgG1mAA. **FIG. 4E**: IgG variants of IgG4m46 and IgG4m30. **FIG. 4F**: IgG variants of IgG1m27, IgG2m19, IgG2m1, IgG4m2 and IgG4m20.

FIGs. 5A-5D include a set of bar graphs showing the activity of exemplary anti-CD40 antibody 383 IgG variants as indicated in activation of human dendritic cells (DC) from a healthy donor by the antibodies either in solution (**FIG. 5A and 5B**) or in co-culture of CHO cells expressing human FcγRIIB (**FIG. 5C and 5D**). DC activation is indicated by the bar graphs signal of IL-8 in the culture supernatant.

FIGs. 6A-6B are charts showing binding activity of anti-CD40 antibody 383 IgG variants as indicated to human CD40 expressed on CHO-K1 cells. The concentrations of each IgG variant, from left to right, are 0.01 μg/ml, 0.1 μg/ml, 1 μg/ml, and 10 μg/ml. The three rightmost bars ("Herceptin", "2nd only" and "blank") served as controls. **FIG. 6A**: a number of anti-CD40 antibody 383 IgG variants as indicated. **FIG. 6B**: a number of anti-CD40 antibody 383 IgG variants as indicated.

FIGs. 7A-7B are charts showing tumor growth curves of various anti-CD40 antibody 383 IgG variants as indicated in a mouse tumor model. **FIG. 7A**: a chart showing tumor volume changes at various time points after antibody treatment in homozygous B-hCD40 C57BL6 mice. The average ± SEM of tumor sizes are shown. **FIG. 7B**: is a chart showing serum alanine transaminase (ALT, a liver enzyme released into serum upon liver damage) level after treatment of antibodies as shown in homozygous B-hCD40 C57BL6 mice. The average ± SEM of tumor sizes are shown.

DETAILED DESCRIPTION OF THE INVENTION

Provided herein are CD40-binding molecules (*e.g.*, CD40 agonists or CD40 antagonists) comprising a CD40 binding moiety (*e.g.*, an extracellular domain of a CD40

ligand or an anti-CD40 antibody fragment) and an engineered (variant) Fc regions, which may have altered binding affinity and/or specificity to one or more Fc receptors, for example, enhanced binding affinity to FcγRIIB, enhanced binding specificity to FcγRIIB, and/or substantially reduced binding affinity to one or more FcγR receptors (*e.g.*, low or no binding activity to all FcγR receptors).

Such CD40-binding molecules are expected to exhibit unexpected, superior therapeutic activity. For example, CD40-binding molecules having a variant Fc region that has enhanced binding affinity to FcγRIIB would be expected to exhibit enhanced agonistic activity and CD40-binding molecules having a variant Fc region that has enhanced binding specificity to FcγRIIB would be expected to exhibit higher tumor selectivity relative to the wild-type counterpart. Further, CD40-binding molecules having low or no binding affinity to FcγR receptors would help activate CD40-positive immune cells in tumor microenvironment and/or block CD40-positive immune cells in immune disorders.

Accordingly, described herein are approaches for designing CD40-binding molecules comprising a CD40-binding moiety and an engineered Fc region (an Fc variant) which may be of an IgG molecule (*e.g.*, IgG1, IgG2, and IgG4 molecules such as human IgG1, human IgG2, and human IgG4 molecules), and uses thereof for modulating immune responses. Such an Fc variant may have enhanced binding affinity to FcγRIIB (CD32B) relative to the wild-type counterpart and/or binding selectivity as relative to other Fc receptors such as FcγRIII (CD16). Alternatively, such an Fc variant may have substantially reduced binding affinity to one or more FcγR receptors (*e.g.*, to all FcγR receptors) relative to the wild-type counterpart. "Substantially reduced" means that the binding affinity of a Fc variant to a FcγR receptor is at least 60% lower (*e.g.*, 70% lower, 80% lower, 90% lower, 95% lower, 98% lower, or 99% lower) than the binding affinity of the wild-type counterpart to the same FcγR receptor. In some examples, the Fc variant may have low or no binding affinity to all FcγR receptors, *i.e.*, binding affinity cannot be detected by conventional assays or binding affinity is substantially low such that no significant bioactivity would be triggered.

I. CD40-Binding Molecules

Described herein are CD40-binding molecules that comprise a CD40-binding moiety linked to an engineered Fc region having altered binding affinity and/or specificity to one or

more Fc receptors as described herein. Such CD40-binding molecules may be CD40 agonists, which are capable of triggering the signaling mediated by CD40/CD40L upon binding to cell surface CD40. Alternatively, the CD40-binding molecules described herein are CD40 antagonists, which are capable of inhibiting the signaling mediated by CD40/CD40L upon binding to cell surface CD40. The CD40-binding molecules are useful in modulating (selectively modulating) immune responses when administered to a subject in need of the treatment.

(i) CD40-Binding Moieties

A CD40-binding moiety as described herein may be any peptide or polypeptide that binds CD40, for example human CD40. CD40 is an immune cell receptor well known in the art. For example, NCBI GenBank Accession Nos. P25942.1 and AAB08705.1 provide information for human and mouse CD40, respectively. Provided below is an amino acid sequence of an exemplary human CD40 polypeptide.

Human CD40:

MVRLPLQCVLWGCLLTAVHPEPPTACREKQYLINSQCCSLCQPGQKLVSDCTEFTETECLPCGESEFLDT
WNRETHCHQHKYCDPNLGLRVQQKGTSETDTICTCEEGWHCTSEACESCVLHRSCSPGFGVKQIATGVSD
TICEPCPVGFFSNVSSAFEKCHPWTSCETKDLVVQQAGTNKTDVVCGPQDRLRALVVIPIIFGILFAILL
VLVFIKKVAKKPTNKAPHPKQEPQEINFPDDLPGSNTAAPVQETLHGCQPVTQEDGKESRISVQERQ (SEQ ID NO: 141)

CD40 polypeptides from other species are known in the art and can be obtained from publicly available gene databases, for example, GenBank, using either the human sequence or the mouse sequence as a query.

In some embodiments, the CD40-binding moieties can be a polypeptide comprising an extracellular domain of a CD40 ligand (CD40L or CD154). CD40L is a membrane glycoprotein expressed on the surface of T cells. The molecule has been shown to stimulate B cell proliferation and the secretion of immunoglobulins in the presence of cytokines. In addition, CD40L may induce cytokine production and tumoricidal activity in peripheral blood monocytes. The sequence of CD40L and its extracellular domain are well known in the art. For example, NCBI GenBank Accession No. NP_000065.1 (extracellular domain, amino acids 47-261) provides information for human CD40L. Provided below is an amino acid sequence of an extracellular domain of an exemplary human CD40L.

Human CD40L (extracellular domain):

HRRLDKIEDERNLHEDFVFMKTIQRCNTGERSLSLLNCEEIKSQFEGFVKDIMLNKEETKKENSFEMQKGDQNPQ
IAAHVISEASSKTTSVLQWAEKGYYTMSNNLVTLENGKQLTVKRQGLYYIYAQVTFCSNREASSQAPFIASLCLK
SPGRFERILLRAANTHSSAKPCGQQSIHLGGVFELQPGASVFVNVTDPSQVSHGTGFTSFGLLKL (SEQ ID
NO: 140)

CD40L polypeptides from other species are known in the art and can be obtained from publicly available gene databases, for example, GenBank, using the human sequence as a query.

In other embodiments, the CD40-binding moiety described herein can comprise an anti-CD40 antibody. As used herein, the term "anti-CD40 antibody" refers to any antibody capable of binding to a CD40 polypeptide, which can be of a suitable source, for example, human or a non-human mammal (*e.g.*, mouse, rat, rabbit, primate such as monkey, etc.).

The anti-CD40 antibodies described herein comprise a heavy chain that comprises a heavy chain variable domain, which is linked to any of the Fc variants described herein, and optionally a light chain that comprises a light chain variable region and a light chain constant region. The heavy chain variable region (V_H) and optionally the light chain variable region (V_L) are usually involved in antigen (CD40 in this case) binding.

The V_H and V_L regions can be further subdivided into regions of hypervariability, also known as "complementarity determining regions" ("CDR"), interspersed with regions that are more conserved, which are known as "framework regions" ("FR"). Each V_H and V_L is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the Chothia definition, the AbM definition, and/or the contact definition, all of which are well known in the art. See, *e.g.*, Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). See also hgmp.mrc.ac.uk and bioinf.org.uk/abs).

In some embodiments, the anti-CD40 antibody as described herein can bind and inhibit the activity of CD40 by at least 50% (*e.g.*, 60%, 70%, 80%, 90%, 95% or greater,

including any increment therein). The apparent inhibition constant (Ki^{app} or $K_{i,app}$), which provides a measure of inhibitor potency, is related to the concentration of inhibitor required to reduce enzyme activity and is not dependent on enzyme concentrations. The inhibitory activity of an anti-CD40 antibody described herein can be determined by routine methods known in the art.

The $K_{i,}^{app}$ value of an antibody may be determined by measuring the inhibitory effect of different concentrations of the antibody on the extent of the reaction (*e.g.*, enzyme activity); fitting the change in pseudo-first order rate constant (v) as a function of inhibitor concentration to the modified Morrison equation (Equation 1) yields an estimate of the apparent Ki value. For a competitive inhibitor, the Ki^{app} can be obtained from the y-intercept extracted from a linear regression analysis of a plot of $K_{i,}^{app}$ versus substrate concentration.

$$v = A \cdot \frac{([E]-[I]-K_i^{app}) + \sqrt{([E]-[I]-K_i^{app})^2 + 4[E] \cdot K_i^{app}}}{2} \qquad \text{(Equation 1)}$$

Where A is equivalent to v_o/E, the initial velocity (v_o) of the enzymatic reaction in the absence of inhibitor (I) divided by the total enzyme concentration (E).

In some embodiments, the anti-CD40 antibody described herein may have a Ki^{app} value of 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 50, 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5 pM or less for the target antigen or antigen epitope. In some embodiments, any of the anti-CD40 antibodies may be further affinity matured to reduce the Ki^{app} of the antibody to the target antigen or antigenic epitope thereof.

In some instances, the anti-CD40 antibody may suppress the signaling triggered by CD40/CD40L interaction by at least 50% (*e.g.*, 60%, 70%, 80%, 90%, 95% or greater, including any increment therein). Such inhibitory activity can be determined by conventional methods or the assays described herein.

The antibodies described herein can be murine, rat, human, or any other origin (including chimeric or humanized antibodies). Such antibodies are non-naturally occurring, *i.e.*, would not be produced in an animal without human act (*e.g.*, immunizing such an animal with a desired antigen or fragment thereof or isolated from antibody libraries).

In some embodiments, the anti-CD40 antibody is a humanized antibody, which may have one of more of the elements or characteristics described below or elsewhere herein. Humanized antibodies refer to forms of non-human (*e.g.*, murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or antigen-binding fragments thereof that contain minimal sequence derived from non-human immunoglobulin. In general, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In some instances, the humanized antibody may comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, or six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody. Humanized antibodies may also involve affinity maturation.

Methods for constructing humanized antibodies are also well known in the art. See, *e.g.*, Queen *et al.*, Proc. Natl. Acad. Sci. USA, 86:10029-10033 (1989). In one example, variable regions of V_H and V_L of a parent non-human antibody are subjected to three-dimensional molecular modeling analysis following methods known in the art. Next, framework amino acid residues predicted to be important for the formation of the correct CDR structures are identified using the same molecular modeling analysis. In parallel, human V_H and V_L chains having amino acid sequences that are homologous to those of the

parent non-human antibody are identified from any antibody gene database using the parent V_H and V_L sequences as search queries. Human V_H and V_L acceptor genes are then selected.

The CDR regions within the selected human acceptor genes can be replaced with the CDR regions from the parent non-human antibody or functional variants thereof. When necessary, residues within the framework regions of the parent chain that are predicted to be important in interacting with the CDR regions can be used to substitute for the corresponding residues in the human acceptor genes.

In some embodiments, the anti-CD40 antibodies described herein specifically bind to the corresponding target antigen or an epitope thereof, *e.g.*, CD40 antigen or epitope. An antibody that "specifically binds" to an antigen or an epitope is a term well understood in the art. A molecule is said to exhibit "specific binding" if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen than it does with alternative targets. An antibody "specifically binds" to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically (or preferentially) binds to an antigen (CD40) or an antigenic epitope therein is an antibody that binds this target antigen with greater affinity, avidity, more readily, and/or with greater duration than it binds to other antigens or other epitopes in the same antigen. It is also understood with this definition that, for example, an antibody that specifically binds to a first target antigen may or may not specifically or preferentially bind to a second target antigen. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. In some examples, an antibody that "specifically binds" to a target antigen or an epitope thereof may not bind to other antigens or other epitopes in the same antigen *(i.e.*, only baseline binding activity can be detected in a conventional method). In some embodiments, the anti-CD40 antibodies described herein specifically bind to CD40. Alternatively, or in addition, the anti-CD40 antibody described herein specifically binds human CD40 or a fragment thereof as relative to the mouse counterpart, or *vice versa* (*e.g.*, having a binding affinity at least 10-fold higher to one antigen than the other as determined in the same assay under the same assay conditions). In other instances, the anti-CD40 antibody described herein may cross-react to human and a non-human CD40 (*e.g.*, mouse), *e.g.*, the

difference in binding affinity to the human and the non-human CD40 is less than 5-fold, *e.g.*, less than 2-fold, or substantially similar.

In some embodiments, an anti-CD40 antibody as described herein has a suitable binding affinity for the target antigen (*e.g.*, CD40) or antigenic epitopes thereof. As used herein, "binding affinity" refers to the apparent association constant or K_A. The K_A is the reciprocal of the dissociation constant (K_D). The anti-CD40 antibody described herein may have a binding affinity (K_D) of at least 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10} M, or lower for the target antigen or antigenic epitope. An increased binding affinity corresponds to a decreased K_D. Higher affinity binding of an antibody for a first antigen relative to a second antigen can be indicated by a higher K_A (or a smaller numerical value K_D) for binding the first antigen than the K_A (or numerical value K_D) for binding the second antigen. In such cases, the antibody has specificity for the first antigen (*e.g.*, a first protein in a first conformation or mimic thereof) relative to the second antigen (*e.g.*, the same first protein in a second conformation or mimic thereof; or a second protein). Differences in binding affinity (*e.g.*, for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold. In some embodiments, any of the anti-CD40 antibodies may be further affinity matured to increase the binding affinity of the antibody to the target antigen or antigenic epitope thereof.

Binding affinity (or binding specificity) can be determined by a variety of methods including equilibrium dialysis, equilibrium binding, gel filtration, ELISA, surface plasmon resonance, or spectroscopy (*e.g.*, using a fluorescence assay). Exemplary conditions for evaluating binding affinity are in HBS-P buffer (10 mM HEPES pH7.4, 150 mM NaCl, 0.005% (v/v) Surfactant P20). These techniques can be used to measure the concentration of bound binding protein as a function of target protein concentration. The concentration of bound binding protein ([Bound]) is generally related to the concentration of free target protein ([Free]) by the following equation:

$$[Bound] = [Free]/(Kd+[Free])$$

It is not always necessary to make an exact determination of K_A, though, since sometimes it is sufficient to obtain a quantitative measurement of affinity, *e.g.*, determined using a method such as ELISA or FACS analysis, is proportional to K_A, and thus can be used

for comparisons, such as determining whether a higher affinity is, *e.g.*, 2-fold higher, to obtain a qualitative measurement of affinity, or to obtain an inference of affinity, *e.g.*, by activity in a functional assay, *e.g.*, an *in vitro* or *in vivo* assay.

Provided below is an example anti-CD40 antibody 383 (V_H and V_L amino acid sequences; CDRs are indicated in boldface):

V_H:

QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTGYYMH**WVRQAPGQGLEWMG**WINPDSGGTNYAQKFQG**RVTMTR DTSISTAYMELNRLRSDDTAVYYCAR**DQPLGYCTNGVCSYFDY**WGQGTLVTVSS (SEQ ID NO: 128)

V_L:

DIQMTQSPSSVSASVGDRVTITC**RASQGIYSWLA**WYQQKPGKAPNLLIY**TASTLQS**GVPSRFSGSGSGTDFT LTISSLQPEDFATYYC**QQANIFPLT**FGGGTKVEIK (SEQ ID NO: 129)

Further exemplary anti-CD40 antibodies are provided below (CDRs are indicated in boldface).

19G6D6

V_H:

EVQLQQSGPELVKPGASVKIPCKAS**GYTFTDYNMD**WVKQSHGKSLEWIG**DINPNNDISIYNQKFRG**KATLTV DKSSSTAYMELRSLTSEDTAVYYCAR**RFAY**WGQGTLVTVSA (SEQ ID NO: 130)

V_L:

DVVMTQIPLSLPVSIGDQASISC**RSSQSLVYSYGNTYLH**WFLQKPGQSPKLLIY**NVSNRFS**GVPDRFSGSGS GTDFTLRISRVEAEDLGVYFC**SQGTHVPWT**FGGGTKLEIK(SEQ ID NO: 131)

36G7B8

V_H:

QVQLQQPGAELVRPGASVKLSCKAS**GYIFISYWIH**WLKQRPGRGLEWIG**RIDPNNGGTKYNEKFRY**KASLTV DKSSSTAYMQLSSLTSEDSAVYYCTK**GVITTLVAGDY**WGQGTTLTVSS (SEQ ID NO: 132)

V_L:

DIQMTQSPASLSASLGETVSIEC**LASEDISNDLA**WYQQKSGKSPQLLIY**FVDRLLD**GVPSRFSGSGSGTRHS LKISGMQPEDEADYFC**QQSYKYPPT**FGGGTKLELK (SEQ ID NO: 133)

13F1A7

V_H:

EVQILETGGGLVKPGGSLRLSCATS**GFNFNDSFMN**WVRQAPGKGLEWVA**QIRNKNYNYATYYTESLEG**RVTI SRDDSKSRVYLQVSSLRAEDSAVYYCTS**YYYDGFADYFDY**WGQGVMVTVSS (SEQ ID NO: 134)

V_L:

EIVLTQSPTTMAASPGEKITITC**SASSSISSNYLH**WYQQKPGSSPKVLIY**RTSNLAS**GVPVRFSGSGSGTSY
SLTIGTMEAEDVATYYC**QQGSSIPYT**FGGGTKLEIK(SEQ ID NO: 135)

9F12D9

V_H:

EVHLVESGGGLVQPGRSLKLSCAAS**GFTFTNYGLH**WIRQAPTKGLEWVA**SISPSGGVTYYRDSVKG**RFTISR
DNGKTTLHLQMDSLRSEDTATYYCAL**PFLGWGGANWIAH**WGQGTLVTVSS(SEQ ID NO: 136)

V_L:

DIKVTQSPSFLSASVGDRATINC**KASQNLNKYLN**WYQQKPGEPPKLLIY**NTDNLYT**GIPSRFSGSGSVADFT
LTISGLQPEDVATYFC**MQHNVRRT**FGGGTKLELK(SEQ ID NO: 137)

17C5C2

V_H:

EVHILETGGGLVKPGGSLGLSCTTS**GFNFNDYFMN**WVRQAPGKGLEWVA**QIRNGNYDYAAYYAESLEG**RVTI
SRDDSKSSVNLQVSSLRAEDTAIYYCTS**YYYDGHFDYFDN**WGHGVMVTVSS (SEQ ID NO: 138)

V_L:

DIKMTQSPSFLSASVGDSVTFTC**KASQNIYIYLN**WYQQKFGEAPKLLIY**NTNNLQT**GIPSRFSGSESGTVFT
LTISSLQPEDVATYFC**LQHSSRRT**FGGGTKLELK (SEQ ID NO: 139)

In some embodiments, the anti-CD40 antibodies described herein bind to the same epitope as any of the exemplary antibodies described herein or competes against the exemplary antibody from binding to the CD40 antigen.

An "epitope" refers to the site on a target antigen that is recognized and bound by an antibody. The site can be entirely composed of amino acid components, entirely composed of chemical modifications of amino acids of the protein (*e.g.*, glycosyl moieties), or composed of combinations thereof. Overlapping epitopes include at least one common amino acid residue. An epitope can be linear, which is typically 6-15 amino acids in length. Alternatively, the epitope can be conformational. The epitope to which an antibody binds can be determined by routine technology, for example, the epitope mapping method (see, *e.g.*, descriptions below). An antibody that binds the same epitope as an exemplary antibody described herein may bind to exactly the same epitope or a substantially overlapping epitope (*e.g.*, containing less than 3 non-overlapping amino acid residue, less than 2 non-overlapping amino acid residues, or only 1 non-overlapping amino acid residue) as the exemplary antibody. Whether two antibodies compete against each other from binding to the cognate antigen can be determined by a competition assay, which is well known in the art.

In some embodiments, the anti-CD40 antibodies disclosed herein comprise the same heavy chain and light chain CDRs as those in (a) SEQ ID NO: 128 and SEQ ID NO: 129, (b) SEQ ID NO: 130 and SEQ ID NO: 131 (19G6D6); (c) SEQ ID NO: 132 and SEQ ID NO: 133 (36G7B8); (d) SEQ ID NO: 134 and SEQ ID NO: 135 (13F1A7); (e) SEQ ID NO: 136 and SEQ ID NO: 137 (9F12D9), or (f) SEQ ID NO: 138 and SEQ ID NO: 139 (17C5C2). In some examples, the anti-CD40 antibody comprises a heavy chain variable domain of SEQ ID NO: 128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, or SEQ ID NO:138, and/or a light chain variable domain of SEQ ID NO: 129, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, or SEQ ID NO:139.

Also within the scope of the present disclosure are functional variants of any one of the exemplary anti-CD40 antibodies as disclosed herein. Such functional variants are substantially similar to any one of the exemplary anti-CD40 antibodies, both structurally and functionally. A functional variant comprises substantially the same V_H and V_L CDRs as any one of the exemplary anti-CD40 antibodies. For example, it may comprise only up to 10 (*e.g.*, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1) amino acid residue variations in the total CDR regions of the antibody (collectively) and binds the same epitope of CD40 with substantially similar affinity (*e.g.*, having a K_D value in the same order). Alternatively or in addition, the amino acid residue variations are conservative amino acid residue substitutions. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, *e.g.* Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

In some embodiments, the anti-CD40 antibody described herein may comprise heavy chain CDRs, which in combination (collectively) have at least 80% (*e.g.*, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) sequence identity with the

heavy chain CDRs in SEQ ID NO: 128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, or SEQ ID NO:138. Alternatively or in addition, the anti-CD40 antibody may comprises light chain CDRs, which collectively have at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) sequence identity with those in SEQ ID NO: 129, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, or SEQ ID NO:139.

In some embodiments, the anti-CD40 antibody described herein may comprise a heavy chain variable domain that is at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) to SEQ ID NOs: 128, 130, 132, 134, 136, or 138 and/or a light chain variable domain that is at least 80% (*e.g.*, 85%, 90%, 95%, 96%, 97%, 98%, 99% and any incremental percent therein) identical to SEQ ID NOs: 129, 131, 133, 135, 137, or 139.

The "percent identity" of two amino acid sequences is determined using the algorithm of Karlin and Altschul Proc. Natl. Acad. Sci. USA 87:2264-68, 1990, modified as in Karlin and Altschul Proc. Natl. Acad. Sci. USA 90:5873-77, 1993. Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) of Altschul, et al. J. Mol. Biol. 215:403-10, 1990. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the protein molecules of interest. Where gaps exist between two sequences, Gapped BLAST can be utilized as described in Altschul et al., *Nucleic Acids Res.* 25(17):3389-3402, 1997. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used.

(ii) Engineered Fc Regions

The CD40-binding molecules described herein comprise a modified heavy chain constant region, in which the Fc domain is modified to modulate its binding affinity and/or specificity to Fc receptors such as FcγRs.

In some embodiments, the Fc variants in the CD40-binding molecules described herein have enhanced selectivity to FcγRIIB relative to its wild-type counterpart. An Fc fragment having selectivity to FcγRIIB, selectively binding to FcγRIIB, or specifically binding to FcγRIIB is a term well understood in the art. A molecule is said to exhibit

"selective binding" or "specific binding" if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen (*e.g.*, an FcγRIIB receptor) than it does with alternative targets (*e.g.*, FcγRIII receptors). An Fc fragment "specifically binds" to an Fc receptor if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other Fc receptors. For example, an Fc fragment that specifically (or preferentially) binds to FcγRIIB is an Fc fragment that binds this Fc receptor with greater affinity, avidity, more readily, and/or with greater duration than it binds to other Fc receptors. It is also understood with this definition that, for example, an Fc fragment that selectively or specifically binds to a first Fc receptor may or may not specifically or preferentially bind to a second Fc receptor. As such, "selective binding," "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. In some examples, an Fc fragment that "selectively binds," or "specifically binds" to a target Fc receptor (*e.g.*, FcγRIIB) may not bind to other Fc receptors (*i.e.*, binding not detectable by routine methods). In other embodiments, the variant Fc fragment does not bind to any FcγRs.

Relative binding affinities of IgG1, IgG2, and IgG4 to different Fc receptors are given in Table 1 below.

Table 1. Relative Binding Affinities of Human and Mouse Immunoglobulins to Fc Receptors

Human				Mouse			
FcγR	IgG1	IgG2	IgG4	FcγR	IgG1	IgG2a	IgG2b
I	++++	-	++++	I	-	++++	++++
IIA (H131)	+++	++	++	III	++	++	++
IIA (R131)	+++	+	++				
IIB	++	+/-	++	IIB	+++	++	+++
IIIA (V158)	+++	+	++	IV	-	+++	++
IIIA (F158)	++	+/-	++				

The Fc variants described herein may have enhanced selectivity to FcγRIIB relative to their wild-type counterparts (the wild-type parent Fc region in which mutations are introduced to produce the Fc variants). The relative binding activity to FcγRIIB *versus* another Fc receptor (*e.g.*, FcγRIII) of such an Fc variant is higher than the relative binding activity to FcγRIIB *versus* the other Fc receptor (*e.g.*, FcγRIII) of the wild-type counterpart.

The Fc variant may have enhanced binding activity to FcγRIIB and/or decreased binding activity to another Fc receptor, for example, FcγRIII. In some embodiments, the Fc variants described herein may have decreased binding activity to both FcγRIIB and another Fc receptor (for example, FcγRIII); however, the level of decreased binding activity to the other Fc receptor (*e.g.*, FcγRIII) is greater than the level of decreased binding activity to FcγRIIB.

In some embodiments, an Fc variant as described herein has a suitable binding affinity for FcγRIIB, *e.g.*, enhanced as compared with the wild-type parent Fc from which the Fc variant is derived. As used herein, "binding affinity" refers to the apparent association constant or K_A. The K_A is the reciprocal of the dissociation constant (K_D). The Fc variant described herein may have a binding affinity (K_D) of at least 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10} M, or lower for FcγRIIB. An increased binding affinity corresponds to a decreased K_D. Higher affinity binding of an Fc fragment for a first Fc receptor relative to a second Fc receptor can be indicated by a higher K_A (or a smaller numerical value K_D) for binding the first Fc receptor than the K_A (or numerical value K_D) for binding the second Fc receptor. In such cases, the Fc variant has specificity for the first Fc receptor relative to the second Fc receptor. In some embodiments, the Fc variants described herein have a higher binding affinity (a higher K_A or smaller K_D) to FcγRIIB as compared to the binding affinity to FcγRIII (either FcγRIIIA or FcγRIIIB). Differences in binding affinity (*e.g.*, for specificity or other comparisons) can be at least 1.5, 2, 3, 4, 5, 10, 15, 20, 37.5, 50, 70, 80, 91, 100, 500, 1000, 10,000 or 10^5 fold.

In some embodiments, the Fc variants described herein may be designed by mutating one or more amino acid residues in the wild-type of human IgG1, IgG2, or IgG4 Fc fragments in light of the amino acid residues in the corresponding mouse IgG, for example, mouse IgG1. A sequence comparison of human and mouse IgGs (hIgG and mIgG, respectively) is provided below (SEQ ID NOs: 60-64, from top to bottom, each representing a combination of fragments 211-245, 260-278, and 320-332 of the corresponding Fc region):

```
          21-       22-       23-       24-    …26-       27-       …32-       33-
          12345678 9012345678901234567890123456…0123456789012345678…0123456789012
               Upper       CoreLower     CH2
hIgG1     VDKKVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP…TCVVVDVSHEDPEVKFNWY…KCKVSNKALPAPI
hIgG2     VDKTVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP…TCVVVDVSHEDPEVQFNWY…KCKVSNKGLPAPI
hIgG4     VDKRVESKYG----PPCPSCPAPEFLGGPSVFLFPP…TCVVVDVSQEDPEVQFNWY…KCKVSNKGLPSSI
mIgG1     VDKKIVPR-DC--GCKPCICTVPEVS---SVFIFPP…TCVVVDISKDDPEVQFSWF…KCRVNSAAFPAPI
mIgG2a    VDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPP…TCVVVDVSEDDPDVQISWF…KCKVNNKDLPAPI
```

The amino acid sequences of wild-type murine IgG1 and IgG2 Fc fragments, as well as exemplary Fc variants with reduced FcγR binding are provided below:

Amino acid sequence of wild-type mouse IgG1 Fc fragment:

VDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQ
PREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSL
TCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKS
LSHSPGK (SEQ ID NO: 142)

Amino acid sequence of wild-type mouse IgG2a Fc fragment:

VDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEV
HTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMT
KKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHN
HHTTKSFSRTPGK (SEQ ID NO: 143)

Amino acid sequence of mutant mouse IgG1mDANA Fc fragment:

VDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVAISKDDPEVQFSWFVDDVEVHTAQTQ
PREEQFASTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSL
TCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKS
LSHSPGK (SEQ ID NO: 144)

Amino acid sequence of mutant mouse IgG2a1mDANA Fc fragment:

VDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVAVSEDDPDVQISWFVNNVEV
HTAQTQTHREDYASTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMT
KKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHN
HHTTKSFSRTPGK (SEQ ID NO: 145)

In some embodiments, the Fc variants described herein is a human IgG1, G2, or G4 Fc variants comprising one or more mutations (*e.g.*, amino acid substitutions, deletions, or additions) in the hinge domain of an Fc fragment. Human IgGs contain a core motif of CPPC or CPSC in the hinge domain (positions 226-229 according to the EU index). Positions 216 to 225 are deemed as the upper portion of the hinge domain and positions 230-238 are deemed as the lower portion of the hinge domain. The numbering system used herein, unless explicitly indicated, is according to the EU index. In some examples, the one or more mutations can be located in the upper portion of the hinge domain. Alternatively or in addition, the one or more mutations can be located in the lower portion of the hinge domain. In some embodiments, the Fc region of any of the anti-CD40 molecules disclosed herein may comprise at least one mutation at any of positions 220-331, preferably at any of positions 228-329. Such Fc variants may have altered binding affinity and/or specificity to one or

more of Fc receptors (*e.g.*, FcγIIB, FcγRI, FcγRIIA, or FcγRIIIA) as compared with their native counterparts.

In some embodiments, the mutations to a human IgG Fc can be made according to the corresponding amino acid residues in the hinge domain of mouse IgG1. For example, mouse IgG1 does not contain the GGP motif at positions 236-238. Accordingly, one or more of the residues in this GGP motif can be deleted from a human IgG1, IgG2, or IgG4 Fc fragment to produce the Fc variants described herein.

Alternatively or in addition, the human Fc variants may contain one or more amino acid substitutions in the upper portion, in the lower portion, or both of the hinge domain. For example, the Fc variant may comprise one or more amino acid substitutions at one or more of positions 233, 234, 235, and/or 236. Such an amino acid substitution may be in combination with the deletion of one or more of the GGP motif (236-238) noted herein. These mutations may be introduced into a human IgG2 or IgG4 Fc fragment to produce the Fc variants described herein. In some examples, the Fc variants described herein contains a deletion at one or more of the positions 236-238 (*e.g.*, 236, 237, 238 or any combination thereof)

Any of the mutations in the hinge domain described herein may be in combination with a mutation (*e.g.*, amino acid substitutions) at one or more positions that are involved in interaction with an Fc receptor. Such positions include, but are not limited to, positions 265, 267, 273, 297, and 327-331, or a combination thereof. Exemplary amino acid substitutions at those positions include D265A, S267E, V273E, N297A, L328F, P329G, A330S, and/or P331S.

In some embodiments, the Fc variants disclosed herein can be derived from an IgG1 molecule (e.g., human IgG1) and contain one or more mutations at positions at one or more of positions 220, 226, 229, 234-238, 265, 267, 297, and 327-331. For example, the Fc variant may comprise a substitution or deletion within positions 234-238, a substitution at position 265 (*e.g.*, D265A), a substitution at position 267 (*e.g.*, S267E), a substitution at position 297 (*e.g.*, N297A), a substitution at position 328 (*e.g.*, L328F), a substitution at position 329 (*e.g.*, P329G), or a combination thereof. Alternatively or in addition, it may comprise a substitution at one or more of the positions 220 (*e.g.*, C220S), 226 (*e.g.*, C226S), 229 (*e.g.*, C229S), 327 (*e.g.*, A327G), 330 (*e.g.*, A330S), and 331 (*e.g.*, P331S). In some instances, the

Fc variants derived from an IgG1 molecule may comprise a deletion at one or more of positions 236-238.

In some embodiments, the Fc variants disclosed herein can be derived from an IgG2 molecule (*e.g.*, human IgG2) and contain one or more mutations at one or more of positions 233-235, 237-238, 265-268, 273, 297, 328, 330, and 331. In some examples, such a Fc variant may comprise comprises a deletion within positions 237-238 (*e.g.*, a deletion at position 237 or a deletion of both positions 237 and 238), a substitution at position 265 (*e.g.*, D265A), a substitution at position 267 (*e.g.*, S267E), a substitution at position 297 (*e.g.*, N297A), a substitution at position 328 (*e.g.*, L328F), or a combination thereof. Alternatively or in addition, the Fc variant derived from an IgG2 molecule may comprise a substitution at one or more of positions 233-235, 237, 238, 268, 273, 330, and 331 (*e.g.*, P233E, V234A, V234L, A235L, A235S, G237A, P238S, H268A, H268Q, V273E, A330S, and P331S).

In yet other embodiments, the Fc variants disclosed herein can be derived from an IgG4 molecule (e.g., human IgG4) and contain one or more mutations at one or more positions of 228, 233-238, 265, 267, 273, 297, and 328. In some examples, such a Fc variant may comprise a substitution at position 228 (*e.g.*, S228P), a substitution or deletion at any of positions 235-238 (*e.g.*, a deletion at one of positions 236-238, for example, position 236 and position 237), a substitution at position 265 (*e.g.*, D265A), a substitution at position 267 (*e.g.*, S267E), a substitution at position 273 (*e.g.*, V273E), a substitution at position 297 (*e.g.*, N297A), a substitution at position 328 (*e.g.*, L328F), or a combination thereof. Alternatively or in addition, the Fc variant may comprise a substitution at one or more of positions 233-235 and 237 (e.g., E233P, F234V, F234A, L235S, L235E, L235A, and G237A).

Fc variants derived from IgG2 or IgG4 molecules that contain one or more mutations at positions 265, 267, 273, 297, 328, and/or 329 are also within the scope of the present disclosure. Such mutations may include amino acid substitutions at one or more of these positions, for example, D265A, S267E, V273E, N297A, L328F, and/or P329G.

In some instances, any of the Fc variants disclosed herein may further comprise a mutation at position 309, for example, a substitution (*e.g.*, V309L). Such an Fc variant may be derived from an IgG2 molecule (*e.g.*, human IgG2). In some embodiments, the mutation at position 309 may be in combination with mutations at one or more of positions 234, 268, 330, and 331. Examples of such Fc variants include G2m43.

In some embodiments, an Fc variant described herein may comprise an amino acid sequence at least 85% identical (*e.g.*, 90%, 95%, 98%, 99%, or above) to that of its wild-type counterpart (*e.g.*, the Fc fragment of wild-type human IgG1, IgG2, or IgG4 described herein).

In one example, the amino acid residue substitutions in an Fc variant described herein are conservative amino acid residue substitutions.

Provided below is a sequence alignment showing exemplary positions where mutations can be introduced into hIgG1, hIgG2, and IgG4 to produce various Fc variants for the present disclosure.

Sequence alignment of human IgG1 variants relative to wild-type human IgG1 (SEQ ID NOs:70-88 and 163-168, from top to bottom):

```
                21-       22-       23-       24-    ...26-       27-       ...32-       33-
                12345678  90123456789012345678901234...0123456789012345...0123456789012
                   Upper       CoreLower     CH2
hIgG1     VDKKVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m1      KVEPK-SCDKTHTCPPCPAPELL---SVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m2      KVEPK-SCDKTHTCPPCPAPELL-GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m-2   KKVEPK-CC-v-e-CPPCPAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m-4   KKVEPKYG---ppCPPCPAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m5      KVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP...TCVVVDVSHEDPEeKFNWY...KCKVSNKALPAPI
hIgG1m7      KVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP...TCVVVDVeHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m8      KVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKfPAPI
hIgG1m9      KVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP...TCVVVDVeHEDPEVKFNWY...KCKVSNKfPAPI
hIgG1m15     KVEPK-SCDKTHTCPPCPAPELL---SVFLFPP...TCVVVDVSHEDPEeKFNWY...KCKVSNKALPAPI
hIgG1m17     KVEPK-SCDKTHTCPPCPAPELL---SVFLFPP...TCVVVDVeHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m18     KVEPK-SCDKTHTCPPCPAPELL---SVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKfPAPI
hIgG1m19     KVEPK-SCDKTHTCPPCPAPELL---SVFLFPP...TCVVVDVeHEDPEVKFNWY...KCKVSNKfPAPI
hIgG1m25     KVEPK-SCDKTHTCPPCPAPELL-GPSVFLFPP...TCVVVDVSHEDPEeKFNWY...KCKVSNKALPAPI
hIgG1m27     KVEPK-SCDKTHTCPPCPAPELL-GPSVFLFPP...TCVVVDVeHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m28     KVEPK-SCDKTHTCPPCPAPELL-GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKfPAPI
hIgG1m29     KVEPK-SCDKTHTCPPCPAPELL-GPSVFLFPP...TCVVVDVeHEDPEVKFNWY...KCKVSNKfPAPI
hIgG1mAA   KKVEPK-SCDKTHTCPPCPAPEaaGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1mAG   KKVEPK-SCDKTHTCPPCPAPEaaGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALgAPI
hIgG1m40 VDKKVEPK-SCDKTHTCPPCPAPELLGGPSVFLFPP...TCVVVaVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m45 VDKKVEPK-SCDKTHTCPPCPAPpva-GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m240VDKKVEPK-SCDKTHTCPPCPAPELL-GPSVFLFPP...TCVVVaVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m47 VDKKVEPK-SCDKTHTCPPCPAPpva-GPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKgLPssI
hIgG1m48 VDKKVEPK-SsDKTHTsPPsPAPELLGGsSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m49 VDKKVEPK-SCDKTHTsPPsPAPpvaGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAPI
hIgG1m50 VDKKVEPK-SCDKTHTCPPCPAPEfeGGPSVFLFPP...TCVVVDVSHEDPEVKFNWY...KCKVSNKALPAsI
```

Sequence alignment of human IgG2 variants relative to wild-type human IgG2 (SEQ ID NOs: 89-105 and 169-173, from top to bottom):

```
                21-       22-       23-       24-    ...26-       27-       ...32-       33-
                12345678  90123456789012345678901234...0123456789012345...0123456789012
                   Upper       CoreLower     CH2

hIgG2     VDKTVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m1      TVERK-CC-V-E-CPPCPAPPVA-==SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m-1   KTVERK-SCDKTHTCPPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m2      TVERK-CC-V-E-CPPCPAPPflgGPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
```

```
hIgG2m-4   KTVERKYG--P-PPCPPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m5     TVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEeQFNWY...KCKVSNKGLPAPI
hIgG2m7     TVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVeHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m8     TVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGfPAPI
hIgG2m9     TVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVeHEDPEVQFNWY...KCKVSNKGfPAPI
hIgG2m10    TVERK-CC-V-E-CPPCPAPevs---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGfPAPI
hIgG2m15    TVERK-CC-V-E-CPPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEeQFNWY...KCKVSNKGLPAPI
hIgG2m17    TVERK-CC-V-E-CPPCPAPPVA---SVFLFPP...TCVVVDVeHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m18    TVERK-CC-V-E-CPPCPAPPVA---SVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGfPAPI
hIgG2m19    TVERK-CC-V-E-CPPCPAPPVA---SVFLFPP...TCVVVDVeHEDPEVQFNWY...KCKVSNKGfPAPI
hIgG2m20    TVERK-CC-V-E-CPPCPAPPVA--PSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m27    TVERK-CC-V-E-CPPCPAPPVA--PSVFLFPP...TCVVVDVeHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m28    TVERK-CC-V-E-CPPCPAPPVA--PSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGfPAPI
hIgG2m40 VDKTVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVaVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2m43 VDKTVERK-CC-V-E-CPPCPAPPaA-asSVFLFPP...TCVVVDVSaEDPEVQFNWY...KCKVSNKGLPssI
hIgG2m44 VDKTVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVSqEDPEVQFNWY...KCKVSNKGLPssI
hIgG2mAA VDKTVERK-CC-V-E-CPPCPAPPaA-aPSVFLFPP...TCVVVDVSHEDPEVQFNWY...KCKVSNKGLPAPI
G2m2040  VDKTVERK-CC-V-E-CPPCPAPPVA--PSVFLFPP...TCVVVaVSHEDPEVQFNWY...KCKVSNKGLPAPI
hIgG2G4  VDKTVERK-CC-V-E-CPPCPAPPVA-GPSVFLFPP...TCVVVDVSqEDPEVQFNWY...KCKVSNKGLPssI
```

Sequence alignment of human IgG4 variants relative to wild-type human IgG4 (SEQ ID NOs: 65, 106-127, and 174-177, from top to bottom)

```
            21-       22-       23-       24-    ...26-       27-       ...32-       33-
           12345678 90123456789012345...01234567890123456789012345678...012345678901 2
              Upper      CoreLower    CH2
hIgG4    VDKRVESKYG----PPCPSCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m1    KRVESKYG----PPCPPCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m-1   KRVESK-SCDKTHTCPPCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m2    KRVESKYG----PPCPPCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m-2   KRVESK-CC-v-e-CPPCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m3    KRVESKYG----PPCPPCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEeQFNWY...KCKVSNKGLPSSI
hIgG4m4    KRVESKYG----PPCPPCPAPEFL---SVFLFPP...TCVVVDVSQEDPEeQFNWY...KCKVSNKGLPSSI
hIgG4m5    KRVESKYG----PPCPPCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEeQFNWY...KCKVSNKGLPSSI
hIgG4m7    KRVESKYG----PPCPPCPAPEFLGGPSVFLFPP...TCVVVDVeQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m8    KRVESKYG----PPCPPCPAPEFLGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m9    KRVESKYG----PPCPPCPAPEFLGGPSVFLFPP...TCVVVDVeQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m10   KRVESKYG----PPCPPCPAPEvs---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m15   KRVESKYG----PPCPPCPAPEFL---SVFLFPP...TCVVVDVSQEDPEeQFNWY...KCKVSNKGLPSSI
hIgG4m17   KRVESKYG----PPCPPCPAPEFL---SVFLFPP...TCVVVDVeQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m18   KRVESKYG----PPCPPCPAPEFL---SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m19   KRVESKYG----PPCPPCPAPEFL---SVFLFPP...TCVVVDVeQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m20   KRVESKYG----PPCPPCPAPEFLG--SVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m25   KRVESKYG----PPCPPCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEeQFNWY...KCKVSNKGLPSSI
hIgG4m27   KRVESKYG----PPCPPCPAPEFL-GPSVFLFPP...TCVVVDVeQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m28   KRVESKYG----PPCPPCPAPEFL-GPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m29   KRVESKYG----PPCPPCPAPEFL-GPSVFLFPP...TCVVVDVeQEDPEVQFNWY...KCKVSNKGfPSSI
hIgG4m30   KRVESKYG----PPCPPCPAPEFL--PSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4mPE   KRVESKYG----PPCPPCPAPEfeGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m40 VDKRVESKYG----PPCPPCPAPEFLGGPSVFLFPP...TCVVVaVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m41 VDKRVESKYG----PPCPPCPAPpvaGGPSVFLFPP...TCVVVaVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m42 VDKRVESKYG----PPCPPCPAPpvaGGPSVFLFPP...TCVVVaVSQEDPEVQFNWY...KCKVSNKGLPSSI
hIgG4m46 VDKRVESKYG----PPCPPCPAPEaLGaPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI*
hIgG4mAA VDKRVESKYG----PPCPPCPAPEaaGGPSVFLFPP...TCVVVDVSQEDPEVQFNWY...KCKVSNKGLPSSI
```

The amino acid sequences of wild-type human IgG1, IgG2, and IgG4 Fc fragments, and a number of exemplary hIgG1, hIgG2, and hIgG4 Fc variants (position 221 and onward based on EU numbering) are provided below:

Amino acid sequence of wild-type human IgG1 Fc fragment:

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 1)

Amino acid sequence of wild-type human IgG2 Fc fragment:

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 2)

Amino acid sequence of wild-type human IgG4 Fc fragment:

VDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 3)

Amino acid sequence of human IgG4 S228P Fc variant:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 4)

Amino acid sequences of exemplary human IgG1 Fc variants:

G1m1:

VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 5)

G1m2:

VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 6)

G1m-2:

VDKKVEPKCCVECPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 7)

G1m-4:

VDKKVEPKYGPPCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 8)

G1m5:

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 9)

G1m7:

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 10)

G1m8:

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 11)

G1m9:

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 12)

G1m15:

VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 13)

G1m17:

VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 14)

G1m18:

VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 15)

G1m19:

VDKKVEPKSCDKTHTCPPCPAPELLSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 16)

G1m25:

VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY

TQKSLSLSPGK (SEQ ID NO: 17)

G1m27:

VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 18)

G1m28:

VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 19)

G1m29:

VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAFPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 20)

G1mAA:

VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 21)

G1mAG:

VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 22)

G1m40:

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 160)

G1m45

VDKKVEPKSCDKTHTCPPCPAPpvaGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 178)

G1m240

VDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 179)

G1 N297A

VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYaSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 180)

G1m47

VDKKVEPKSCDKTHTCPPCPAPpvaGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKgLPssIEKTISKAKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 181)

G1m48

VDKKVEPKSsDKTHTsPPsPAPELLGGsSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 182)

G1m49

VDKKVEPKSCDKTHTsPPsPAPpvaGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 183)

G1m50

VDKKVEPKSCDKTHTCPPCPAPEfeGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAsIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 184)

Amino acid sequences of exemplary human IgG2 Fc variants:

G2m1:

VDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 23)

G2m-1:

VDKTVERKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 24)

G2m2:

VDKTVERKCCVECPPCPAPPFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ

KSLSLSPGK (SEQ ID NO: 25)

G2m-4:

VDKTVERKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 26)

G2m5:

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 27)

G2m7:

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 28)

G2m8:

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 29)

G2m9:

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 30)

G2m10:

VDKTVERKCCVECPPCPAPEVSSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 31)

G2m15:

VDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEEQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 32)

G2m17:

VDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 33)

G2m18:

VDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 34)

G2m19:

VDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 35)

G2m20:

VDKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO: 36)

G2m27:

VDKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVEHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO: 37)

G2m28:

VDKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO: 38)

G2m40:

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFASTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 161)

G2m43

VDKTVERKCCVECPPCPAPPaaasSVFLFPPKPKDTLMISRTPEVTCVVVDVSaEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVlHQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 185)

G2m44

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSqEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVlHQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 186)

G2mAA

VDKTVERKCCVECPPCPAPPaaaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 213)

G2m2040

VDKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVQFNWYVDGVEVHNAKTK
PREEQFASTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK (SEQ ID NO: 187)

G2G4

VDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK
SLSLSLGK (SEQ ID NO: 188)

Amino acid sequences of exemplary human IgG4 Fc variants:

G4m1:

VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (SEQ ID NO: 39)

G4m-1:

VDKRVESKSCDKTHTPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH
NHYTQKSLSLSLGK (SEQ ID NO: 40)

G4m2:

VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK
SLSLSLGK (SEQ ID NO: 41)

G4m-2:

VDKRVESKCCVEPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLGK (SEQ ID NO: 42)

G4m3:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 43)

G4m4:

VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDGVEVHNAKTKP

REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (SEQ ID NO: 44)

G4m5:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 45)

G4m7:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 46)

G4m8:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 47)

G4m9:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 48)

G4m10:

VDKRVESKYGPPCPPCPAPEVSSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (SEQ ID NO: 49)

G4m17:

VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (SEQ ID NO: 50)

G4m18:

VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (SEQ ID NO: 51)

G4m19:

VDKRVESKYGPPCPPCPAPEFLSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEVHNAKTKP
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLT

CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (SEQ ID NO: 52)

G4m20:

VDKRVESKYGPPCPPCPAPEFLGSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSLGK (SEQ ID NO: 53)

G4m25:

VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEEQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK
SLSLSLGK (SEQ ID NO: 54)

G4m27:

VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK
SLSLSLGK (SEQ ID NO: 55)

G4m28:

VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK
SLSLSLGK (SEQ ID NO: 56)

G4m29:

VDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVEQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGFPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQK
SLSLSLGK (SEQ ID NO: 57)

G4m30:

VDKRVESKYGPPCPPCPAPEFLPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTK
PREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSLGK (SEQ ID NO: 58)

G4mPE:

VDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 59)

G4m40:

VDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQFNWYVDGVEVHNAK

TKPREEQFASTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 162)

G4m41

VDKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 189)

G4m42

VDKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 190)

G4m46

VDKRVESKYGPPCPPCPAPEaLGaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKaYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 191)

G4mAA

VDKRVESKYGPPCPPCPAPEaaGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 192)

The Fc variants described herein may exhibit an enhanced binding activity to FcγRIIB as compared with the wild-type counterpart. Examples include G2m2, G2m5, G2m7, G2m8, G2m9, G2m19, G2m44, G1m7, G1m9, G1m27, G1m45, G1m47, G1m49, G1m50, G4m7, G4m46 and G4mPE. Alternatively or in addition, the Fc variants may have an enhanced selectivity to FcγRIIB as compared with their wild-type counterparts, for example, G2m1, G2m20, G2m43, G2m44, G2G4, G2mAA, G1m2, G1m15, G1m17, G1m18, G1m19, G1m27, G1m28, G1m29, G4m1, G4m2, G4m7, G4m8, G4m9, G4m20, G4m25, G4m27, G4m28, G4m30, G4m46 and G4mPE. Such Fc variants may retain the binding activity to FcRn. These Fc variants can be used for constructing therapeutic agents described herein capable of cross-linking immune receptors and FcγRIIB receptor.

Alternatively, certain Fc variants as described herein may have selectivity to FcγRIIB and/or apparent low or no binding activity to any FcγR. Examples include G1m2, G1m25, G1m40, G1mAAG, G1m240, G2m1, G2m20, G2m40, G2m2040, G4m5, G4m18, G4m19, G4m20, G4m30, G4m40, G4m41, and G4m42. Such Fc variants may retain the binding

activity to FcRn. Therapeutic agents (*e.g.*, antibodies) containing such Fc variants may be capable of cross-linking immune receptors and FcγRIIB receptor due to avidity effect.

The changes of binding affinity/specificity of the exemplary Fc variants as compared with their wild-type counterparts are provided in Tables 2-4 below. "N/A" indicates no data available. When the binding activity of an Fc variant is found to be "no change" as compared with the wild-type counterpart, it means that there is no significant variation of the binding activity between the Fc variant and the wild-type counterpart as indicated by the same assay under the same experimental conditions. When the binding activity of an Fc variant is "increased" or "decreased" as relative to its wild-type counterpart means that the binding activity of the Fc variant is higher or lower than that of the wild-type counterpart as determined by the same assay under the same experimental conditions and the variation is significant (*e.g.*, biologically significant) as known to those skilled in the art. When the binding activity of an Fc variant is "slightly increased" or "slightly decreased" as relative to its wild-type counterpart means that the binding activity of the Fc variant is higher or lower than that of the wild-type counterpart as determined by the same assay under the same experimental conditions and the variation is statistically significant but to a limited level (*e.g.*, up to 10%).

Table 2. FcγR Binding Activity of Human IgG1 Mutants as Relative to Wild-Type Human IgG1

	Changes of Binding Activity Relative to Wild-Type Counterparts					
IgG1 Mutant	**FcγRI**	**FcγRIIA(H131)**	**FcγRIIA(R131)**	**FcγRIIB**	**FcγRIIC**	**FcγRIII**
G1m1	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
G1m2	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
G1m-2	No change	N/A	N/A	No change	N/A	No change
G1m-4	No change	N/A	N/A	No change	N/A	No change
G1m5	Increased	Increased	Increased	No change	Increased	Slightly decreased
G1m7	Increased	Increased	Increased	Increased	Increased	Slightly decreased
G1m8	Increased	Slightly decreased	No change	Increased	Slightly increased	Slightly decreased
G1m9	Increased	Decreased	Increased	Increased	Increased	No change
G1m15	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
G1m17	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
G1m18	Decreased	Decreased	No change	Decreased	Decreased	Decreased
G1m19	Decreased	Increased	Increased	Increased	Increased	Decreased
G1m25	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
G1m27	Decreased	Decreased	Decreased	Increased	Decreased	Decreased

G1m28	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
G1m29	Decreased	Decreased	Increased	Increased	Increased	Decreased
G1mAA	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1mAAG	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1m240	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1m45	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1 N297A	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1m47	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1m48	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1m49	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G1m50	Decreased	N/A	Decreased	Decreased	N/A	Decreased

Table 3. FcγR Binding Activity of Human IgG2 Mutants as Relative to Wild-Type Human IgG2

	Change of Binding Activity Relative to Wild-Type Counterpart					
IgG2 Mutant	**FcγRI**	**FcγRIIA(H131)**	**FcγRIIA(R131)**	**FcγRIIB**	**FcγRIIC**	**FcγRIII**
G2m1	No change	Decreased	Decreased	Decreased	No change	No change
G2m2	Increased	Decreased	No change	Increased	No change	No change
G2m10	No change	Decreased	No change	Slightly decreased	No change	No change
G2m5	Slightly increased	Decreased	No change	Decreased	No change	No change
G2m7	No change	Slightly increased	Increased	Increased	Slightly increased	No change
G2m8	No change	Decreased	No change	No change	No change	No change
G2m9	No change	No change	Increased	Increased	Increased	No change
G2m-1	Increased	N/A	N/A	Decreased	N/A	No change
G2m-4	Increased	N/A	N/A	Decreased	N/A	No change
G2m15	No change	N/A	N/A	Decreased	N/A	No change
G2m17	No change	N/A	Increased	No change	Increased	No change
G2m18	Slightly increased	N/A	No change	Decreased	No change	No change
G2m19	No change	N/A	Increased	Increased	No change	No change
G2m20	No change	N/A	No change	Decreased	No change	No change
G2m27	Slightly increased	N/A	N/A	Increased	N/A	No change
G2m28	No change	N/A	N/A	Increased	N/A	No change
G2m20 40	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G2m43	No change	N/A	Decreased	Decreased	N/A	Decreased
G2m44	No change	N/A	Decreased	No change	N/A	Decreased
G2mA A	No change	N/A	Decreased	No change	N/A	Decreased
G2G4	Decreased	N/A	Decreased	No change	N/A	Decreased

Table 4. FcγR Binding Activity of Human IgG4 Mutants as Relative to Wild-Type Human IgG4

	Change of Binding Activity Relative to Wild-Type Counterpart					
IgG4 Mutant	**FcγRI**	**FcγRIIA(H131)**	**FcγRIIA(R131)**	**FcγRIIB**	**FcγRIIC**	**FcγRIII**
G4m1	Decreased	Increased	No change	Slightly decreased	Slightly increased	No change
G4m2	Decreased	No change	Decreased	Slightly decreased	No change	No change
G4m10	Decreased	No change	Decreased	Decreased	No change	No change
G4m20	Decreased	No change	Decreased	Decreased	No change	No change
G4m3	Decreased	No change	No change	Decreased	No change	No change
G4m7	No change	Increased	Increased	Increased	Increased	Slightly increased
G4m8	No change	No change	Increased	Slightly increased	No change	No change
G4m9	No change	No change	Increased	Increased	Increased	No change
G4m17	Decreased	No change	Increased	Increased	Increased	Increased
G4m18	Decreased	No change	No change	Decreased	No change	Increased
G4m19	Decreased	No change	No change	Decreased	No change	Slightly increased
G4m25	Decreased	No change	Increased	Slightly decreased	No change	Increased
G4m27	Decreased	No change	No change	Decreased	No change	Slightly increased
G4m28	Decreased	No change	Slightly increased	Increased	Increased	No change
G4m29	Decreased	No change	Increased	Increased	Increased	Slightly increased
G4m4	Decreased	No change	No change	Decreased	No change	No change
G4m-1	No change	N/A	N/A	No change	N/A	No change
G4m-2	No change	N/A	N/A	Decreased	N/A	No change
G4mPE	Decreased	N/A	N/A	Slightly decreased	No change	No change
G4m30	Decreased	N/A	No change	Decreased	No change	No change
G4m40	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G4m41	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G4m42	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G4mAA	Decreased	N/A	Decreased	Decreased	N/A	Decreased
G4m46	Decreased	N/A	Decreased	Decreased	N/A	Decreased

An Fc variant as described herein can be designed following the guidance provided herein and produced via routine recombinant technology. Its binding affinity and specificity to various Fc receptors can be determined via routine methods. See also Examples below.

In specific examples, the CD40-binding molecules (anti-CD40 molecules) disclosed herein may maintain the hinge region of the IgG1 parent, contain one or more mutations (*e.g.*, one or more deletions at positions 236-238 in light of mouse IgG1 as discussed above) that lead to reduced binding affinity to Fc receptors such as FcγR2B but maintain residual binding activity to the Fc receptor. Exemplary Fc variants having such properties include, but are not limited to, G1m2, G4m20, G4m30 and G4m46. The CD40 binding moiety in such anti-CD

molecules may be derived from an agonistic anti-CD40 antibody. Such a CD40 binding moiety may be derived from the anti-CD40 antibody 383 disclosed herein. In some instances, the CD40 binding moiety comprises the same V_H and V_L CDRs as antibody 383. In some examples, the CD40 binding moiety may comprise the same VH and/or VL chains as antibody 383 (SEQ ID NOs: 128 and 129, respectively). Alternatively, the CD40 binding moiety can be a functional variant of antibody 383 as disclosed herein. Such CD40 binding molecules would have a number of advantageous features as demonstrated in the Examples below. Examples include enhanced anti-tumor efficacy with improved therapeutic window and reduced side effects (e.g., less liver toxicity) *in vivo*, which may be attributable to the baseline CD40 agonistic activity and the residual FcγRIIB binding activity. Too high CD40 agonist activity and/or FcγRIIB binding activity are expected to induce side effects such as cell toxicity.

In other specific examples, the CD40-binding molecule disclosed herein may comprise a Fc variant domain derived from IgG2 (e.g., maintain the IgG2 hinge) and contain one or more mutations (*e.g.*, deletions or substitutions) at one or more of positions 236-238 in light of the mouse counterpart to reduce binding affinity to Fc receptors, particularly binding affinity to FcγRIIB. In some instances, such Fc variants have deletions at one or more of positions 236-238. Alternatively or in addition, the Fc variants may have substitutions at positions 234, 237, 238, 268 or a combination thereof. Such Fc variants may contain further mutations at one or more positions involved in binding to Fc receptors, for example, position 265 (*e.g.*, D265A). The Fc variants may maintain residual binding activity to a Fc receptor such as FcγRIIB (*e.g.*, G2m20 and G2m43). Alternatively, the Fc variants may not bind to Fc receptors such as FcγRIIB (*e.g.*, G2m40). The CD40 binding moiety in such anti-CD molecules may be derived from an agonistic anti-CD40 antibody. Such a CD40 binding moiety may be derived from the anti-CD40 antibody 383 disclosed herein. In some instances, the CD40 binding moiety comprises the same V_H and V_L CDRs as antibody 383. In some examples, the CD40 binding moiety may comprise the same VH and/or VL chains as antibody 383 (SEQ ID NOs: 128 and 129, respectively). Alternatively, the CD40 binding moiety can be a functional variant of antibody 383 as disclosed herein. Such CD40 binding molecules would have a number of advantageous features as demonstrated in the Examples below. Examples include enhanced anti-tumor efficacy with improved therapeutic window

and reduced side effects (*e.g.*, less liver toxicity) *in vivo*, which may be attributable to the combination of baseline CD40 agonistic activity and the residual FcγRIIB binding activity (e.g., 383-IghuG2m20), or the combination of relatively high CD40 agonistic activity and no binding to FcγRIIB (*e.g.*, 383-IghuG2m40).

Besides the FACS binding assay described herein, the activity of Fc variants for Fcγ receptors can be examined in alternative assays. For example, CD40 reporter assays with or without co-culture of FcγRIIB expressing cells can be used to demonstrate effect of receptor cross-linking and activation. Because of avidity effect resulting from simultaneous binding of antibody to two targets (*e.g.*, CD40 and FcγRIIB), this assay is more sensitive to detect FcγRIIB binding. Minimal or no apparent binding detectable by FACS may show positive results in the reporter assay.

II. Preparation of CD40-binding Molecules Comprising Fc Variants

The CD40-binding molecules described herein may be prepared by conventional methodology, for example, recombinant technology. Some examples follow.

For CD40-binding molecules comprising an extracellular domain of a CD40L, a coding sequence of the CD40L extracellular domain can be fused in frame with a coding sequence of a suitable Fc variant. The coding sequence for the whole CD40-binding molecule can be cloned into a suitable expression vector, which can be introduced into a suitable host cell for protein expression.

Antibodies binding to CD40 can be prepared by any method known in the art. See, for example, Harlow and Lane, (1998) Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York. In some embodiments, antibodies specific to CD40 or an extracellular domain thereof can be made by the conventional hybridoma technology. The full-length target receptor or a fragment thereof, optionally coupled to a carrier protein such as KLH, can be used to immunize a host animal for generating antibodies binding to that antigen. The route and schedule of immunization of the host animal are generally in keeping with established and conventional techniques for antibody stimulation and production, as further described herein. General techniques for production of mouse, humanized, and human antibodies are known in the art and are described herein. It is contemplated that any mammalian subject including humans or antibody producing cells therefrom can be

manipulated to serve as the basis for production of mammalian, including human hybridoma cell lines. Typically, the host animal is inoculated intraperitoneally, intramuscularly, orally, subcutaneously, intraplantar, and/or intradermally with an amount of immunogen, including as described herein.

Hybridomas can be prepared from the lymphocytes and immortalized myeloma cells using the general somatic cell hybridization technique of Kohler, B. and Milstein, C. (1975) Nature 256:495-497 or as modified by Buck, D. W., et al., In Vitro, 18:377-381 (1982). Available myeloma lines, including but not limited to X63-Ag8.653 and those from the Salk Institute, Cell Distribution Center, San Diego, Calif., USA, may be used in the hybridization. Generally, the technique involves fusing myeloma cells and lymphoid cells using a fusogen such as polyethylene glycol, or by electrical means well known to those skilled in the art. After the fusion, the cells are separated from the fusion medium and grown in a selective growth medium, such as hypoxanthine-aminopterin-thymidine (HAT) medium, to eliminate unhybridized parent cells. Any of the media described herein, supplemented with or without serum, can be used for culturing hybridomas that secrete monoclonal antibodies. As another alternative to the cell fusion technique, EBV immortalized B cells may be used to produce the anti-immune cell receptor monoclonal antibodies described herein. The hybridomas are expanded and subcloned, if desired, and supernatants are assayed for anti-immunogen activity by conventional immunoassay procedures (*e.g.*, radioimmunoassay, enzyme immunoassay, or fluorescence immunoassay).

Hybridomas that may be used as source of antibodies encompass all derivatives, progeny cells of the parent hybridomas that produce monoclonal antibodies capable of modulating the activity of the target immune cell receptor. Hybridomas that produce such antibodies may be grown in vitro or in vivo using known procedures. The monoclonal antibodies may be isolated from the culture media or body fluids, by conventional immunoglobulin purification procedures such as ammonium sulfate precipitation, gel electrophoresis, dialysis, chromatography, and ultrafiltration, if desired. Undesired activity if present, can be removed, for example, by running the preparation over adsorbents made of the immunogen attached to a solid phase and eluting or releasing the desired antibodies off the immunogen. Immunization of a host animal with a target antigen or a fragment containing the target amino acid sequence conjugated to a protein that is immunogenic in the

species to be immunized, *e.g.*, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl, or R1N=C=NR, where R and R1 are different alkyl groups, can yield a population of antibodies (*e.g.*, monoclonal antibodies).

If desired, an antibody (monoclonal or polyclonal) of interest (*e.g.*, produced by a hybridoma) may be sequenced and the polynucleotide sequence may then be cloned into a vector for further construction of the anti-CD40 antibodies described herein. The sequence encoding the antibody of interest may be maintained in vector in a host cell and the host cell can then be expanded and frozen for future use.

In an alternative, the polynucleotide sequence may be used for genetic manipulation to "humanize" the antibody or to improve the affinity (affinity maturation), or other characteristics of the antibody. For example, the constant region may be engineered to more resemble human constant regions to avoid immune response if the antibody is used in clinical trials and treatments in humans. It may be desirable to genetically manipulate the antibody sequence to obtain greater affinity to the target antigen and greater efficacy in inhibiting or activating the activity of the immune cell receptor. It will be apparent to one of skill in the art that one or more polynucleotide changes can be made to the antibody and still maintain its binding specificity to the target receptor.

In other embodiments, fully human antibodies can be obtained by using commercially available mice that have been engineered to express specific human immunoglobulin proteins. Transgenic animals that are designed to produce a more desirable (*e.g.*, fully human antibodies) or more robust immune response may also be used for generation of humanized or human antibodies. Examples of such technology are Xenomouse^{RTM} from Amgen, Inc. (Fremont, Calif.) and HuMAb-Mouse^{RTM} and TC MouseTM from Medarex, Inc. (Princeton, N.J.). In another alternative, antibodies may be made recombinantly by phage display or yeast technology. *See*, for example, U.S. Pat. Nos. 5,565,332; 5,580,717; 5,733,743; and 6,265,150; and Winter et al., (1994) Annu. Rev. Immunol. 12:433-455.

Alternatively, antibody library technology, such as the phage display technology (McCafferty et al., (1990) Nature 348:552-553), yeast display technology, or mammalian cell

display technology, can be used to isolated antibodies such as human antibodies specific to a target immune receptor.

Methods for constructing humanized antibodies are also well known in the art. See, *e.g.*, Queen et al., Proc. Natl. Acad. Sci. USA, 86:10029-10033 (1989). In one example, variable regions of V_H and V_L of a parent non-human antibody are subjected to three-dimensional molecular modeling analysis following methods known in the art. Next, framework amino acid residues predicted to be important for the formation of the correct CDR structures are identified using the same molecular modeling analysis. In parallel, human VH and VL chains having amino acid sequences that are homologous to those of the parent non-human antibody are identified from any antibody gene database using the parent VH and VL sequences as search queries. Human VH and VL acceptor genes are then selected.

The CDR regions within the selected human acceptor genes can be replaced with the CDR regions from the parent non-human antibody or functional variants thereof. When necessary, residues within the framework regions of the parent chain that are predicted to be important in interacting with the CDR regions (see above description) can be used to substitute for the corresponding residues in the human acceptor genes.

Once an antibody capable of binding to a target immune cell receptor is obtained, the coding sequence of its heavy chain can be fused in-frame with the coding sequence of a suitable Fc variant, which may selectively bind FcgRIIB or which does not bind any FcγRs, for example, any of the Fc variants described herein *via* routine recombinant technology. In some instances, the antibody is first investigated for its agonistic effect to activate the immune cell receptor to which it binds. Such an agonistic antibody can be selected for making the CD40-binding molecules described herein to enhance the agonistic effects.

In other instances, the antibody is first investigated for its antagonistic effect to inhibit the immune cell receptor to which it binds. Such an antagonistic antibody can be selected for making the CD40-binding molecule described herein to down-regulate immune responses. Alternatively, an Fc variant having low or no binding activity to any Fc receptor can be selected for making CD40 antagonists.

The resultant antibody molecules or CD40-binding molecules described herein can be produced *via* routine recombinant technology as exemplified below. Nucleic acids encoding

the heavy and light chain of an antibody or the polypeptide of a CD40-binding molecule as described herein can be cloned into one expression vector, each nucleotide sequence being in operable linkage to a suitable promoter. In one example, each of the nucleotide sequences encoding the heavy chain and light chain is in operable linkage to a distinct prompter. Alternatively, the nucleotide sequences encoding the heavy chain and the light chain can be in operable linkage with a single promoter, such that both heavy and light chains are expressed from the same promoter. When necessary, an internal ribosomal entry site (IRES) can be inserted between the heavy chain and light chain encoding sequences.

In some examples, the nucleotide sequences encoding the two chains of the antibody are cloned into two vectors, which can be introduced into the same or different cells. When the two chains are expressed in different cells, each of them can be isolated from the host cells expressing such and the isolated heavy chains and light chains can be mixed and incubated under suitable conditions allowing for the formation of the antibody.

Generally, a nucleic acid sequence encoding one or all chains of an antibody can be cloned into a suitable expression vector in operable linkage with a suitable promoter using methods known in the art. For example, the nucleotide sequence and vector can be contacted, under suitable conditions, with a restriction enzyme to create complementary ends on each molecule that can pair with each other and be joined together with a ligase. Alternatively, synthetic nucleic acid linkers can be ligated to the termini of a gene. These synthetic linkers contain nucleic acid sequences that correspond to a particular restriction site in the vector. The selection of expression vectors/promoter would depend on the type of host cells for use in producing the antibodies.

A variety of promoters can be used for expression of the antibodies described herein, including, but not limited to, cytomegalovirus (CMV) intermediate early promoter, a viral LTR such as the *Rous sarcoma* virus LTR, HIV-LTR, HTLV-1 LTR, the simian virus 40 (SV40) early promoter, *E. coli* lac UV5 promoter, and the herpes simplex tk virus promoter.

Regulatable promoters can also be used. Such regulatable promoters include those using the lac repressor from *E. coli* as a transcription modulator to regulate transcription from lac operator-bearing mammalian cell promoters [Brown, M. et al., Cell, 49:603-612 (1987)], those using the tetracycline repressor (tetR) [Gossen, M., and Bujard, H., Proc. Natl. Acad. Sci. USA 89:5547-5551 (1992); Yao, F. et al., Human Gene Therapy, 9:1939-1950 (1998);

Shockelt, P., et al., Proc. Natl. Acad. Sci. USA, 92:6522-6526 (1995)]. Other systems include FK506 dimer, VP16 or p65 using astradiol, RU486, diphenol murislerone, or rapamycin. Inducible systems are available from Invitrogen, Clontech and Ariad.

Regulatable promoters that include a repressor with the operon can be used. In one embodiment, the lac repressor from *E. coli* can function as a transcriptional modulator to regulate transcription from lac operator-bearing mammalian cell promoters [M. Brown et al., Cell, 49:603-612 (1987)]; Gossen and Bujard (1992); [M. Gossen et al., Natl. Acad. Sci. USA, 89:5547-5551 (1992)] combined the tetracycline repressor (tetR) with the transcription activator (VP 16) to create a tetR-mammalian cell transcription activator fusion protein, tTa (tetR-VP 16), with the tetO-bearing minimal promoter derived from the human cytomegalovirus (hCMV) major immediate-early promoter to create a tetR-tet operator system to control gene expression in mammalian cells. In one embodiment, a tetracycline inducible switch is used. The tetracycline repressor (tetR) alone, rather than the tetR-mammalian cell transcription factor fusion derivatives can function as potent trans-modulator to regulate gene expression in mammalian cells when the tetracycline operator is properly positioned downstream for the TATA element of the CMVIE promoter (Yao et al., Human Gene Therapy). One particular advantage of this tetracycline inducible switch is that it does not require the use of a tetracycline repressor-mammalian cells transactivator or repressor fusion protein, which in some instances can be toxic to cells (Gossen et al., Natl. Acad. Sci. USA, 89:5547-5551 (1992); Shockett et al., Proc. Natl. Acad. Sci. USA, 92:6522-6526 (1995)), to achieve its regulatable effects.

Additionally, the vector can contain, for example, some or all of the following: a selectable marker gene, such as the neomycin gene for selection of stable or transient transfectants in mammalian cells; enhancer/promoter sequences from the immediate early gene of human CMV for high levels of transcription; transcription termination and RNA processing signals from SV40 for mRNA stability; SV40 polyoma origins of replication and ColE1 for proper episomal replication; internal ribosome binding sites (IRESes), versatile multiple cloning sites; and T7 and SP6 RNA promoters for in vitro transcription of sense and antisense RNA. Suitable vectors and methods for producing vectors containing transgenes are well known and available in the art.

Examples of polyadenylation signals useful to practice the methods described herein include, but are not limited to, human collagen I polyadenylation signal, human collagen II polyadenylation signal, and SV40 polyadenylation signal.

One or more vectors (*e.g.*, expression vectors) comprising nucleic acids encoding any of the antibodies may be introduced into suitable host cells for producing the antibodies. The host cells can be cultured under suitable conditions for expression of the antibody or any polypeptide chain thereof. Such antibodies or polypeptide chains thereof can be recovered by the cultured cells (*e.g.*, from the cells or the culture supernatant) via a conventional method, *e.g.*, affinity purification. If necessary, polypeptide chains of the antibody can be incubated under suitable conditions for a suitable period of time allowing for production of the antibody.

In some embodiments, methods for preparing an antibody described herein involve a recombinant expression vector that encodes both the heavy chain and the light chain of an antibody as described herein. The recombinant expression vector can be introduced into a suitable host cell (*e.g.*, a dhfr- CHO cell) by a conventional method, *e.g.*, calcium phosphate-mediated transfection. Positive transformant host cells can be selected and cultured under suitable conditions allowing for the expression of the two polypeptide chains that form the antibody, which can be recovered from the cells or from the culture medium. When necessary, the two chains recovered from the host cells can be incubated under suitable conditions allowing for the formation of the antibody.

In one example, two recombinant expression vectors are provided, one encoding the heavy chain of the anti-immune cell receptor antibody and the other encoding the light chain of the same antibody. Both of the two recombinant expression vectors can be introduced into a suitable host cell (*e.g.*, dhfr- CHO cell) by a conventional method, *e.g.*, calcium phosphate-mediated transfection. Alternatively, each of the expression vectors can be introduced into a suitable host cells. Positive transformants can be selected and cultured under suitable conditions allowing for the expression of the polypeptide chains of the antibody. When the two expression vectors are introduced into the same host cells, the antibody produced therein can be recovered from the host cells or from the culture medium. If necessary, the polypeptide chains can be recovered from the host cells or from the culture medium and then incubated under suitable conditions allowing for formation of the antibody. When the two

expression vectors are introduced into different host cells, each of them can be recovered from the corresponding host cells or from the corresponding culture media. The two polypeptide chains can then be incubated under suitable conditions for formation of the antibody.

Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recovery of the antibodies from the culture medium. For example, some antibodies can be isolated by affinity chromatography with a Protein A or Protein G coupled matrix.

The bioactivity of the antibodies described herein can be verified using assays known in the art or described herein.

III. Pharmaceutical Compositions

The present disclosure provides pharmaceutical compositions comprising the CD40-binding molecules or any of the anti-CD40 antibodies described herein and uses of such for modulating immune responses triggered by CD40/CD40L signaling. Such CD40-binding molecules as described herein or anti-CD40 antibodies as also described herein can be used for treating diseases such as cancer or immune-related disorders.

The CD40-binding molecules or anti-CD40 antibodies as described herein can be mixed with a pharmaceutically acceptable carrier (excipient) to form a pharmaceutical composition for use in treating a target disease. "Acceptable" means that the carrier must be compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. Pharmaceutically acceptable excipients (carriers) including buffers, which are well known in the art. See, e.g., Remington: The Science and Practice of Pharmacy 20th Ed. (2000) Lippincott Williams and Wilkins, Ed. K. E. Hoover.

The pharmaceutical compositions to be used in the present methods can comprise pharmaceutically acceptable carriers, excipients, or stabilizers in the form of lyophilized formulations or aqueous solutions. (Remington: The Science and Practice of Pharmacy 20th Ed. (2000) Lippincott Williams and Wilkins, Ed. K. E. Hoover). Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations used, and may comprise buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl

ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

In some examples, the pharmaceutical composition described herein comprises liposomes containing the antibodies (or the encoding nucleic acids) which can be prepared by methods known in the art, such as described in Epstein, et al., Proc. Natl. Acad. Sci. USA 82:3688 (1985); Hwang, et al., Proc. Natl. Acad. Sci. USA 77:4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

The CD40-binding molecules, anti-CD40 antibodies, or the encoding nucleic acid(s), may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are known in the art, see, e.g., Remington, The Science and Practice of Pharmacy 20th Ed. Mack Publishing (2000).

In other examples, the pharmaceutical composition described herein can be formulated in sustained-release format. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-

methacrylate), or poly(v nylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

The pharmaceutical compositions to be used for *in vivo* administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Therapeutic antibody compositions are generally placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The pharmaceutical compositions described herein can be in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient can be mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric

layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (*e.g.*, Tween™ 20, 40, 60, 80 or 85) and other sorbitans (*e.g.*, Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and can be between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (*e.g.*, soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (*e.g.*, egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion can comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

The emulsion compositions can be those prepared by mixing an antibody with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Pharmaceutical compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect.

Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

IV. Therapeutic Applications

Any of the CD40-binding molecules or anti-CD40 antibodies disclosed herein may be used to modulating (*e.g.*, enhancing or inhibiting) immune responses against invading pathogens and/or diseased cells such as cancer cells.

To practice the method disclosed herein, an effective amount of the pharmaceutical composition described herein can be administered to a subject (*e.g.*, a human) in need of the treatment via a suitable route, 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, inhalation or topical routes. Commercially available nebulizers for liquid formulations, including jet nebulizers and ultrasonic nebulizers are useful for administration. Liquid formulations can be directly nebulized and lyophilized powder can be nebulized after reconstitution. Alternatively, the antibodies as described herein can be aerosolized using a fluorocarbon formulation and a metered dose inhaler, or inhaled as a lyophilized and milled powder.

The subject to be treated by the methods described herein can be a mammal, more preferably a human. Mammals include, but are not limited to, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats.

In some instances, the subject is a human patient having or at risk for a cell-mediated disease or disorder, such as cancer including but not limited to lung cancer, stomach cancer, liver cancer, breast cancer, skin cancer, pancreatic cancer, brain cancer, prostate cancer, bladder cancer, or colorectal cancer. Further exemplary cancers include, but are not limited to, breast cancer; biliary tract cancer; bladder cancer; brain cancer including glioblastomas and medulloblastomas; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms including acute lymphocytic and myelogenous leukemia, *e.g.*, B Cell CLL; T-cell acute lymphoblastic leukemia/lymphoma; hairy cell leukemia; chronic myelogenous leukemia, multiple myeloma; AIDS-associated leukemias and adult T-cell leukemia/lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas

including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Merkel cell carcinoma, Kaposi's sarcoma, basal cell carcinoma, and squamous cell cancer; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratomas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor. A subject having a cancer can be identified by routine medical examination, *e.g.*, laboratory tests, organ functional tests, CT scans, or ultrasounds. In some embodiments, the subject to be treated by the method described herein may be a human cancer patient who has undergone or is subjecting to an anti-cancer therapy, for example, chemotherapy, radiotherapy, immunotherapy, or surgery.

In other instances, the subject is a human patient having or at risk for an immune-related disorder. Immune-related disorders refer to a dysfunction of the immune system, including autoimmune diseases, immunodeficiencies, and/or allergies. In one embodiment, the immune-related disorder is an autoimmune disease. Examples of immune-related disorders include, but are not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Myasthenia Gravis (MG), Graves' Disease, Idiopathic Thrombocytopenia Purpura (ITP), Guillain-Barre Syndrome, autoimmune myocarditis, Membrane Glomerulonephritis, diabetes mellitus, Type I or Type II diabetes, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, gastritis, Celiac Disease, Vitiligo, Hepatitis, primary biliary cirrhosis, inflammatory bowel disease, spondyloarthropathies, experimental autoimmune encephalomyelitis, immune neutropenia, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines, T-lymphocytes typically found in tuberculosis, sarcoidosis, and polymyositis, polyarteritis, cutaneous vasculitis, pemphigus, pemphigold, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, Sjogren's syndrome, graft-versus-host (GVH) disease, and immune thrombocytopenia. A subject having an immune-related disorder can be identified by routine medical examination, e.g., with laboratory tests. In some embodiments, the subject to be treated by the method described herein may be a human subject with an immune-related disorder who has undergone or is subjecting to an immune-related disorder treatment, for example, immunosuppressive mediation, hormone replacement therapy, blood transfusions, anti-inflammatory medication, and/or pain medication.

As used herein, "an effective amount" refers to the amount of each active agent required to confer therapeutic effect on the subject, either alone or in combination with one or more other active agents. In some embodiments, the therapeutic effect is modulating (*e.g.*, activating) the target immune receptor, thereby triggering or enhancing immune responses mediated by the receptor. Determination of whether an amount of the antibody achieved the therapeutic effect would be evident to one of skill in the art. Effective amounts vary, as recognized by those skilled in the art, depending on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment.

Empirical considerations, such as the half-life, generally will contribute to the determination of the dosage. For example, molecules that are compatible with the human immune system, such as humanized antibodies or fully human antibodies, may be used to prolong half-life of the antibody and to prevent the antibody being attacked by the host's immune system. Frequency of administration may be determined and adjusted over the course of therapy, and is generally, but not necessarily, based on treatment and/or suppression and/or amelioration and/or delay of a target disease/disorder. Alternatively, sustained continuous release formulations of an antibody may be appropriate. Various formulations and devices for achieving sustained release are known in the art.

In one example, dosages for a CD40-binding molecule or an anti-CD40 antibody as described herein may be determined empirically in individuals who have been given one or more administration(s) of the antibody. Individuals are given incremental dosages of the agonist. To assess efficacy of the agonist, an indicator of the disease/disorder can be followed.

Generally, for administration of any of the therapeutic agents such as the CD40-binding molecule or an anti-CD40 antibody described herein, an initial candidate dosage can be about 2 mg/kg. For the purpose of the present disclosure, a typical daily dosage might

range from about any of 0.1 μg/kg to 3 μg/kg to 30 μg/kg to 300 μg/kg to 3 mg/kg, to 30 mg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of symptoms occurs or until sufficient therapeutic levels are achieved to alleviate a target disease or disorder, or a symptom thereof. An exemplary dosing regimen comprises administering an initial dose of about 2 mg/kg, followed by a weekly maintenance dose of about 1 mg/kg of the antibody, or followed by a maintenance dose of about 1 mg/kg every other week. However, other dosage regimens may be useful, depending on the pattern of pharmacokinetic decay that the practitioner wishes to achieve. For example, dosing from one-four times a week is contemplated. In some embodiments, dosing ranging from about 3 μg/mg to about 2 mg/kg (such as about 3 μg/mg, about 10 μg/mg, about 30 μg/mg, about 100 μg/mg, about 300 μg/mg, about 1 mg/kg, and about 2 mg/kg) may be used. In some embodiments, dosing frequency is once every week, every 2 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, or every 10 weeks; or once every month, every 2 months, or every 3 months, or longer. The progress of this therapy is easily monitored by conventional techniques and assays. The dosing regimen (including the therapeutic used) can vary over time.

In some embodiments, for an adult patient of normal weight, doses ranging from about 0.3 to 5.00 mg/kg may be administered. In some examples, the dosage of the therapeutic agents such as antibodies described herein can be 10 mg/kg. The particular dosage regimen, *i.e.*, dose, timing and repetition, will depend on the particular individual and that individual's medical history, as well as the properties of the individual agents (such as the half-life of the agent, and other considerations well known in the art).

For the purpose of the present disclosure, the appropriate dosage of a CD40-binding molecule or anti-CD40 antibody as described herein will depend on the specific antibody, antibodies, and/or non-antibody peptide (or compositions thereof) employed, the type and severity of the disease/disorder, whether the CD40-binding molecule or anti-CD40 antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the agonist, and the discretion of the attending physician. Typically the clinician will administer a CD40-binding molecule or anti-CD40 antibody, until a dosage is reached that achieves the desired result. In some embodiments, the desired result is a

decrease in thrombosis. Methods of determining whether a dosage resulted in the desired result would be evident to one of skill in the art. Administration of one or more CD40-binding molecule or anti-CD40 antibody can be continuous or intermittent, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of a CD40-binding molecule or anti-CD40 antibody may be essentially continuous over a preselected period of time or may be in a series of spaced dose, *e.g.*, either before, during, or after developing a target disease or disorder.

As used herein, the term "treating" refers to the application or administration of a composition including one or more active agents to a subject, who has a target disease or disorder, a symptom of the disease/disorder, or a predisposition toward the disease/disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disorder, the symptom of the disease, or the predisposition toward the disease or disorder.

Alleviating a target disease/disorder includes delaying the development or progression of the disease, or reducing disease severity. Alleviating the disease does not necessarily require curative results. As used therein, "delaying" the development of a target disease or disorder means to defer, hinder, slow, retard, stabilize, and/or postpone progression of the disease. This delay can be of varying lengths of time, depending on the history of the disease and/or individuals being treated. A method that "delays" or alleviates the development of a disease, or delays the onset of the disease, is a method that reduces probability of developing one or more symptoms of the disease in a given time frame and/or reduces extent of the symptoms in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a number of subjects sufficient to give a statistically significant result.

"Development" or "progression" of a disease means initial manifestations and/or ensuing progression of the disease. Development of the disease can be detectable and assessed using standard clinical techniques as well known in the art. However, development also refers to progression that may be undetectable. For purpose of this disclosure, development or progression refers to the biological course of the symptoms. "Development" includes occurrence, recurrence, and onset. As used herein "onset" or "occurrence" of a target disease or disorder includes initial onset and/or recurrence.

In some embodiments, the antibodies described herein are administered to a subject in need of the treatment at an amount sufficient to activate the activity of the target receptor by at least 20% (*e.g.*, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) *in vivo*.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical composition to the subject, depending upon the type of disease to be treated or the site of the disease. This composition can also be administered via other conventional routes, *e.g.*, administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques. In addition, it can be administered to the subject via injectable depot routes of administration such as using 1-, 3-, or 6-month depot injectable or biodegradable materials and methods. In some examples, the pharmaceutical composition is administered intraocularly or intravitreally.

Injectable compositions may contain various carriers such as vegetable oils, dimethylactamide, dimethyformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, and polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like). For intravenous injection, water soluble antibodies can be administered by the drip method, whereby a pharmaceutical formulation containing the antibody and a physiologically acceptable excipient is infused. Physiologically acceptable excipients may include, for example, 5% dextrose, 0.9% saline, Ringer's solution or other suitable excipients. Intramuscular preparations, e.g., a sterile formulation of a suitable soluble salt form of the antibody, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

The particular dosage regimen, *i.e.*, dose, timing and repetition, used in the method described herein will depend on the particular subject and that subject's medical history.

In some embodiments, more than one antibody, or a combination of an antibody and another suitable therapeutic agent, may be administered to a subject in need of the treatment. The CD40-binding molecule or anti-CD40 antibody can also be used in conjunction with other agents that serve to enhance and/or complement the effectiveness of the agents.

Treatment efficacy for a target disease/disorder can be assessed by methods well-known in the art.

The therapeutic agent described herein may be utilized in conjunction with other types of therapy for the target disease such as cancer. Additional anti-cancer therapy includes chemotherapy, surgery, radiation, gene therapy, and so forth. When a second therapeutic agent is used, such an agent can be administered simultaneously or sequentially (in any order) with the CD40-binding molecule or anti-CD40 antibody described herein.

When co-administered with an additional therapeutic agent, suitable therapeutically effective dosages for each agent may be lowered due to the additive action or synergy.

The treatments of the disclosure can be combined with other immunomodulatory treatments such as, *e.g.*, therapeutic vaccines (including but not limited to GVAX, DC-based vaccines, *etc.*), or checkpoint inhibitors (including but not limited to agents that block CTLA4, PD1, LAG3, TIM3, *etc.*). Alternatively, the treatment of the present disclosure can be combined with a chemotherapeutic agent, for example, pyrimidine analogs (5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine), purine analogs, folate antagonists and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (etoposide, teniposide), DNA damaging agents (actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, hexamethyhnelamineoxaliplatin, iphosphamide, melphalan, merchlorehtamine, mitomycin, mitoxantrone, nitrosourea, plicamycin, procarbazine, taxol, taxotere, teniposide, triethylenethiophosphoramide and etoposide (VP16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and

methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes-dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (breveldin); immunosuppressives (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); anti-angiogenic compounds (*e.g.*, TNP-470, genistein, bevacizumab) and growth factor inhibitors (*e.g.*, fibroblast growth factor (FGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab); cell cycle inhibitors and differentiation inducers (tretinoin); mTOR inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), amsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin and mitoxantrone, topotecan, irinotecan), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylpednisolone, prednisone, and prenisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; and chromatin disruptors.

For examples of additional useful agents see also Physician's Desk Reference, 59.sup.th edition, (2005), Thomson P D R, Montvale N.J.; Gennaro et al., Eds. Remington's The Science and Practice of Pharmacy 20.sup.th edition, (2000), Lippincott Williams and Wilkins, Baltimore Md.; Braunwald et al., Eds. Harrison's Principles of Internal Medicine, 15.sup.th edition, (2001), McGraw Hill, NY; Berkow et al., Eds. The Merck Manual of Diagnosis and Therapy, (1992), Merck Research Laboratories, Rahway N.J.

V. Kits

The present disclosure also provides kits for use in enhancing the desired immune responses using any of the CD40-binding molecule or anti-CD40 antibody described herein.

In some embodiments, the kit can comprise instructions for use in accordance with any of the methods described herein. The included instructions can comprise a description of administration of the therapeutic agent to treat, delay the onset, or alleviate a target disease as

those described herein. The kit may further comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has the target disease. In still other embodiments, the instructions comprise a description of administering a therapeutic agent such as an antibody to an individual at risk of the target disease.

The instructions relating to the use of the therapeutic agent generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (*e.g.*, a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical storage disk) are also acceptable.

The label or package insert indicates that the composition is used for treating, delaying the onset and/or alleviating a target disease or disorder such as cancer. Instructions may be provided for practicing any of the methods described herein.

The kits of this invention are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (*e.g.*, sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an inhaler, nasal administration device (*e.g.*, an atomizer) or an infusion device such as a minipump. A kit may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is the therapeutic agent as those described herein.

Kits may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container. In some embodiments, the invention provides articles of manufacture comprising contents of the kits described above.

General Techniques

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques),

microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook, et al., 1989) Cold Spring Harbor Press; Oligonucleotide Synthesis (M. J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J. E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R. I. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J. P. Mather and P. E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J. B. Griffiths, and D. G. Newell, eds., 1993-8) J. Wiley and Sons; Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D. M. Weir and C. C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J. M. Miller and M. P. Calos, eds., 1987); Current Protocols in Molecular Biology (F. M. Ausubel, et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis, et al., eds., 1994); Current Protocols in Immunology (J. E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C. A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty., ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995).

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference for the purposes or subject matter referenced herein.

Example 1. Anti-CD40 Antibodies with Engineered Fc Regions

The cDNA sequences encoding the anti-CD40 antibody variable domain with various heavy chain CH1 and Fc region or human kappa light chain constant region were synthesized and cloned. CHO transient expression was carried out with plasmids containing the corresponding heavy and light chain sequences. These antibodies were purified by protein A affinity chromatography. The amino acid sequences of the heavy chain (HC) and the light chain (LC) are provided below:

383-huIgG LC

DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSG
TDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC (SEQ ID NO: 146)

383-huIgG1m2 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 147)

383-huIgG1m27 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVEHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 148)

383-huIgG2m1 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT
QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTIS
KTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 149)

383-huIgG2m19 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT
QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVASVFLFPPKPKDTLMISRTPEVTCVVVDVEHE
DPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGFPAPIEKTIS
KTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 150)

383-huIgG2m20 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT
QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI
SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 151)

383-huIgG4m2 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
QEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKT
ISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 152)

383-huIgG4m20 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 153)

383-huIgG4m30 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQ
EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI
SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 154)

383-msIgG LC

DIQMTQSPSSVSASVGDRVTITCRASQGIYSWLAWYQQKPGKAPNLLIYTASTLQSGVPSRFSGSGSG
TDFTLTISSLQPEDFATYYCQQANIFPLTFGGGTKVEIKRADAAPTVSIFPPSSEQLTSGGASVVCFL
NNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSP
IVKSFNRNEC (SEQ ID NO: 155)

383-msIgG1 DANA HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTTPPSVYP
LAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSE
TVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVAISKD
DPEVQFSWFVDDVEVHTAQTQPREEQFASTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTIS

KTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYF
VYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK (SEQ ID NO: 156)

383-msIgG1 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTTPPSVYP
LAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSE
TVTCNVAHPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKD
DPEVQFSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTIS
KTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMDTDGSYF
VYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKSLSHSPGK (SEQ ID NO: 157)

383-msIgG2a DANA HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTTAPSVYP
LAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQ
SITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVV
VAVSEDDPDVQISWFVNNVEVHTAQTQTHREDYASTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAP
IERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD
SDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK (SEQ ID NO: 158)

383-msIgG2a HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTTAPSVYP
LAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQ
SITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVV
VDVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAP
IERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLD
SDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK (SEQ ID NO: 159)

Additional Fc mutants were made and the amino acid sequences of the heavy chain (HC) are provided below (the light chain (LC) sequence is provided above):

383-huIgG1 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 207)

383-huIgG2 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT
QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKT
ISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 208)

383-huIgG4SP HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 209)

383-huIgG1mAA

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 210)

383-huIgG1m40 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VaVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYaSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 193)

383-huIgG1m45 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPpvaGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 194)

383-huIg G1m240 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT

QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 195)

383-huIgG1 N297A

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYaSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 196)

383-huIgG1m47 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPpvaGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKgLPssIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 197)

383-huIgG1m48 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSsDKTHTsPPsPAPELLGGsSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 198)

383-huIgG1m49 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTsPPsPAPpvaGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 199)

383-huIgG1m50 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEfeGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAsIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ

QGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 199)

383-huIgG1mAAG

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 211)

383-huIgG2m40 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPE
VQFNWYVDGVEVHNAKTKPREEQFASTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 200)

383-huIgG2m43 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKTVERKCCVECPPCPAPPaaasSVFLFPPKPKDTLMISRTPEVTCVVVDVSaEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVlHQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 201)

383-huIgG2m44 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSqEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVlHQDWLNGKEYKCKVSNKGLPssIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 202)

383-huIgG2mAA HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKTVERKCCVECPPCPAPPaaaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNV
FSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 203)

383-huIgG2m2040 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKTVERKCCVECPPCPAPPVAPSVFLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEV
QFNWYVDGVEVHNAKTKPREEQFASTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 204)

383-huIgG2G4 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQ
VYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNV
FSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 205)

383-huIgG4m40 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDP
EVQFNWYVDGVEVHNAKTKPREEQFASTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN
VFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 206)

383-huIgG4m41 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDP
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQEGN
VFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 66)

383-huIgG4m42 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKRVESKYGPPCPPCPAPPVAGGPSVFLFPPKPKDTLMISRTPEVTCVVVAVSQEDP
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN
VFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 67)

383-huIgG4m46 HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV

TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKRVESKYGPPCPPCPAPEaLGaPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKaYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN
VFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 68)

383-huIgG4mPE HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK
TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 212)

383-huIgG4mAA HC

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINPDSGGTNYAQKFQGRV
TMTRDTSISTAYMELNRLRSDDTAVYYCARDQPLGYCTNGVCSYFDYWGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKRVESKYGPPCPPCPAPEaaGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDP
EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGN
VFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO: 69)

Example 2. Determination of Binding Activity of CD40 Antibody with Fc Mutants to Cellular FcγR

To determine the binding activity of CD40 activity in IgG mutants to cellular Fc receptors, CHO cells were genetically engineered to express human FcγRs (FcγRI, FcγRIIA, FcγRIIB, and FcγRIII) using a lentivirus delivery system as known in the art.

Using anti-CD40 antibody 383 disclosed herein as an exemplary anti-CD40 moiety, a number of anti-CD40 IgG Fc mutants, including 383-msIgG1, 383-msIgG1 DANA, 383-msIgG2a, 383-msIgG2a DANA, 383-hIgG2, control huIgG1, 383-huIgG1m27, 383-huIgG2m19, 383-huIgG1m2, 383-huIgG2m1, 383-huIgG2m20, 383-huIgG4m2, 383-huIgG4m20, 383-huIgG4m30, 383-huIgG1mAA, and 383-huIgG4SP (amino acid sequences provided above), were designed and constructed following the disclosures herein. These IgG mutants contain mutations in the upper hinge domain, the lower hinge domain, or within the CH2 domain.

For FACS analysis of the IgG mutants' binding to different FcγRs, FcγR overexpressing CHO cells were harvested using trypsin-EDTA and were suspended in cold staining buffer (3% BSA in PBS). Test IgG mutants, which were diluted in staining buffer, were added into the cells. The mixture was incubated at 4°C for 2 hours, and then washed twice with cold staining buffer and re-suspended in PE-labeled anti-human IgG followed by incubation at 4°C for 2 hours. The mixture was washed twice with staining buffer and re-suspended in 2% PFA in PBS for FACS.

As shown in **FIGs. 1A-1D** and **3A-3D**, a number of anti-CD40 human IgG1, IgG2, and IgG4 mutants showed binding activity to FcγRs expressed on the cell surface, whereas others exhibited no apparent finding to the FcγRs examined. Summary of the binding property changes is listed in **Tables 2-4** above.

Example 3. CD40 Antibodies Having Engineered Fc Regions Showed Differential CD40 Agonist Activity

To determine the agonist activity of the IgG mutants, a CD40 reporter assay was developed, which involves reporter cells over-expressing human CD40 T cells. This GS-H2-huCD40 reporter cells were re-suspended in assay buffer and cell density and viability were determined with trypan blue. The cell suspension was diluted to 1 x 10^4 cells/mL with assay buffer (MEM containing 1% FBS). The cells were added at 100uL/well, such that the final cell number was 1000 cells/well in the assay plate (Nunc, Cat#167425). Serial working dilutions of the test samples were prepared in assay buffer at 2x final concentrations. Samples were added at 100uL/well test sample at 2x final concentrations to the assay plate. The assay plate was incubated in 37°C, 5% CO_2 incubator for 18-20 hours. After the 18-20 hour incubation, 8 ul of the supernatant from each well of the assay plate was collected and added to HTRF detection assay plate (Nunc). A Human Interleukin 8 (reporter of CD40 activation) detection assay was performed using a Human IL-8 Assay Kit (Cisbio, Cat#62IL8PEB). In particular, 16ul assay volume was used. The results were read using Time Resolved Fluorescence by Tecan F200pro and the relative light unit data was recorded.

As shown in **FIG. 2** and **FIGs. 4A-4E**, all of the tested anti-CD40 antibody IgG mutants stimulated human CD40 activation as evidenced by the secretion of IL8. The magnitude of CD40 activation was influenced by the Fc variants contained therein due to the hinge flexibility of each antibody isotype structure.

CD40 reporter assay was also performed in coculture with FcγRIIB-expressing CHO cells and the results are shown in **FIGs 4A-4D**. Binding to CD40 and FcγR2B by the tested antibody molecules simultaneously in a microenvironment would affect individual binding due to the avidity effect, which refers to the accumulated strength of multiple affinities of individual non-covalent binding interactions. The antibodies showed increased activity correlating to their binding activity to FcγRIIB. It was noted that antibodies with Fc variants with weak or no apparent binding to FcγRIIB exhibited enhanced agonist activity in co-culture reporter assay, suggesting higher sensitivity of the reporter assay which may be attributable to the avidity effect. Therefore, the Fc structure of the antibody can affect the agonist activity of the antibodies with the same variable domains.

Example 4. Characterization of Anti-CD40 Antibody IgG Mutants in Dendritic Cell (DC) Function Assays

The exemplary anti-CD40 antibody Ig variants comprising various Fc mutants were tested *in vitro* for CD40 binding activities and agonistic activity as described in Examples above, as well as *in vivo* for antitumor efficacy and toxicity as in Example 6. Their activities in activating human dendritic cells were carried out as following.

Frozen human PBMC from healthy donors (Allcells, Cat#PB005F) were thawed and transferred to a 50ml tube with 25mL RPMI1640 media. EasySep™ Human CD14 Positive Selection Kit II (Stemcell, Cat: 17858) were used to isolate B cells. Centrifuge the PBMC suspension for 15min at 250g, and discard the supernatant and resuspend the cells in 1.5mL EasySep™ Buffer. Add Selection Cocktail to sample to a14 mL (17 x 100 mm) polystyrene round-bottom tube. 100ul/ml, 150ul for each sample. Transfer the cell from 50ml tube to the 14 mL (17 x 100 mm) polystyrene round-bottom tube, mix and incubate for 15min at RT. Mix the Magnetic Particles before transfer to sample. Transfer Magnetic Particles to sample. 50ul/ml, 75ul for eah sample. Mix and incubate for 10mins at RT. Add 8.5ml EasySep™ Buffer to top up the sample to10mL. Mix by gently pipetting up and down 2 - 3 times. Place the tube into the magnet and incubate for 5min. Pick up the magnet, and in one continuous motion invert the magnet and tube, pouring off the supernatant. Collect the supernatant for B cell Enrichment. Repeat the above wash steps for another 2 times. Resuspend cells in 5mL RPMI 1640. Count the cell density.

The isolated $CD14^+$ cells from human PBMCs were adjust to 1x 10^6 cell/ml and add

GM-CSF and IL-4 were added into the cell culture media. Incubate the cells in a 37 °C, 5% CO2 humidified incubator for 3 days. On day 3, the culture media were changed by transferring the culture supernatant to a centrifuge tube and then centrifuged at 250 x g for 5 minutes. 10ml fresh media containing GN-CSF and IL-4 were used to suspend the cell pellet in the centrifuge tube and then added to the flask during the centrifugation so that the cell pellet thus formed would be resuspended in the 10ml fresh media. The resuspended cells were added back to the same well or flask and incubated for an additional 2 days. On day 5, the above steps were repeated for media change. The cells were further incubated for another additional 2 days. On day 7, immature dendritic cells can be observed and are ready to be used in the desired application.

To perform DC Activation Assay, take medium with cells out of the T75-flask into a 50 ml tubes and centrifuge at 500 x g for 5 min at RT. The supernatant was discarded and the cells were and re-suspend in 3mL RPMI1640 10% FBS medium. Count the cell density and adjust the cell density to 1e6/mL. 0.05mL of the cell suspension were added to a 96 well plate, 2.5 x 10^4 cells/well. IL-8 and IL12 P70 were detected with the HuIL-12-P70 detection kit (Cisbio, Cat#: 62HIL12PEH) and HuIL-8 detection kit (Cisbio, Cat#: 62HIL08PEH) in the cell culture supernatant 24h later (day3). The DC activation assay was also performed in co-culture with FcγR2B expressing CHO cells.

As shown **FIGs. 5A-5D**, the tested CD40 antibody IgG mutants stimulated human CD40 activation at various degrees as evidenced by the secretion of IL8 from the DC culture after antibody incubation. The magnitude of DC activation was influenced by Fc variants contained therein due to the hinge flexibility of each antibody isotype structure and interaction with Fc receptors expressed by the DC culture.

To ascertain the effect of Fc-FcγRIIB cross-linking for CD40 activation, DC activation was also performed in coculture with FcγR2B expressing CHO cells. Binding to CD40 and FcγRIIB by antibody molecules simultaneously in a microenvironment would affect individual binding due to avidity effect leading to alteration of CD40 agonistic effect of the antibodies. The antibodies showed increased activity correlating to their binding activity to FcγRIIB, consistent to the observation in the reporter assay described above. Therefore, the Fc structure of the antibody would affect the overall agonist activity of the antibodies with the same variable domains.

Example 5. CD40 Antibody in IgG Mutants Exhibit Similar Binding to Cellular CD40

FACS were used to evaluate the binding properties of exemplary anti-CD40 antibody IgG variants. CHO cells over-expressing human CD40 or cynomolgus monkey CD40 were harvested using trypsin-EDTA partial digestion followed by centrifugation at 1000 rpm for 5 minutes. The cells were resuspended in cold PBS-BSA (2%) at $5x10^6$/ml and aliquoted out to 100ul/tube. The chimeric anti-CD40 antibodies were diluted in PBS-BSA in three times (final concentrations were 0.01, 0.1, 1, and 10 ug/ml) and 50ul of each concentration was added to the CHO-CD40 cells. The cell solutions were mixed and incubated at 4°C in the dark for 2 hours. The cells were then washed with PBS-BSA twice. Secondary antibody conjugates (goat F(ab')2 anti-human IgG - Fc (PE), pre-adsorbed (Abcam #ab98596)) at a concentration of 100 ul/vial was added and the cells were mixed and incubated 4 °C in dark for 1 hour. The cells were then washed twice with PBS-BSA, followed by fixation in 2% PFA in PBS, and were then subjected to FACS analysis with FACScaliber. As shown in **FIGs. 6A-6B**, these antibodies exhibited high binding activity to human CD40 expressed on the surface of CHO cells.

Example 6. CD40 Antibody in IgG Mutants Exhibit Differential Anti-tumor Activity in Animal Models *in Vivo*

Exemplary anti-CD40 antibodies with various Fc mutants were tested in mouse syngeneic tumor models *in vivo* to determine how Fc mutants could affect the efficacy and toxicity of these antibodies. C57BL6 mice with human CD40 extracellular domains knock in were used to develop syngeneic mouse tumor models. Murine colon cancer MC38 cells were subcutaneously implanted into homozygous human CD40 knock-in C57BL6 mice on day 0. Mice were grouped when the tumor size was approximately $150\pm50mm^3$ (n=6). CD40 antibodies were administered by intraperitoneal injections and tumor sizes were measure during 4-6 weeks of antibody treatment. Tumor sizes were measured by caliber 2 times a week and calculated as tumor volume using formula of $0.5\times length\times width^2$. Anti-tumor efficacy was evaluated between tumor sizes of the control group and antibody treatment group.

As shown in **FIG. 7A**, murine IgG2aDANA (Fc null) provided a reference efficacy driven by Fab'2-induced CD40 activation. Human G4m2, G1m2, G2m20 and G2m40 showed efficacy superior or comparable to mIgG2aDANA.

The potential of antibody induced liver toxicity was examined in the mouse model by measuring serum ALT level after antibody treatment. Human G2 showed a very large ALT elevation with its value exceeded upper limit of the assay (>1000 U/L). The efficacious Fc mutants including G1m2, G2m20 and G2m40 showed less or minimal ALT elevation.

As examples, 383-G2m20 and -G2m40 showed higher agonist activity in the absence of cross-linking and showed *in vivo* efficacy with FcγR interaction (G2m40 is FcγR null in both binding and DC activation assays). Further, residual FcgRIIB binding activity of G2m20 enhanced efficacy. Fc variants G2m1 and G2m43 are expected to have similar efficacy but improved toxicity window given their similar *in vitro* activity profiles to those of G2m20 and G2m40.

As another example, 383-G1m2 showed reduced agonist activity in the absence of cross-linking. The residual FcgRIIB binding activity *in vivo* potentiated the *in vivo* agonist activity of this IgG variant but minimally on liver toxicity. Fc variants G1mAA, G1 N279A, G4m20, G4m30 and G4m46 are expected to have similar efficacy and toxicity window given their similar *in vitro* activity profiles to that of G1m2.

OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

EQUIVALENTS

While several inventive embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the function and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the inventive teachings is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

All references, patents and patent applications disclosed herein are incorporated by reference with respect to the subject matter for which each is cited, which in some cases may encompass the entirety of the document.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of

the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e. "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one,

optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

What Is Claimed Is:

1. A CD40-binding molecule, comprising (a) a CD40 binding moiety, and (b) an engineered Fc region, which comprises at least one mutation at any of positions 220-331, preferably at any of positions 228-329, as compared to a wild-type Fc region counterpart, wherein the numbering is according to the EU index.

2. The CD40-binding molecule of claim 1, which is a CD40 agonist or a CD40 antagonist.

3. The CD40-binding molecule of claim 1 or claim 2, wherein the CD40 binding moiety is a CD40 ligand (CD40L).

4. The CD40-binding molecule of claim 3, wherein the CD40L comprises the amino acid sequence of SEQ ID NO: 140.

5. The CD40-binding molecule of claim 1 or claim 2, wherein the CD40 binding moiety is an anti-CD40 antibody fragment, which comprising (a) a heavy chain that comprises a heavy chain variable region, and (b) a light chain that comprises a light chain variable region and a light chain constant region, wherein the heavy chain variable domain is linked to the engineered Fc region.

6. The CD40-binding molecule of any one of claims 1-5, wherein the variant Fc region has an enhanced binding affinity or selectivity to FcγRIIB relative to its wild-type counterpart.

7. The CD40-binding molecule of any one of claims 1-5, wherein the variant Fc region has a reduced binding affinity to one or more FcγR receptors as relative to its wild-type counterpart.

8. The CD40-binding molecule of claim 7, wherein the variant Fc region has

substantially reduced binding affinity to all FcγR receptors as relative to its wild-type counterpart.

9. The CD40-binding molecule of any one of claims 1-8, wherein the molecule is an IgG1, and wherein the at least one mutation comprises a substitution or deletion within positions 233-238, a substitution at position 265, a substitution at position 267, a substitution at position 297, a substitution at position 328, a substitution at position 329, or a combination thereof.

10. The CD40-binding molecule of any one of claims 1-9, wherein the molecule is an IgG1, and wherein the at least one mutation comprises a substitution at one or more of the positions 220, 226, 229, 238, 273, 327, 330, and 331.

11. The CD40-binding molecule of claim 9 or claim 10, wherein the at least one mutation comprises substitutions at any positions 233-236, a deletion at one or more of positions 236-238, or a combination thereof.

12. The CD40-binding molecule of claim 11, wherein the substitutions at positions 233-235 are E233P, L234V, L234F, L235A, and/or L235E.

13. The CD40-binding molecule of any one of claims 9-12, wherein the deletion is at position 236 or at one or more positions 236-238.

14. The CD40-binding molecule of any one of claims 9-13, wherein the substitution at position 238 is P238S, wherein the substitution at position 273 is V273E, and/or wherein the substitution at position 265 is D265A.

15. The CD40-binding molecule of any one of claims 9-14, wherein the substitution at position 267 is S267E.

16. The CD40-binding molecule of any one of claims 9-15, wherein the substitution at position 329 is P329G.

17. The CD40-binding molecule of claim 9, wherein the at least one mutation comprises a substitution at position 265, a substitution at position 297, or a combination thereof.

18. The CD40-binding molecule of claim 15, wherein the substitution at position 265 is D265A and the substitution at position 297 is N297A.

19. The CD40-binding molecule of claim 9 or claim 10, wherein the one or more substitutions at positions 220, 226, 229, 327, 330, and 331 are C220S, C226S, C229S, A327G, A330S, and P331S.

20. The CD40-binding molecule of claim 9, wherein the variant Fc region is selected from the group consisting of G1m2, G1m17, G1m27, G1mAA, G1mAAG, G1N279A, G1m240, and G1m40.

21. The CD40-binding molecule of any one of claims 1-8, wherein the molecule is an IgG2, and wherein the at least one mutation comprises a deletion within positions 237-238, a substitution at position 265, a substitution at position 267, a substitution at position 297, a substitution at position 328, or a combination thereof.

22. The CD40-binding molecule of any one of claims 1-8 and 21, wherein the molecule of an IgG2, and wherein the at least one mutation comprises a substitution at one or more of positions 233-235, 237, 238, 268, 273, 330, and 331.

23. The CD40-binding molecule of claim 21 or claim 22, wherein the deletion is at position 237 or at both positions 237 and 238.

24. The CD40-binding molecule of any one of claims 21-23, wherein the substitution at position 267 is S267E.

25. The CD40-binding molecule of any one of claims 21-24, wherein the

substitution at position 328 is L328F.

26. The CD40-binding molecule of any one of claims 22-25, wherein the substitution at one or more of positions 233-235, 237, 238, 268, 273, 330, and 331 are P233E, V234A, V234L, A235L, A235S, G237A, P238S, H268A, H268Q, V273E, A330S, and P331S.

27. The CD40-binding molecule of any one of claims 21-26, wherein the at least one mutation comprises a substitution at position 265, a substitution at position 297, or a combination thereof.

28. The CD40-binding molecule of claim 27, wherein the substitution at position 265 is D265A and the substitution at position 297 is N297A.

29. The CD40-binding molecule of claim 21, wherein the variant Fc region is selected from the group consisting of G2m1, G2m17, G2m18, G2m19, G2m20, G2m27, G2m28, G2m29, G2m2040, G2m43, G2G4, G2mAA, and G2m40.

30. The CD40-binding molecule of any one of claims 1-8, wherein the molecule is an IgG4, and wherein the at least one mutation comprises a substitution at position 228, a substitution or deletion at any of positions 235-238, a substitution at position 265, a substitution at position 267, a substitution at position 297, a substitution at position 273, a substitution at position 328, or a combination thereof.

31. The CD40-binding molecule of any one of claims 1-8 and 30, wherein the molecule is an IgG4, and wherein the at least one mutation comprises a substitution at one or more of positions 233-235 or 237.

32. The CD40-binding molecule of claim 30 or claim 31, wherein the substitution at position 228 is S228P.

33. The CD40-binding molecule of any one of claims 30-32, wherein the deletion

is at least one of positions 236-238.

34. The CD40-binding molecule of any one of claims 30-33, wherein the substitution at one or more positions 233-235 and 237 comprises E233P, F234V, F234A, L235S, L235E, L235A, and G237A.

35. The CD40-binding molecule of any one of claims 30-34, wherein the deletion is at both positions 236 and 237.

36. The CD40-binding molecule of any one of claims 30-35, wherein the substitution at position 267 is S267E, and/or wherein the substitution at position 273 is V273E.

37. The CD40-binding molecule of any one of claims 30-36, wherein the substitution at position 328 is L328F.

38. The CD40-binding molecule of claim 30, wherein the at least one mutation comprises a substitution at position 265, a substitution at position 297, or a combination thereof.

39. The CD40-binding molecule of claim 38, wherein the substitution at position 265 is D265A and the substitution at position 297 is N297A.

40. The CD40-binding molecule of claim 30, wherein the variant Fc region is selected from the group consisting of G4m2, G4m20, G4m28, G4m30, G4m41, G4m42, G4m46, G4mPE, G4mAA, and G4m40.

41. The CD40-binding molecule of any one of claims 1-40, wherein the variant Fc region exhibits an enhanced binding affinity to FcγRIIB as compared with the parent Fc region.

42. The CD40-binding molecule of any one of claims 1-41, wherein the variant Fc

region exhibits a decreased binding affinity and/or an enhanced selectivity to FcγRIIB as compared with the parent Fc region.

43. The CD40-binding molecule of any one of claims 1-42, wherein the variant Fc region exhibits low or no binding activity to any FcγR.

44. The CD40-binding molecule of any one of claims 1-43, wherein the variant Fc region binds FcRn.

45. The CD40-binding molecule of any one of claims 5-44, wherein the heavy chain variable region comprises the same heavy chain complementary determining regions (HC CDRs) as those in SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, or SEQ ID NO: 138, and/or the light chain variable region comprises the same light chain complementary determining regions (LC CDRs) as those in SEQ ID NO: 129, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 135, SEQ ID NO: 137, or SEQ ID NO: 139.

46. The CD40-binding molecule of claim 45, wherein the heavy chain variable region comprises SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, SEQ ID NO: 134, SEQ ID NO: 136, or SEQ ID NO: 138, and/or the light chain variable region comprises SEQ ID NO: 129, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 135, SEQ ID NO: 137, or SEQ ID NO: 139.

47. The CD40-binding molecule of any one of claims 5-46, wherein the antibody fragment is of a human antibody or a humanized antibody.

48. An isolated nucleic acid or set of nucleic acids which collectively encode a CD40-binding molecule of any one of claims 1-47.

49. A vector or set of vectors, which collectively comprises the nucleic acid or set of nucleic acids of claim 48.

50. The vector or set of vectors of claim 49, which is an expression vector(s).

51. A host cell comprising the vector or set of vectors of claim 49 or claim 50.

52. A pharmaceutical composition, comprising a CD40-binding molecule of any one of claims 1-51 and a pharmaceutically acceptable carrier.

53. A method for selectively modulating an immune response in a subject, the method comprising administering to a subject in need thereof an effective amount of a CD40-binding molecule set forth in any one of claims 1-52.

54. The method of claim 53, wherein the subject is a human patient having or suspected of having a cancer and the CD40-binding molecule is a CD40 agonist.

55. The method of claim 54, wherein the cancer is selected from the group consisting of lung cancer, stomach cancer, liver cancer, breast cancer, skin cancer, pancreatic cancer, brain cancer, prostate cancer, bladder cancer, colorectal cancer, sarcoma, bone cancer, lymphoma and a hematological cancer.

56. The method of claim 53, wherein the subject is a human patient having or suspected of having an immune-related disorder, and wherein the CD40-binding molecule is a CD40 antagonist.

57. The method of claim 56, wherein the immune-related disorder is selected from the group consisting of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Myasthenia Gravis (MG), Graves' Disease, Idiopathic Thrombocytopenia Purpura (ITP), Guillain-Barre Syndrome, autoimmune myocarditis, Membrane Glomerulonephritis, diabetes mellitus, Type I or Type II diabetes, multiple sclerosis, Reynaud's syndrome, autoimmune thyroiditis, gastritis, Celiac Disease, Vitiligo, Hepatitis, primary biliary cirrhosis, inflammatory bowel disease, spondyloarthropathies, experimental autoimmune encephalomyelitis, immune neutropenia, juvenile onset diabetes, and immune responses associated with delayed hypersensitivity mediated by cytokines, T-lymphocytes typically

found in tuberculosis, sarcoidosis, and polymyositis, polyarteritis, cutaneous vasculitis, pemphigus, pemphigold, Goodpasture's syndrome, Kawasaki's disease, systemic sclerosis, anti-phospholipid syndrome, Sjogren's syndrome, graft-versus-host (GVH) disease, and immune thrombocytopenia.

58. An isolated anti-CD40 antibody, which binds to the same epitope of CD40 as a reference antibody selected from the group consisting of 19G6D6, 36G7B8, 13F1A7, 9F12D9, and 17C5C2, or competes against the reference antibody from binding to the epitope.

59. The isolated anti-CD40 antibody of claim 58, wherein the antibody comprises a heavy chain complementary determining region 1 (CDR1), a heavy chain complementary determining region 2 (CDR2), and a heavy chain complementary determining region 3 (CDR3), which collectively are at least 85% identical to the heavy chain CDRs of the reference antibody; and/or wherein the antibody comprises a light chain CDR1, a light chain CDR2, and a light chain CDR3, which collectively are at least 85% identical to the light chain CDRs of the reference antibody.

60. The isolated anti-CD40 antibody of claim 59, wherein the heavy chain CDR1, heavy chain CDR2, and heavy chain CDR3 collectively comprise up to 10 amino acid variations relative to the heavy chain CDRs of the reference antibody; and/or wherein the light chain CDR1, light chain CDR2, and light chain CDR3 collectively comprise up to 10 amino acid variations relative to the light chain CDRs of the reference antibody.

61. The isolated anti-CD40 antibody of any one of claims 58-60, wherein the antibody comprises a heavy chain variable region that is at least 85% identical to the heavy chain variable region of the reference antibody; and/or a light chain variable region that is at least 85% identical to the light chain variable region of the reference antibody.

62. The isolated anti-CD40 antibody of claim 58, wherein the antibody comprises the same heavy chain variable region CDRs as the reference antibody and/or the same light

chain variable region CDRs as the reference antibody.

63. The isolated anti-CD40 antibody of any one of claims 58-62, wherein the antibody is a human antibody or a humanized antibody.

64. An isolated nucleic acid or set of nucleic acids which collectively encode an anti-CD40 antibody of any one of claims 58-63.

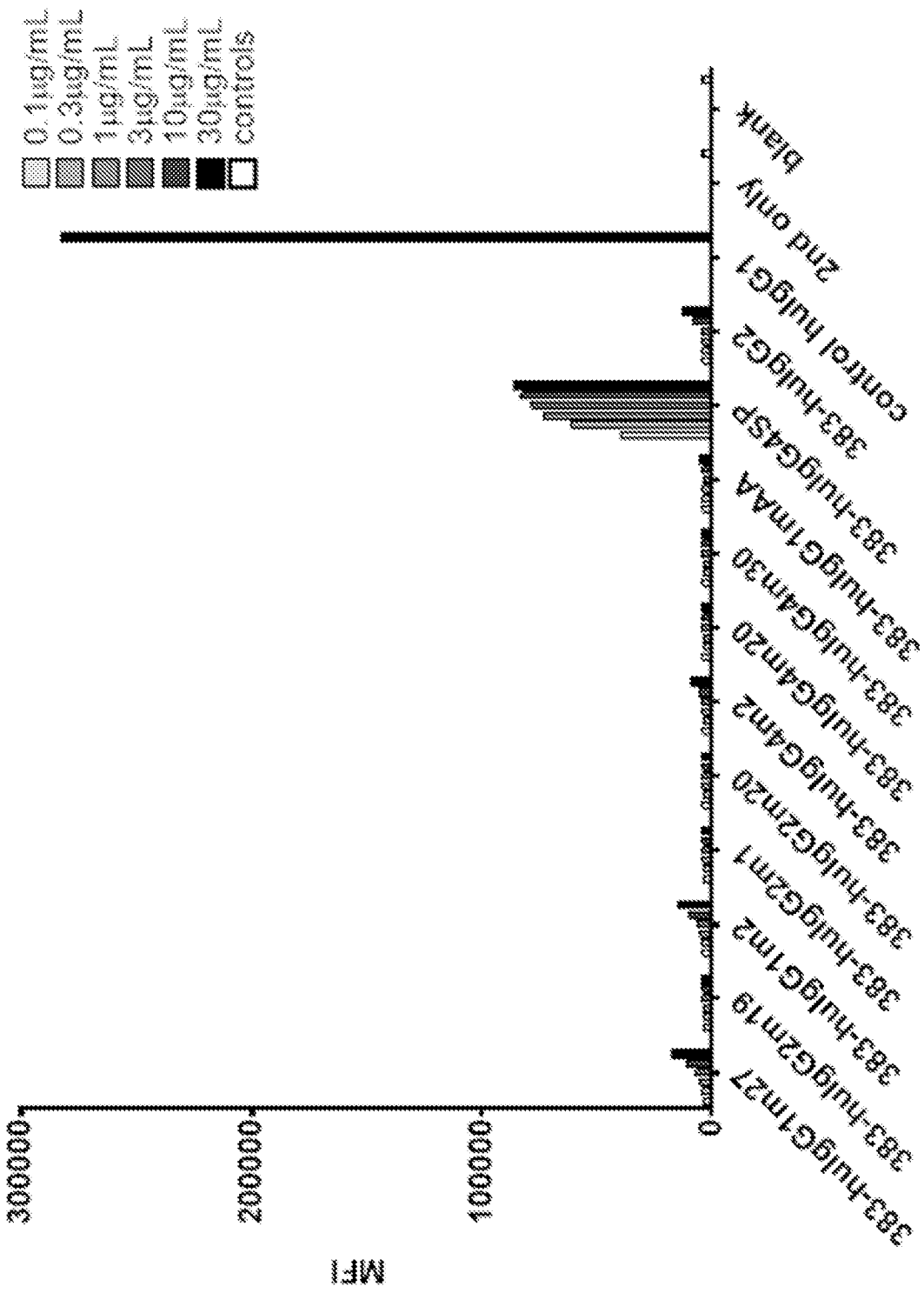
65. A vector or set of vectors, which collectively comprises the nucleic acid or set of nucleic acids of claim 64.

66. The vector or set of vectors of claim 65, which is an expression vector(s).

67. A host cell comprising the vector or set of vectors of claim 65 or claim 66.

68. A pharmaceutical composition, comprising an anti-CD40 antibody of any one of claims 58-63, the encoding nucleic acid of any one of claims 64-66, or the host cell of claim 67, and a pharmaceutically acceptable carrier.

FIG. 1A


FcγRI
MFI
300000
200000
100000
0
0.1µg/mL
0.3µg/mL
1µg/mL
3µg/mL
10µg/mL
30µg/mL
controls
383-huIgG1m27
383-huIgG2m19
383-huIgG1m2
383-huIgG2m1
383-huIgG2m20
383-huIgG4m2
383-huIgG4m20
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control huIgG1
2nd only
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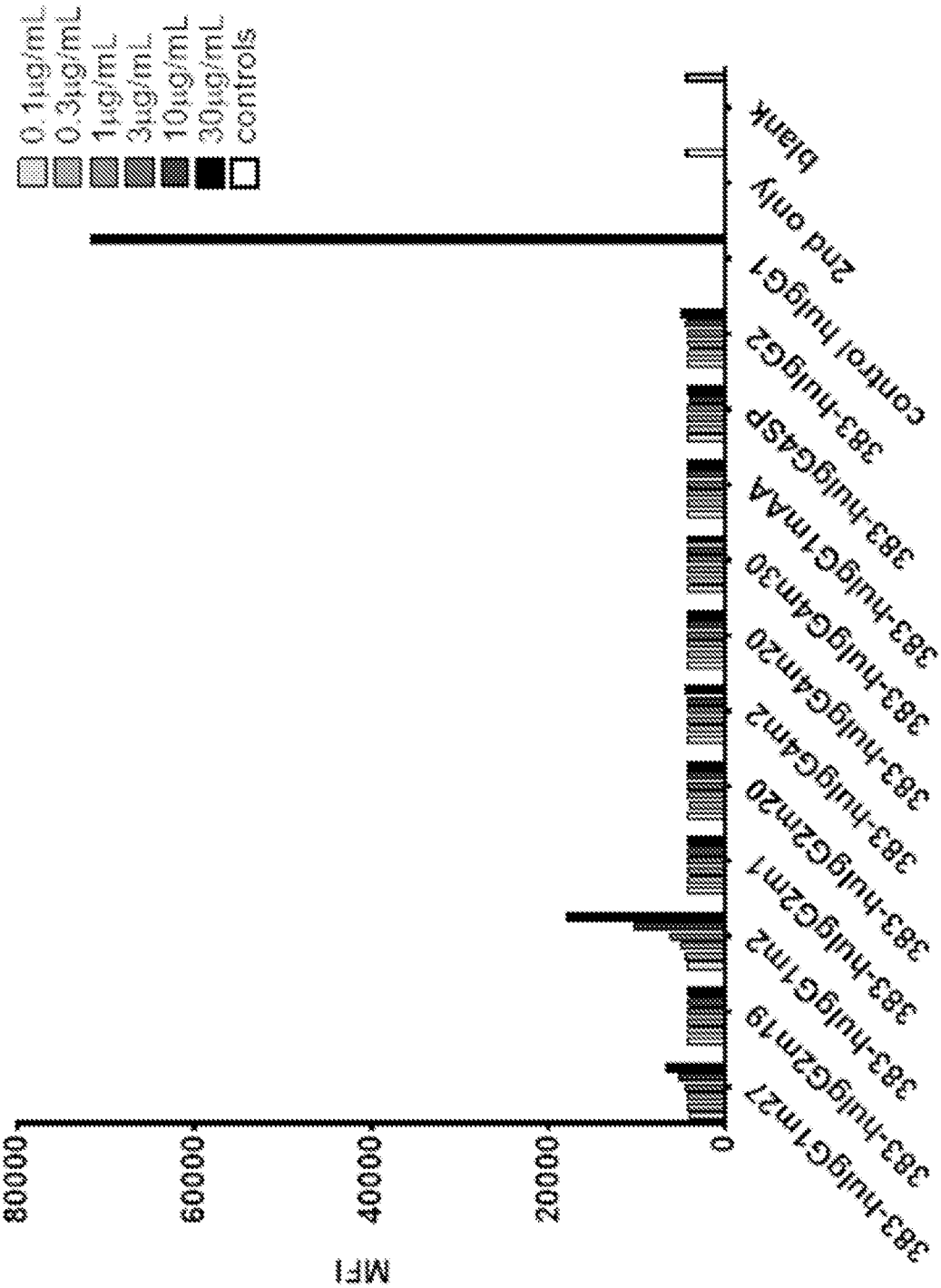
FIG. 1B


FcγRIIA
0.1µg/mL
0.3µg/mL
1µg/mL
3µg/mL
10µg/mL
30µg/mL
controls
MFI
80000
60000
40000
20000
0
blank
2nd only
control huIgG1
383-huIgG2
383-huIgG4SP
383-huIgG1mAA
383-huIgG4m30
383-huIgG4m20
383-huIgG4m2
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383-huIgG1m2
383-huIgG2m19
383-huIgG1m27

FIG. 1C

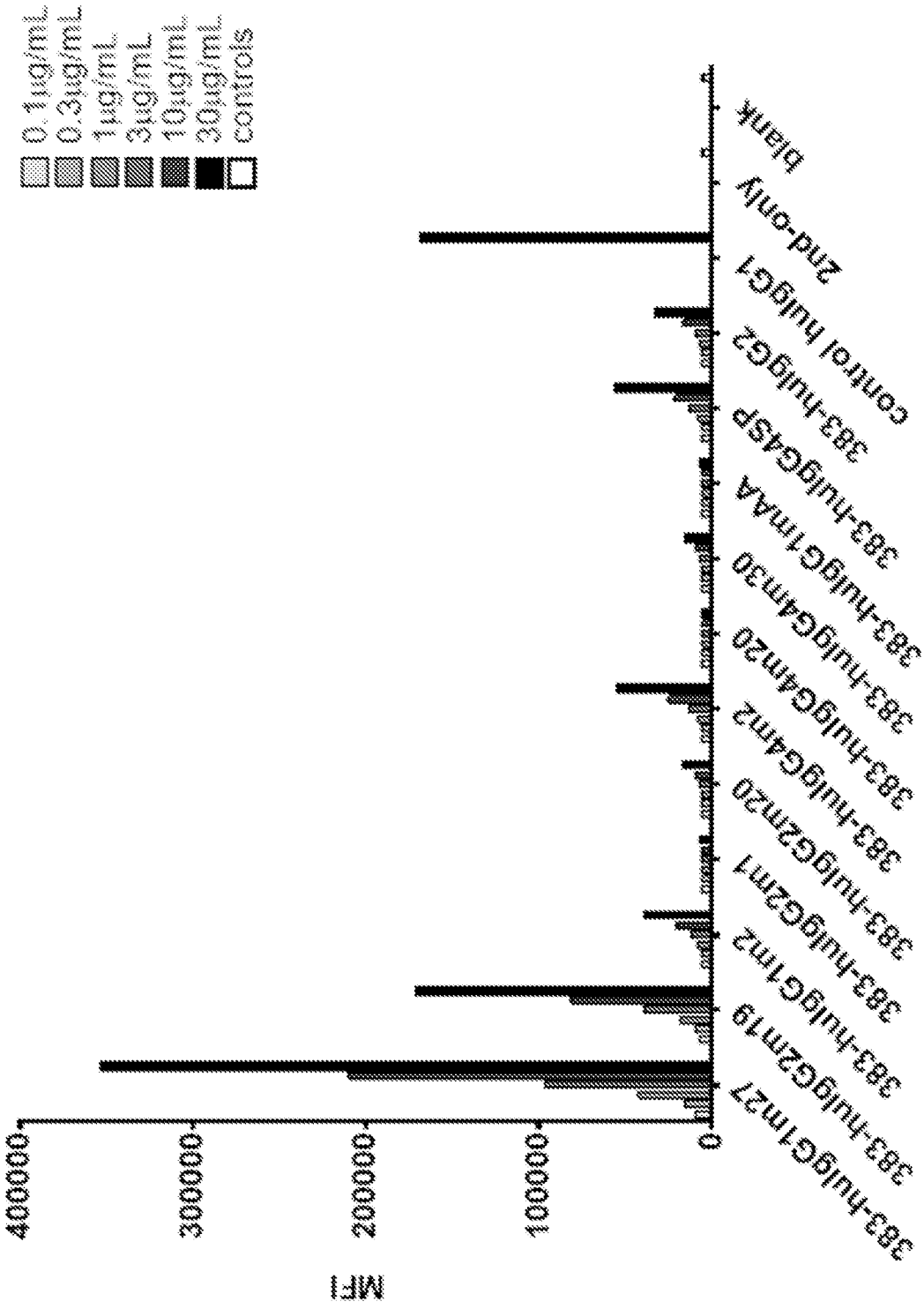
FcγRIIB
0.1μg/mL
0.3μg/mL
1μg/mL
3μg/mL
10μg/mL
30μg/mL
controls
MFI
400000
300000
200000
100000
0
383-huIgG1m27
383-huIgG2m19
383-huIgG1m2
383-huIgG2m1
383-huIgG2m20
383-huIgG4m2
383-huIgG4m20
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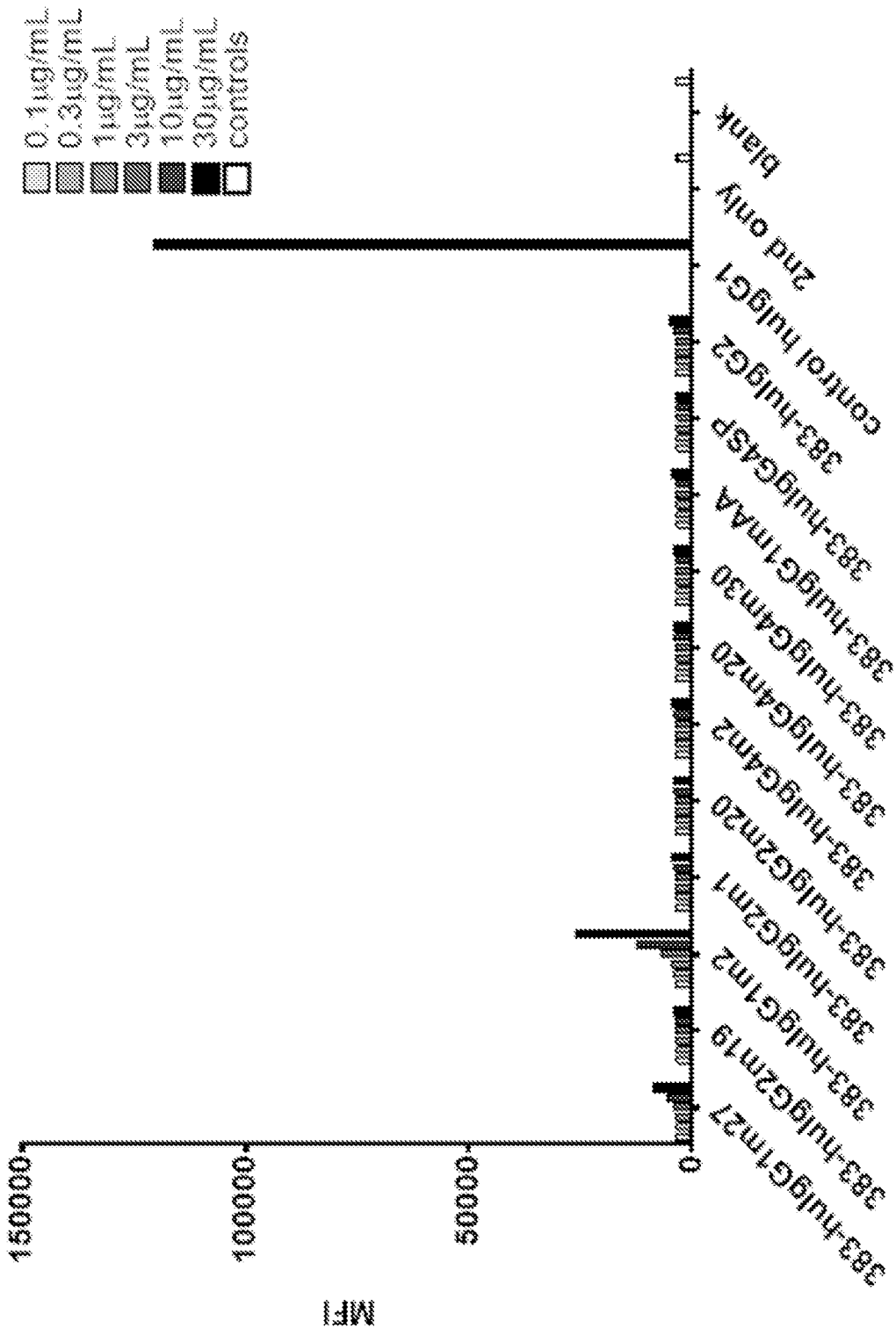
FIG. 1D


FcγRIIIA
MFI
150000
100000
50000
0
0.1μg/mL
0.3μg/mL
1μg/mL
3μg/mL
10μg/mL
30μg/mL
controls
blank
2nd only
control huIgG1
383-huIgG2
383-huIgG4SP
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383-huIgG4m2
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383-huIgG2m1
383-huIgG1m2
383-huIgG2m19
383-huIgG1m27

FIG. 2

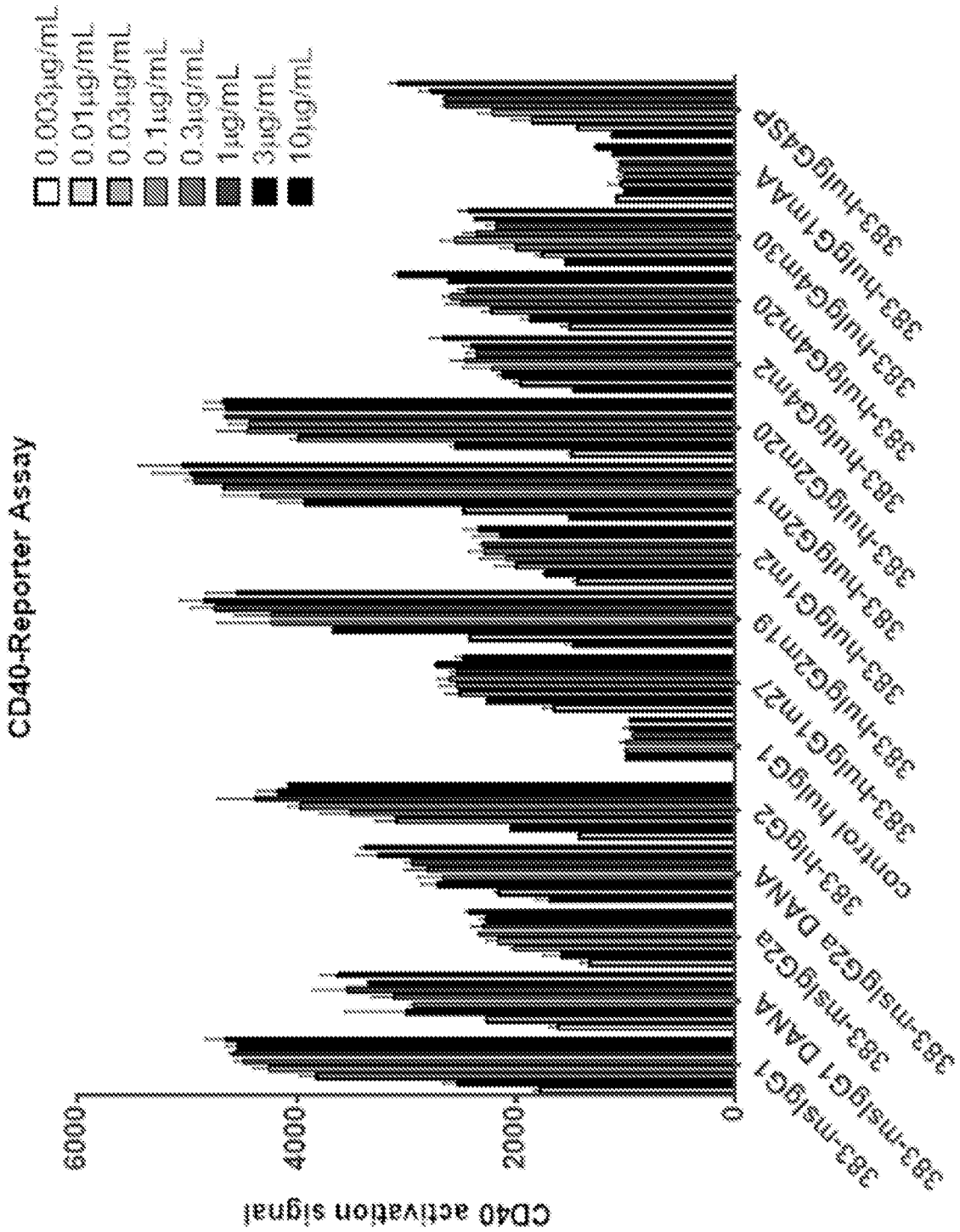
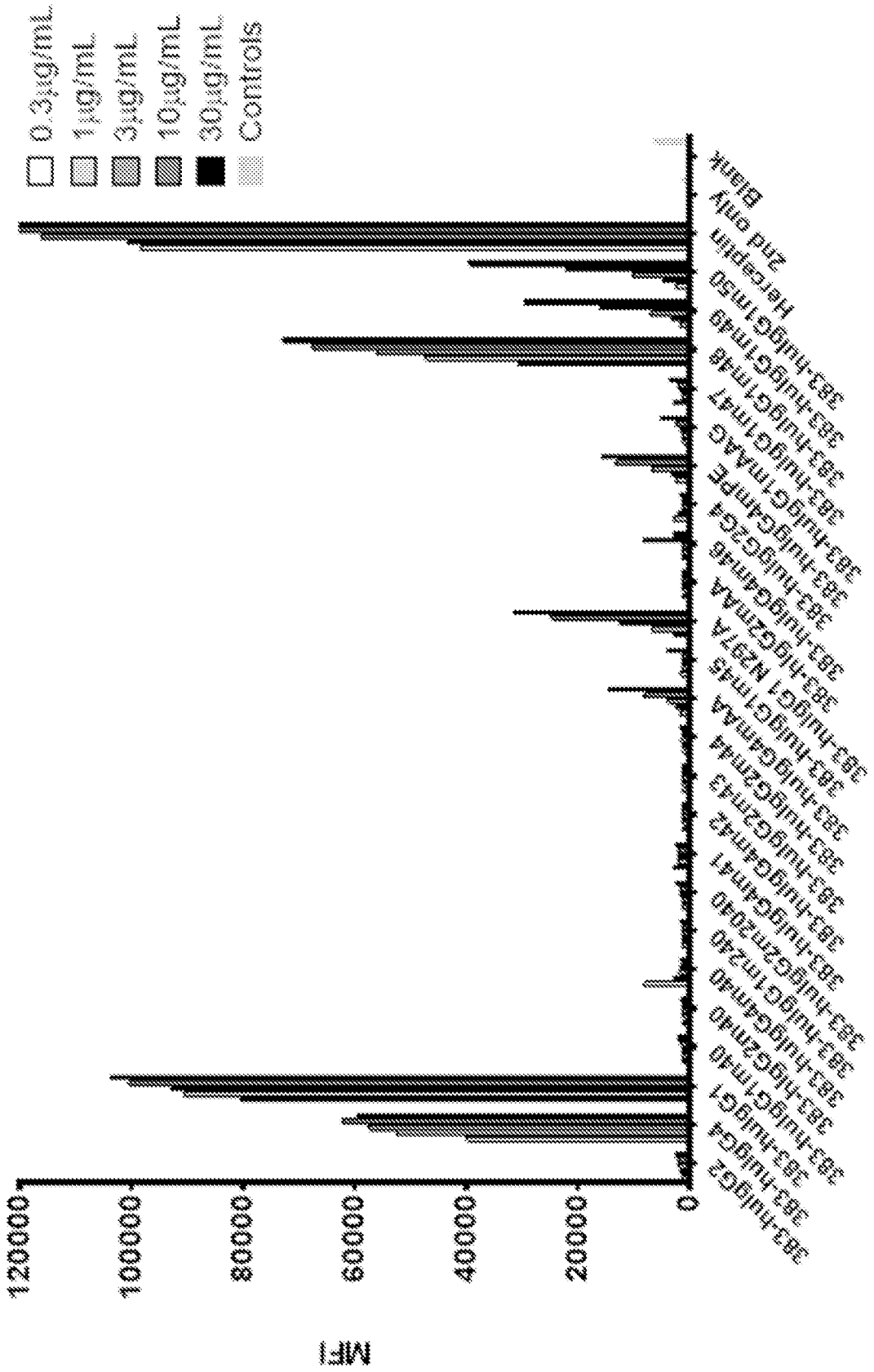

CD40-Reporter Assay
0.003µg/mL
0.01µg/mL
0.03µg/mL
0.1µg/mL
0.3µg/mL
1µg/mL
3µg/mL
10µg/mL
CD40 activation signal
6000
4000
2000
0
383-msIgG1
383-msIgG1 DANA
383-msIgG2a
383-msIgG2a DANA
383-hIgG2
control huIgG1
383-huIgG1
383-huIgG1m17
383-huIgG3m19
383-huIgG1m2
383-huIgG2m1
383-huIgG2m20
383-huIgG4m2
383-huIgG4m20
383-huIgG4m30
383-huIgG1mAA
383-huIgG4SP

FIG. 3A

FcγRI


0.3µg/mL
1µg/mL
3µg/mL
10µg/mL
30µg/mL
Controls
MFI
120000
100000
80000
60000
40000
20000
0
383-huIgG2
383-huIgG4
383-huIgG1
383-huIgG1m40
383-huIgG2m40
383-huIgG4m40
383-huIgG1m240
383-huIgG2m20m40
383-huIgG4m1
383-huIgG4m2
383-huIgG2m43
383-huIgG2m4
383-huIgG4m4A
383-huIgG1m45
383-huIgG1 N297A
383-huIgG2m4A
383-huIgG4m46
383-huIgG2G4
383-huIgG4mPE
383-huIgG1m4G
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Herceptin
2nd only
Blank

FIG. 3B

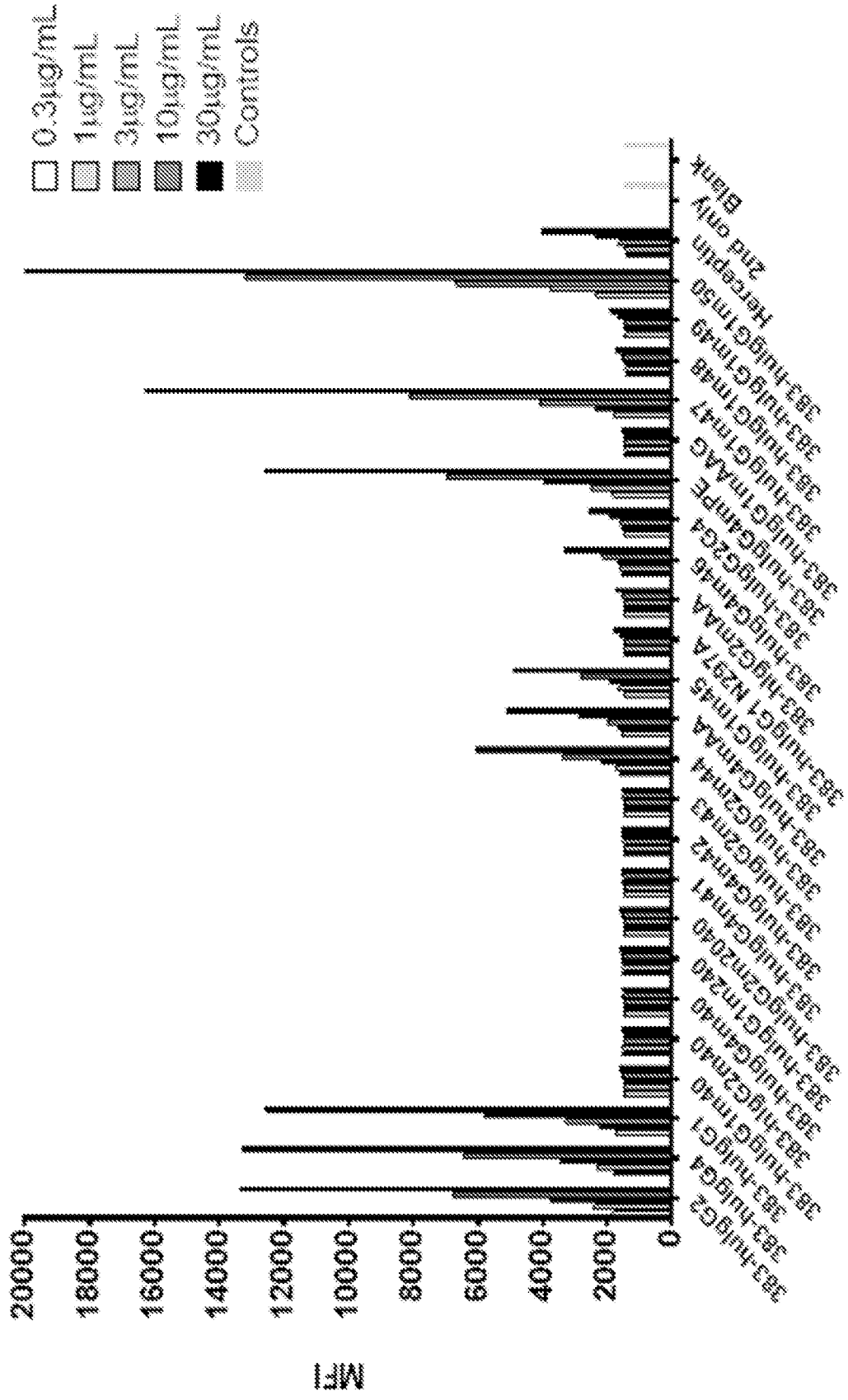

FcγRIIA
MFI
0.3μg/mL
1μg/mL
3μg/mL
10μg/mL
30μg/mL
Controls
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
383-huIgG2
383-huIgA
383-huIgG1
383-huIgG1m40
383-huIgG2m40
383-huIgG4m40
383-huIgG1m240
383-huIgG2m20m40
383-huIgG4m41
383-huIgG4m42
383-huIgG2m43
383-huIgG2m44
383-huIgG4m44
383-huIgG1m45
383-huIgG1 N297A
383-huIgG2m46
383-huIgG4m46
383-huIgG2G4
383-huIgG4mPE
383-huIgG1mAG
383-huIgG1m47
383-huIgG1m48
383-huIgG1m49
Herceptin
2nd only
Blank

FIG. 3C

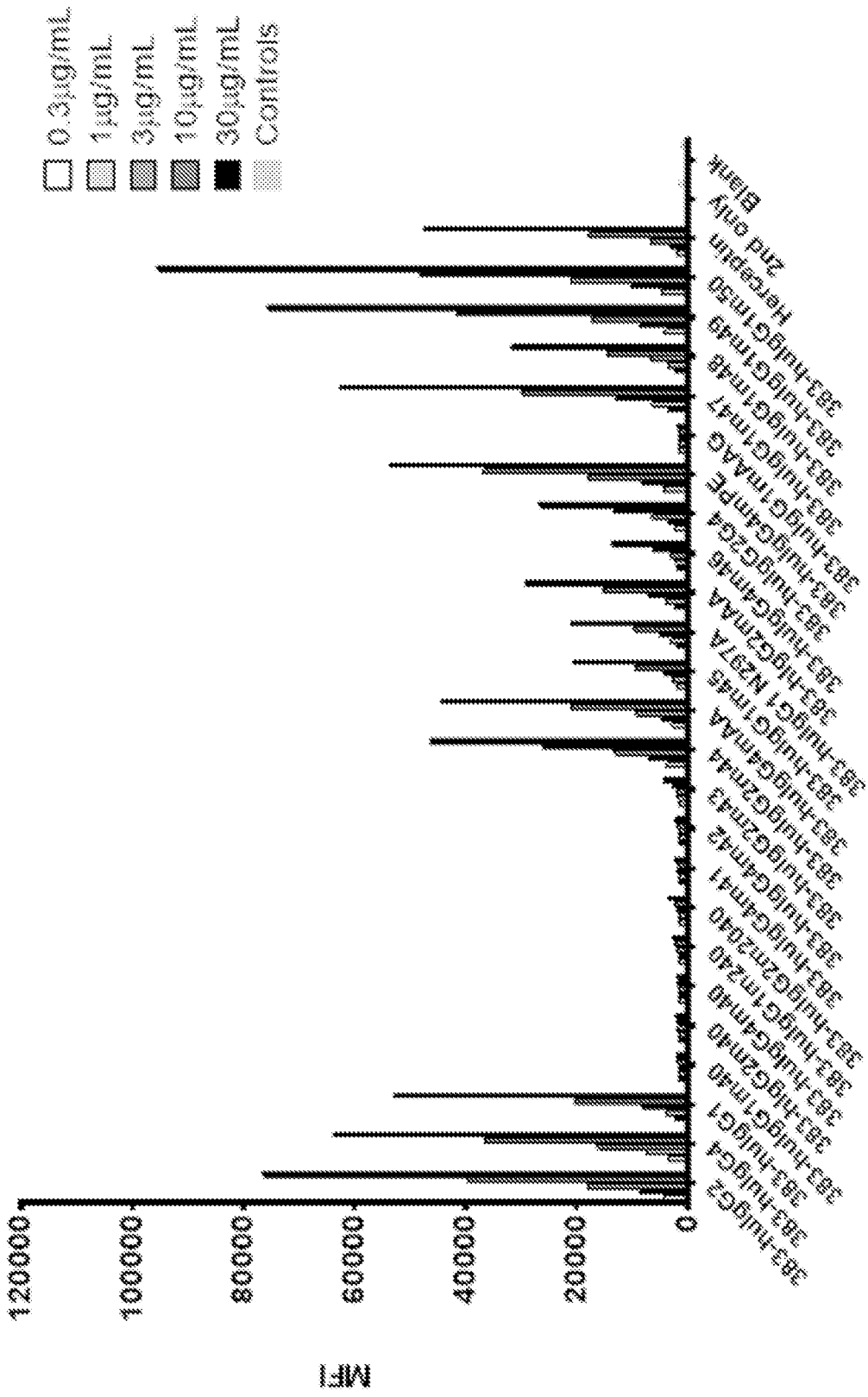

FcγRIIB
MFI
120000
100000
80000
60000
40000
20000
0
0.3µg/mL
1µg/mL
3µg/mL
10µg/mL
30µg/mL
Controls
383-huIgG3
383-huIgG4
383-huIgG1
383-huIgG1m40
383-huIgG2m40
383-huIgG4m40
383-huIgG1m240
383-huIgG2m240
383-huIgG4m1
383-huIgG4m2
383-huIgG2m43
383-huIgG4m44
383-huIgG1m45
383-huIgG1 N297A
383-huIgG2m45
383-huIgG4m48
383-huIgG2G4
383-huIgG4mPE
383-huIgG1mAG
383-huIgG1m47
383-huIgG1m48
383-huIgG1m49
Herceptin
2nd only
Blank

FIG. 3D

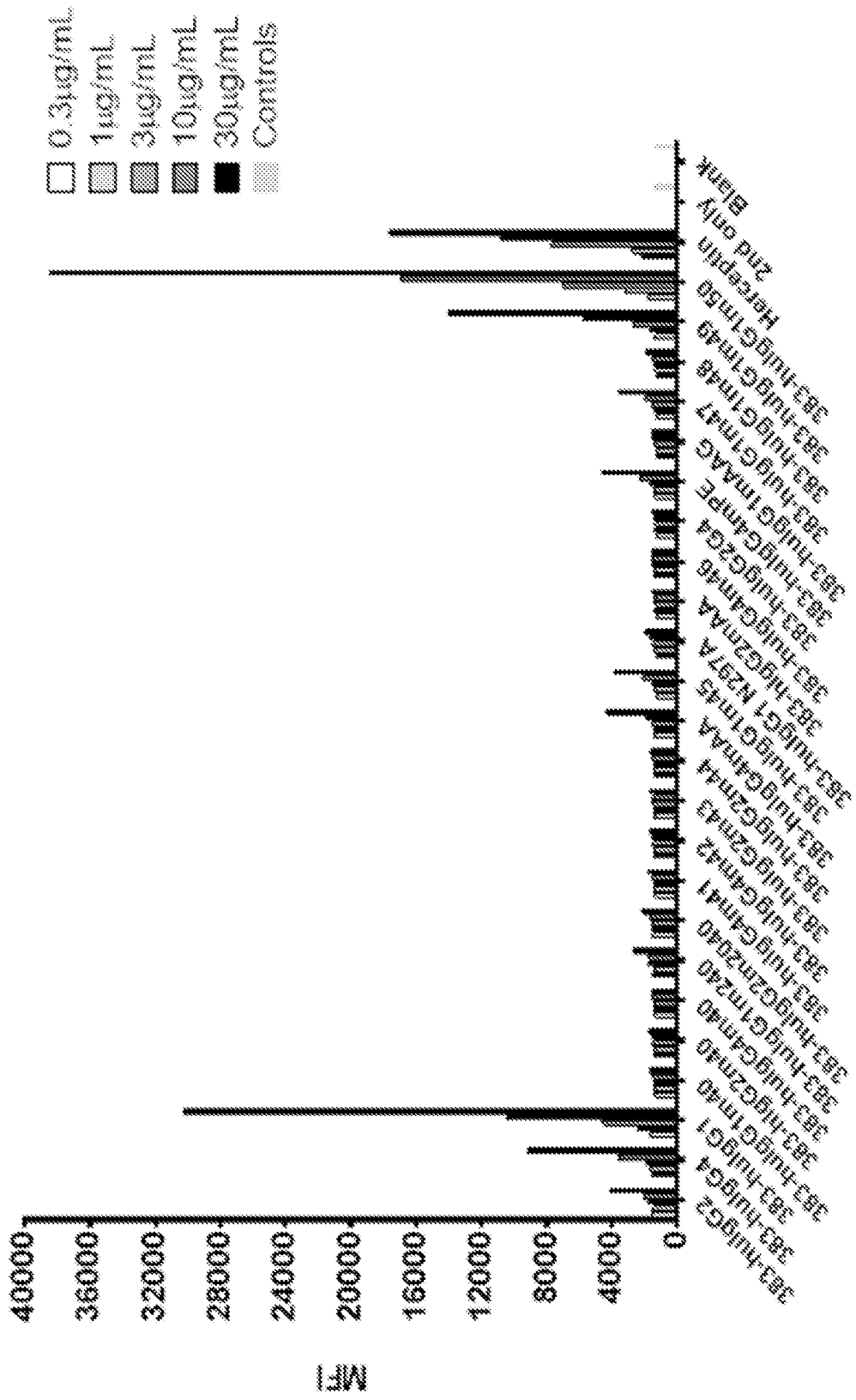

FcγRIIIA
MFI
0.3μg/mL
1μg/mL
3μg/mL
10μg/mL
30μg/mL
Controls
40000
36000
32000
28000
24000
20000
16000
12000
8000
4000
0
383-huIgG2
383-huIgG4
383-huIgG1
383-huIgG1m40
383-huIgG2m40
383-huIgG4m40
383-huIgG1m240
383-huIgG2m240
383-huIgG4m1
383-huIgG4m2
383-huIgG2m43
383-huIgG4m44
383-huIgG1m45
383-huIgG1 M297A
383-huIgG2m44
383-huIgG4m46
383-huIgG2G4
383-huIgG4mPE
383-huIgG1m4AG
383-huIgG1m47
383-huIgG1m48
383-huIgG1m49
Herceptin
2nd only
Blank

FIG. 4A

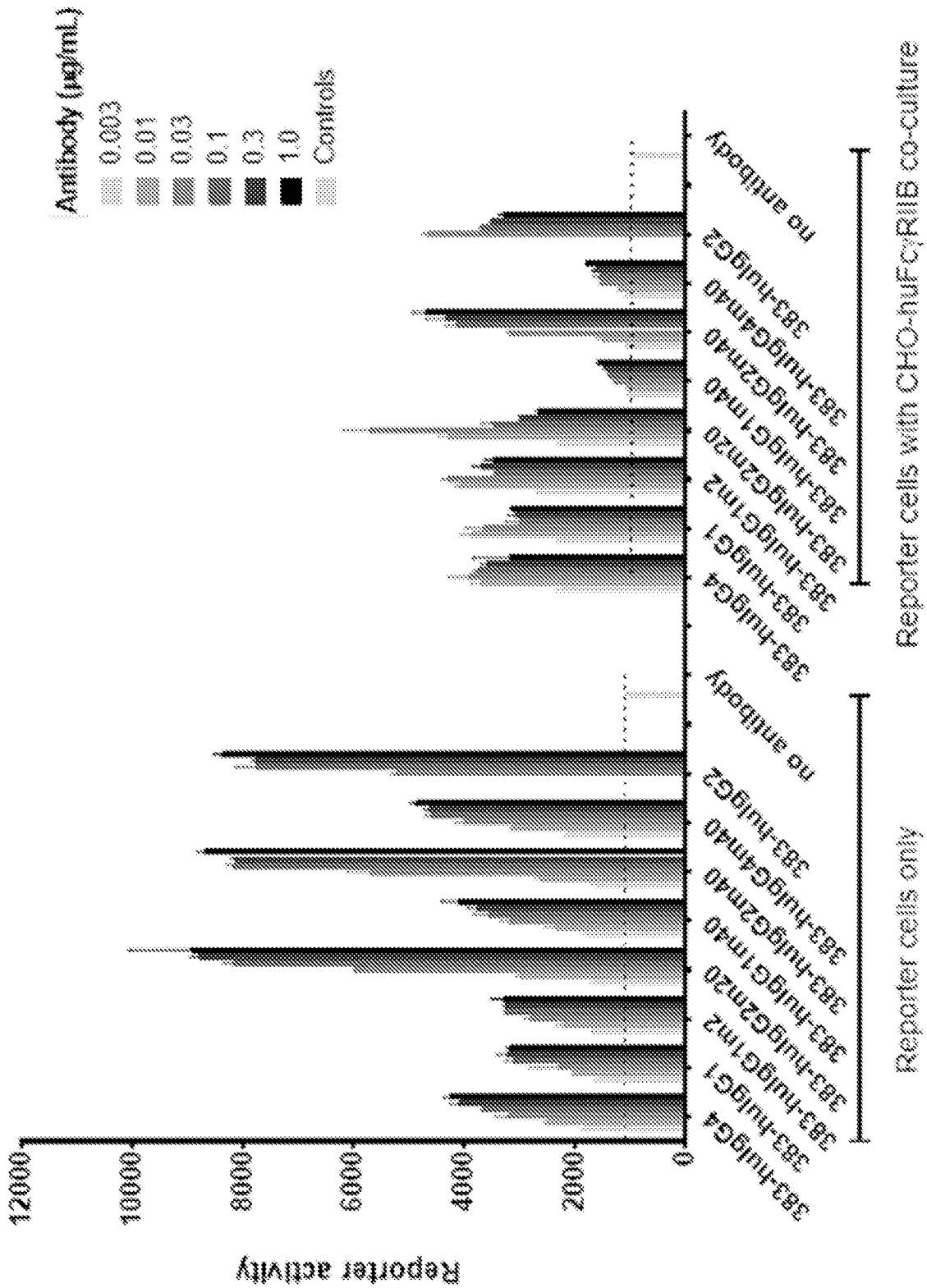

Antibody (µg/mL)
0.003
0.01
0.03
0.1
0.3
1.0
Controls
Reporter activity
12000
10000
8000
6000
4000
2000
0
383-huIgG4
383-huIgG1
383-huIgG1m2
383-huIgG2m20
383-huIgG1m40
383-huIgG2m40
383-huIgG4m40
383-huIgG2
no antibody
Reporter cells only
Reporter cells with CHO-huFcγRIIB co-culture

FIG. 4B

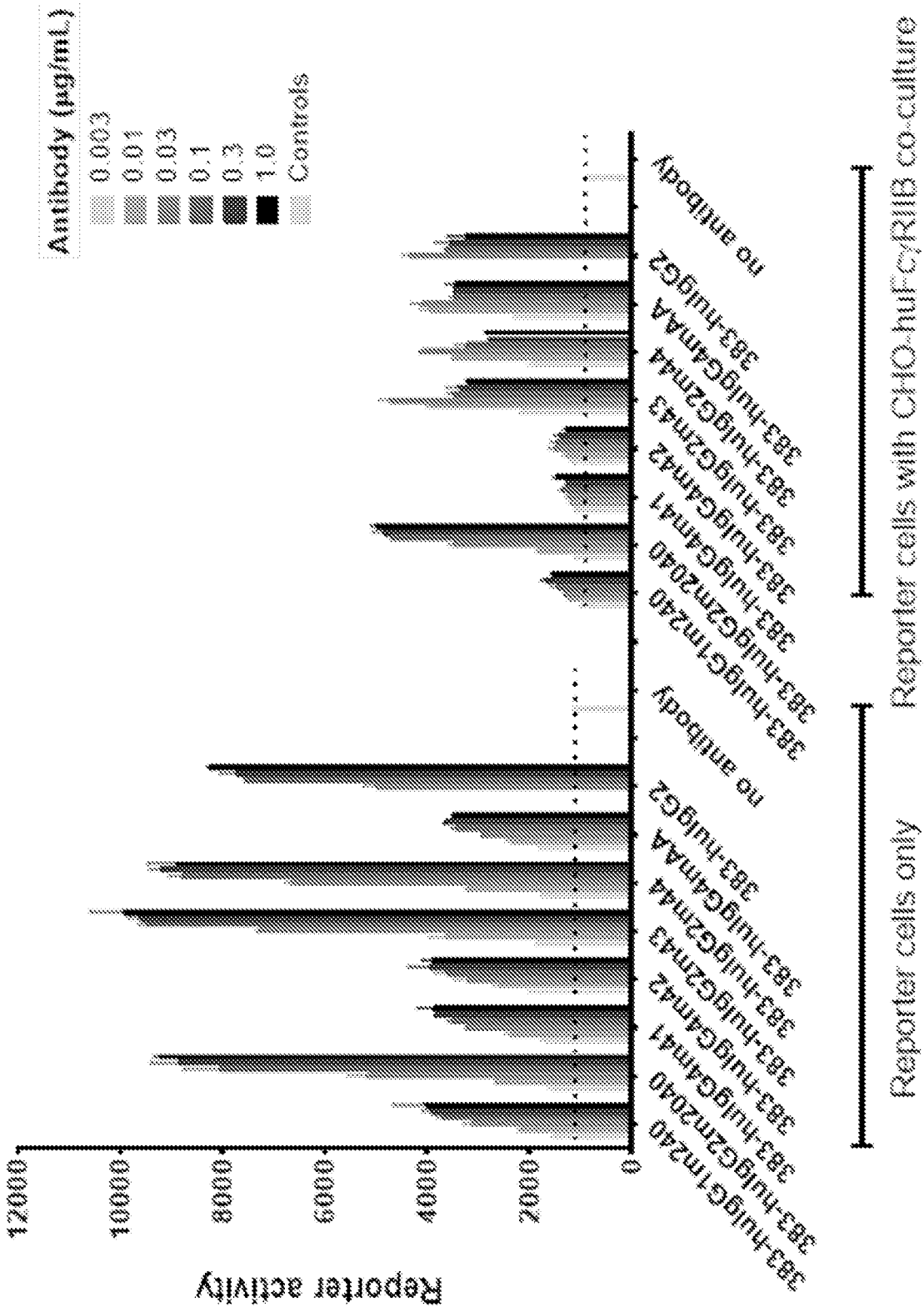

Antibody (μg/mL)
0.003
0.01
0.03
0.1
0.3
1.0
Controls
Reporter activity
12000
10000
8000
6000
4000
2000
0
383-huIgG1m240
383-huIgG2m2040
383-huIgG4m41
383-huIgG2m42
383-huIgG2m43
383-huIgG4m44
383-huIgG4mAA
383-huIgG2
no antibody
Reporter cells only
Reporter cells with CHO-huFcγRIIB co-culture

FIG. 4C

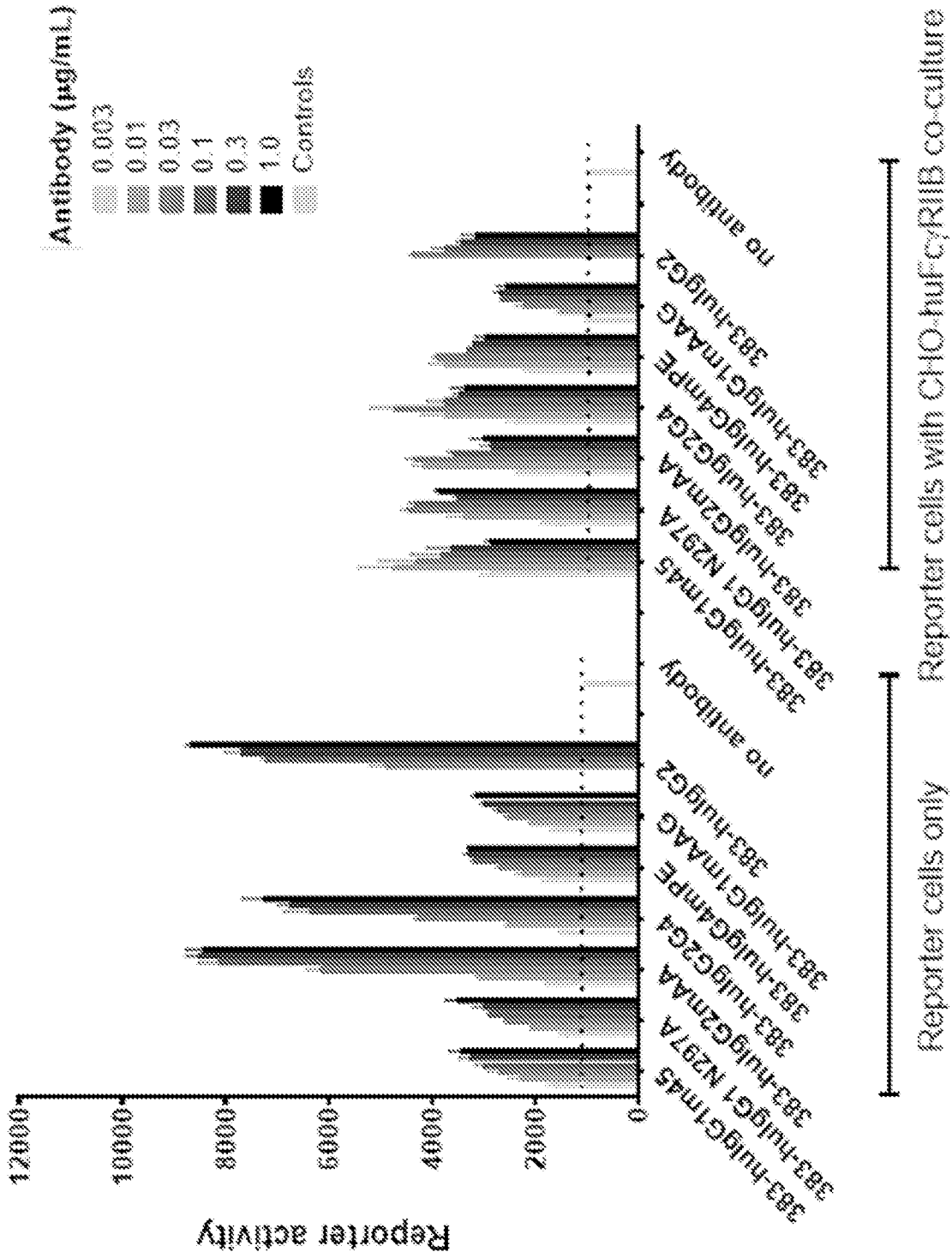

Antibody (µg/mL)
0.003
0.01
0.03
0.1
0.3
1.0
Controls
Reporter activity
12000
10000
8000
6000
4000
2000
0
383-huIgG1-m4s
383-huIgG1 N297A
383-huIgG2m4A
383-huIgG2cA
383-huIgG4mPE
383-huIgG1m4AG
383-huIgG2
no antibody
Reporter cells only
Reporter cells with CHO-huFcγRIIB co-culture

FIG. 4D

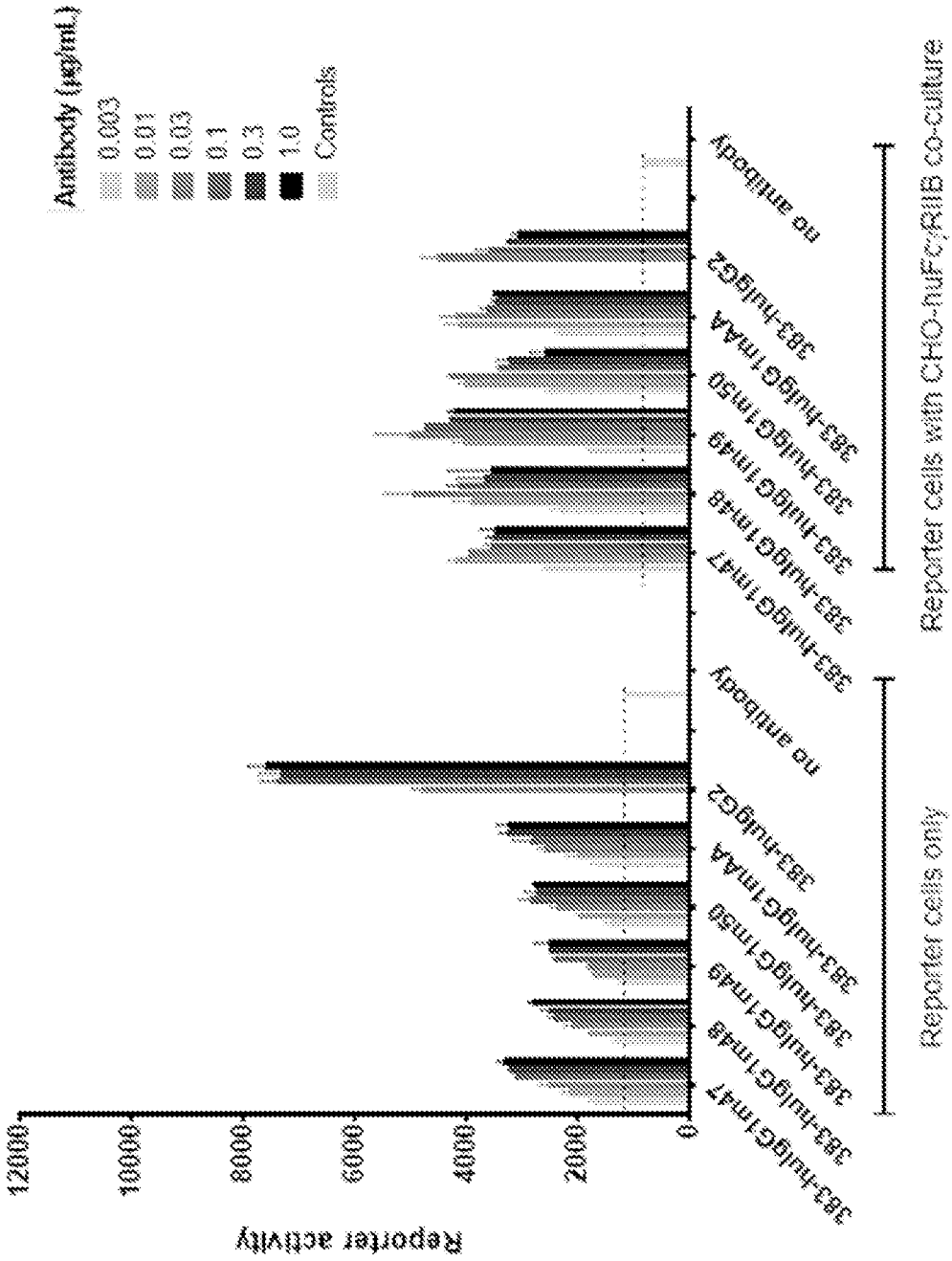

Antibody (μg/mL)
0.003
0.01
0.03
0.1
0.3
1.0
Controls
Reporter activity
12000
10000
8000
6000
4000
2000
0
Reporter cells only
Reporter cells with CHO-huFcγRIIB co-culture
no antibody
383-huIgG1m47
383-huIgG1m48
383-huIgG1m49
383-huIgG1m50
383-huIgG1mAA
383-huIgG2
no antibody
383-huIgG1m47
383-huIgG1m48
383-huIgG1m49
383-huIgG1m50
383-huIgG1mAA
383-huIgG2

FIG. 4E

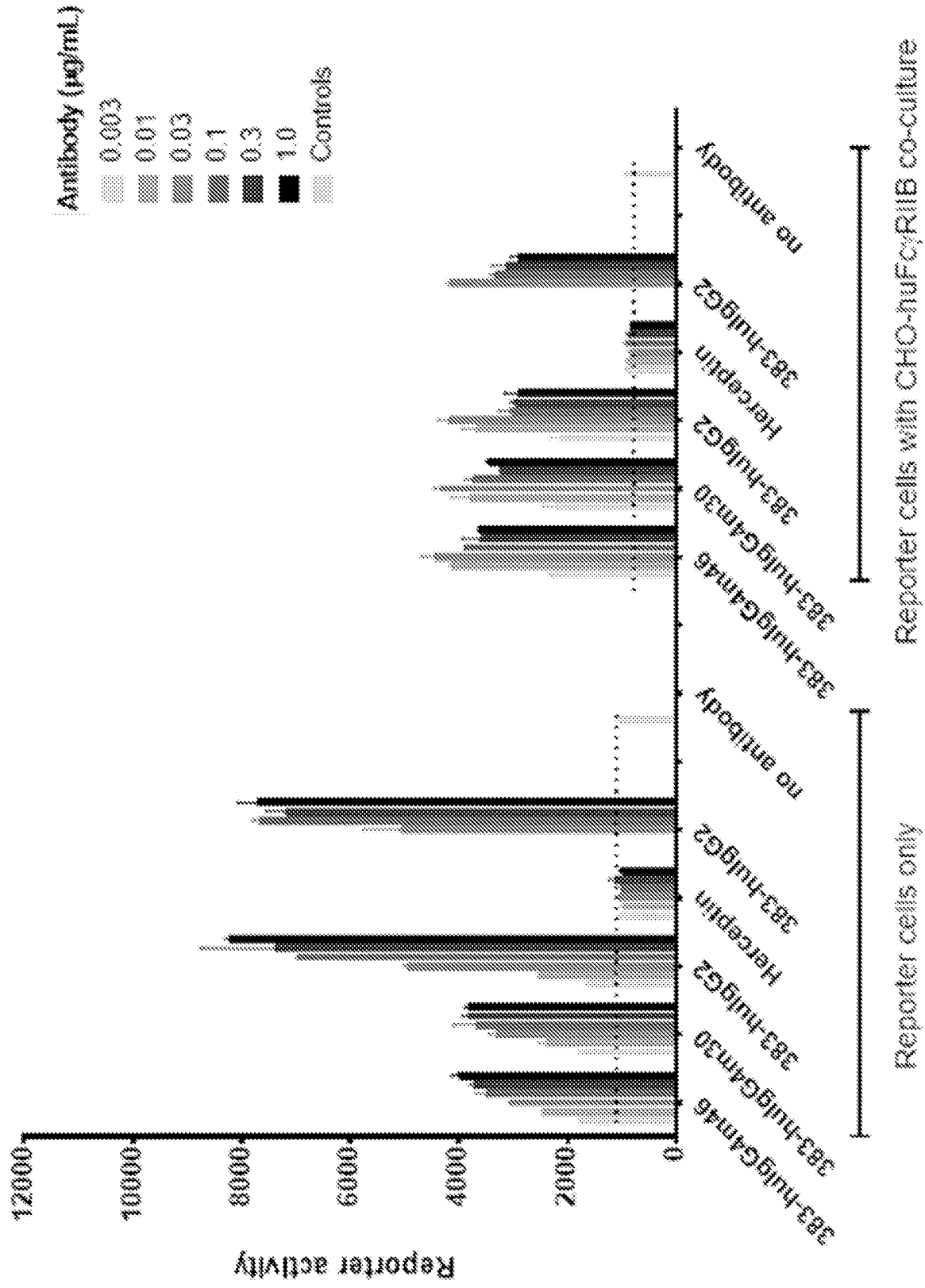

Antibody (μg/mL)
0.003
0.01
0.03
0.1
0.3
1.0
Controls
Reporter activity
12000
10000
8000
6000
4000
2000
0
383-huIgG4m46
383-huIgG4m30
383-huIgG2
Herceptin
383-huIgG2
no antibody
Reporter cells only
383-huIgG4m46
383-huIgG4m30
383-huIgG2
Herceptin
383-huIgG2
no antibody
Reporter cells with CHO-huFcγRIIB co-culture

FIG. 4F

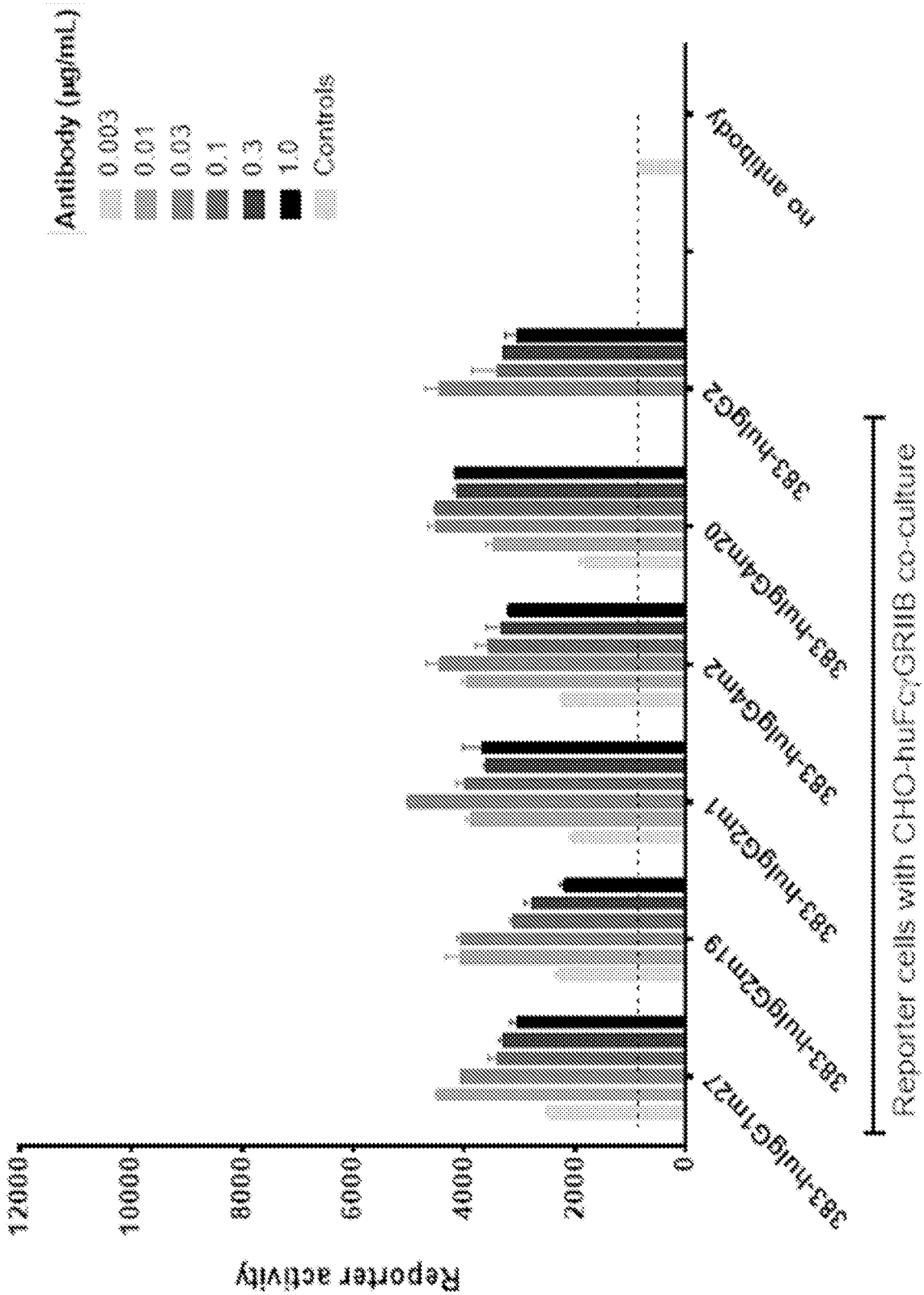

Antibody (µg/mL)
0.003
0.01
0.03
0.1
0.3
1.0
Controls
Reporter activity
12000
10000
8000
6000
4000
2000
0
no antibody
383-huIgG2
383-huIgG4m20
383-huIgG4m2
383-huIgG2m1
383-huIgG2m19
383-huIgG1m27
Reporter cells with CHO-huFcγGRIIIB co-culture

FIG. 5A

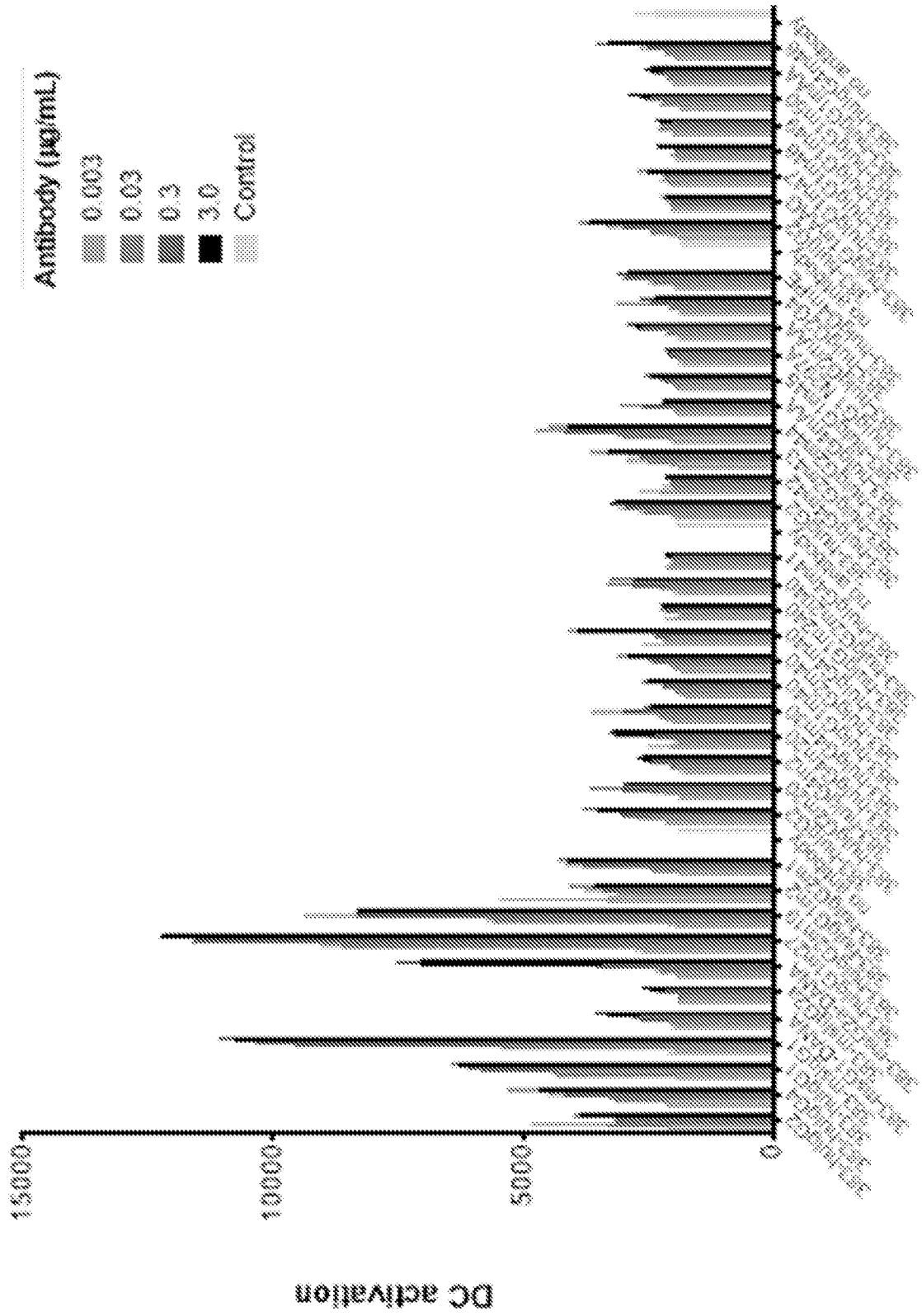

Antibody (µg/mL)
0.003
0.03
0.3
3.0
Control
DC activation
15000
10000
5000
0

FIG. 5B

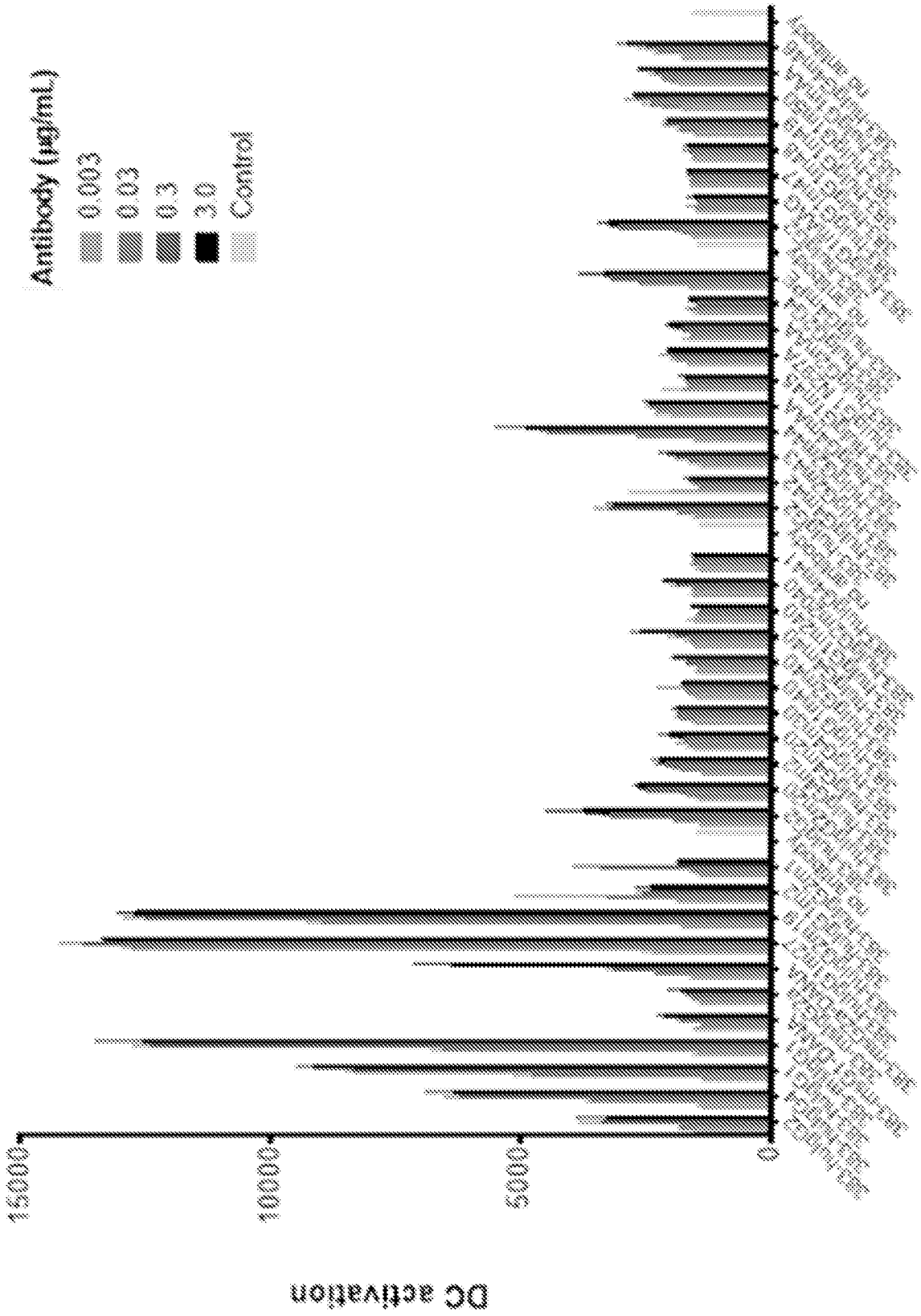

Antibody (µg/mL)
0.003
0.03
0.3
3.0
Control
DC activation
15000
10000
5000
0

FIG. 5C

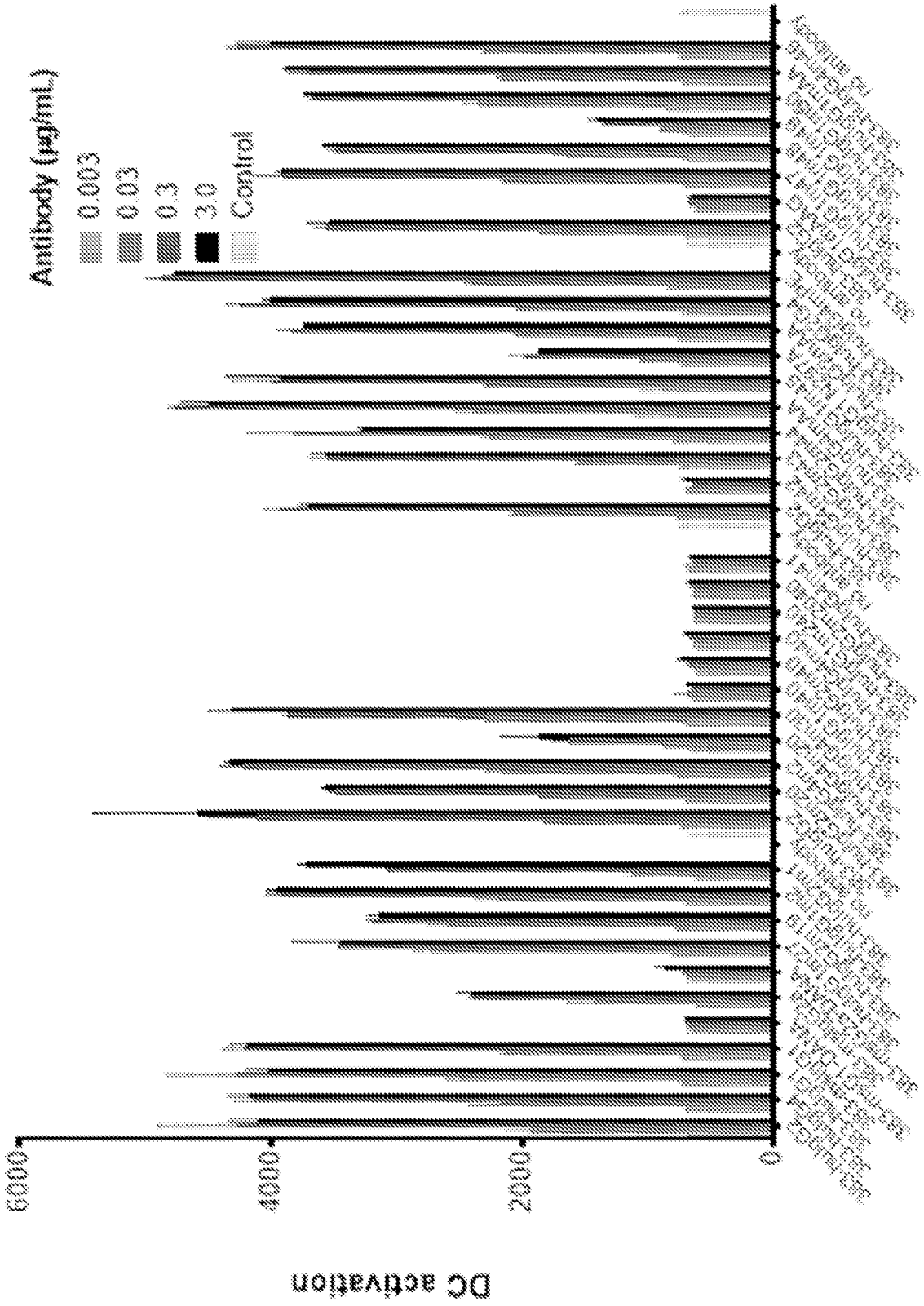

Antibody (μg/mL)
0.003
0.03
0.3
3.0
Control
DC activation
6000
4000
2000
0

FIG. 5D

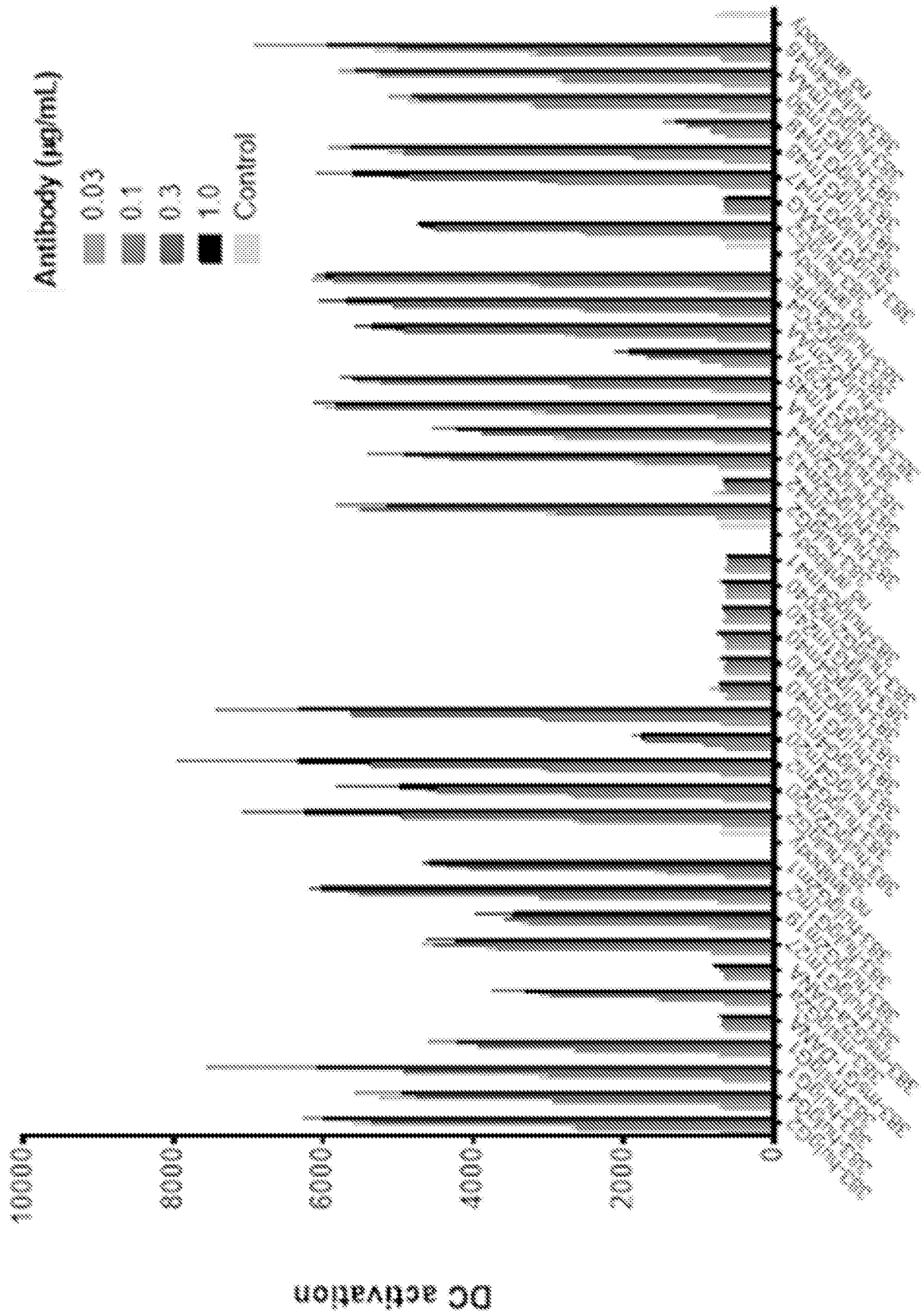

Antibody (μg/mL)
0.03
0.1
0.3
1.0
Control
DC activation
10000
8000
6000
4000
2000
0

FIG. 6A

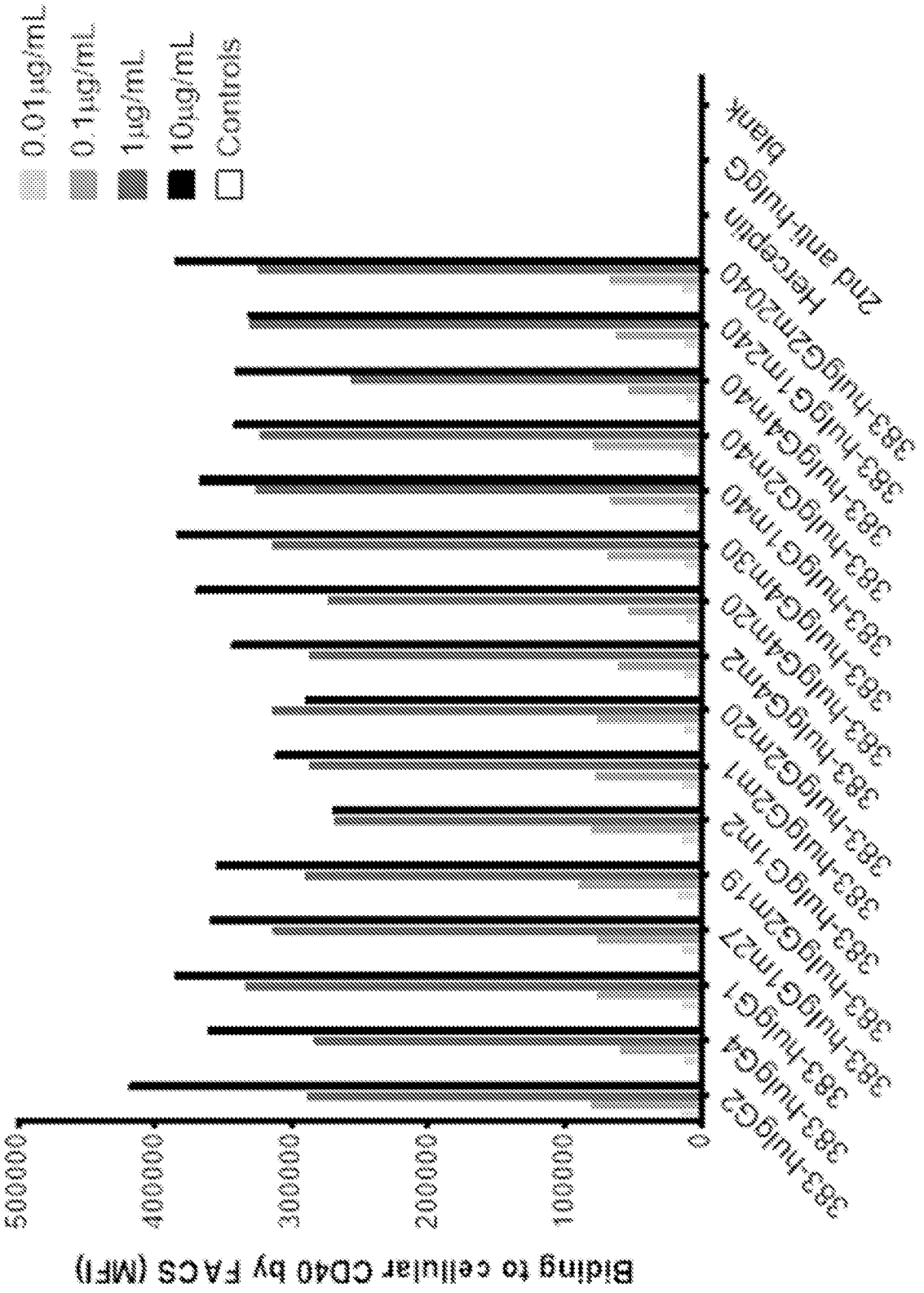

0.01µg/mL
0.1µg/mL
1µg/mL
10µg/mL
Controls
Binding to cellular CD40 by FACS (MFI)
500000
400000
300000
200000
100000
0
383-huIgG2
383-huIgG4
383-huIgG1
383-huIgG1m27
383-huIgG2m19
383-huIgG1m2
383-huIgG2m1
383-huIgG2m20
383-huIgG4m2
383-huIgG4m20
383-huIgG4m30
383-huIgG1m40
383-huIgG2m40
383-huIgG4m40
383-huIgG1m240
383-huIgG2m2040
Herceptin
2nd anti-huIgG
blank

FIG. 6B

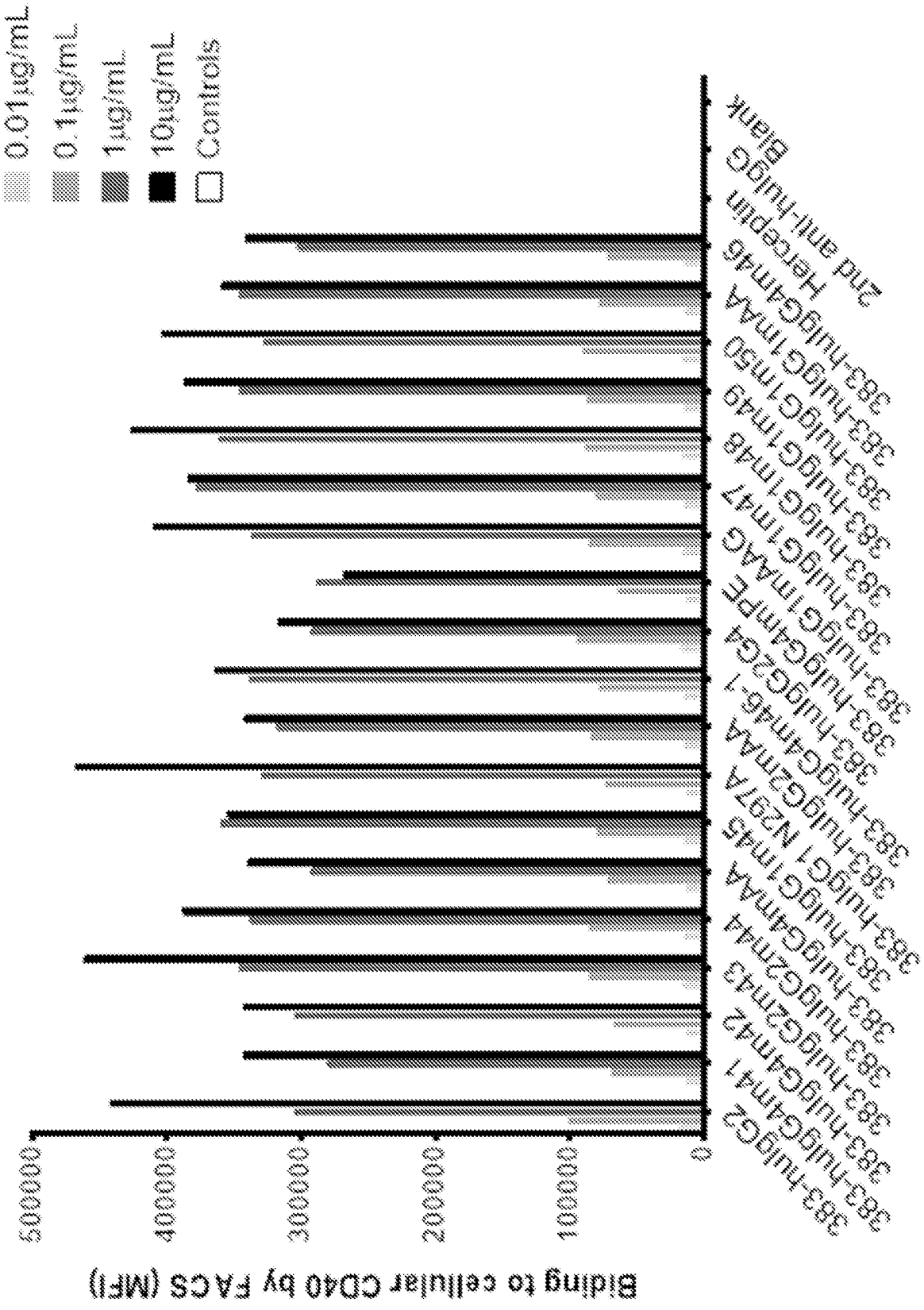

0.01µg/mL
0.1µg/mL
1µg/mL
10µg/mL
Controls
Binding to cellular CD40 by FACS (MFI)
500000
400000
300000
200000
100000
0
383-huIgG2
383-huIgG4m41
383-huIgG4m42
383-huIgG2m43
383-huIgG2m44
383-huIgG4mAA
383-huIgG1m45
383-huIgG1 N297A
383-huIgG2mAA
383-huIgG4m46-1
383-huIgG2GA
383-huIgG4mPE
383-huIgG1mAG
383-huIgG1m47
383-huIgG1m48
383-huIgG1m49
383-huIgG1m50
383-huIgG1mAA
383-huIgG4m48
Herceptin
2nd anti-huIgG
Blank

FIG. 7A

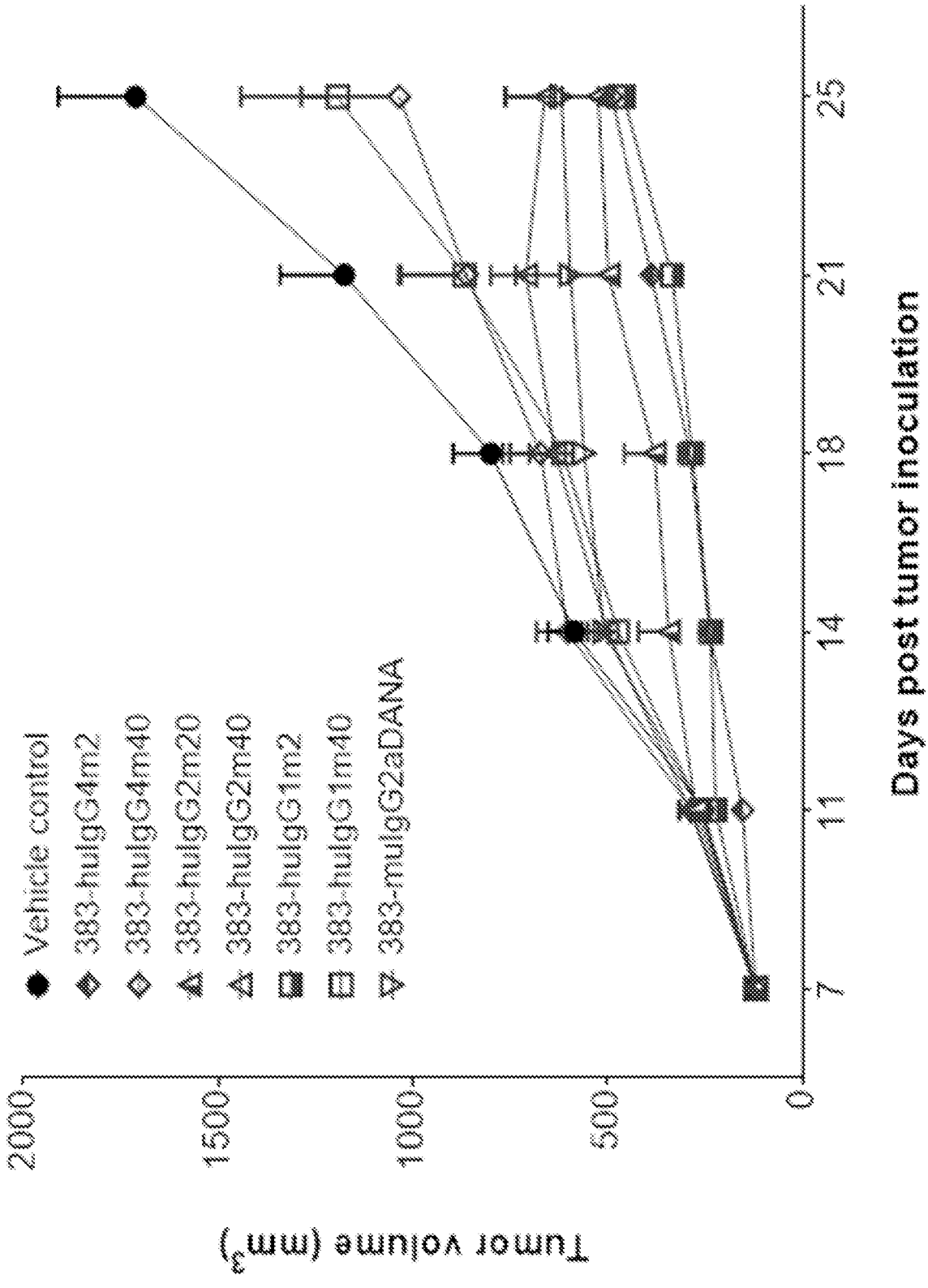
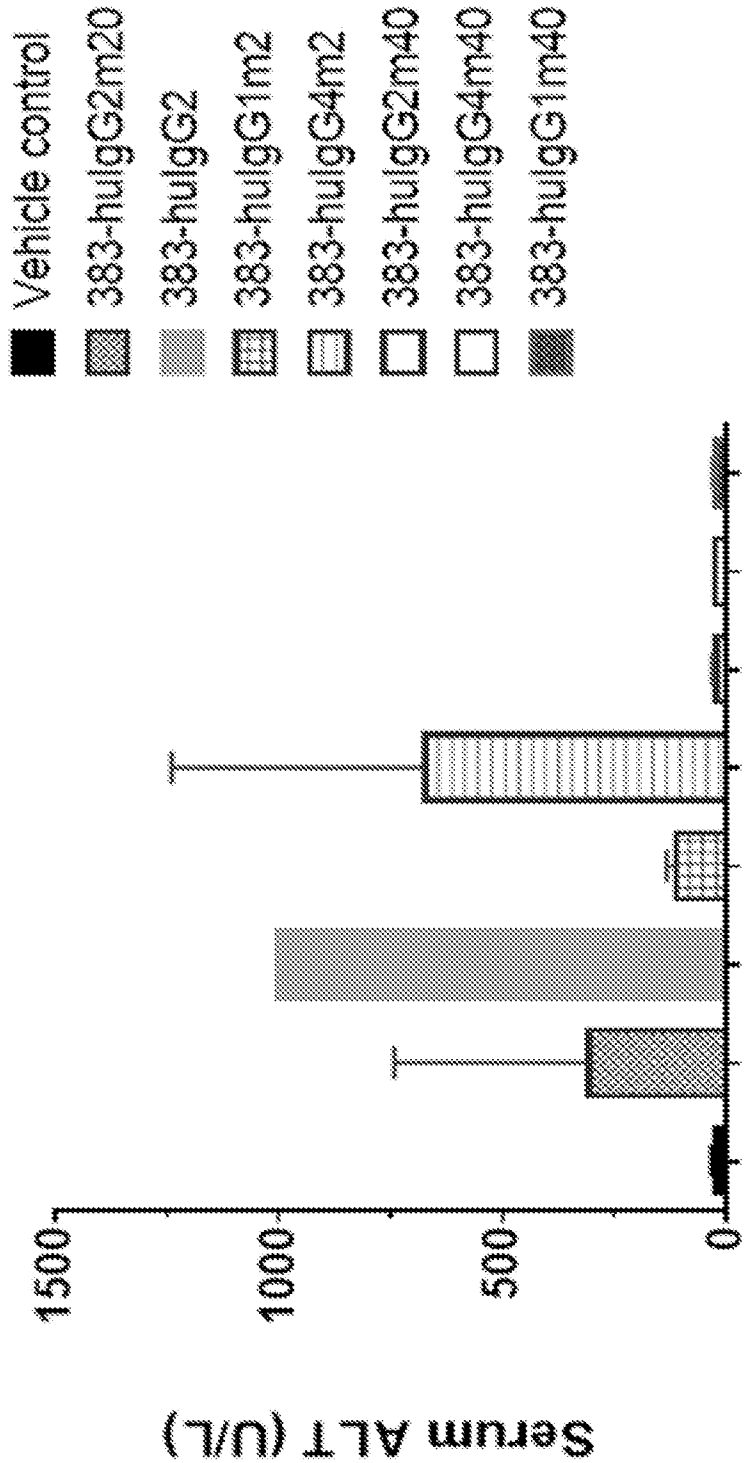

Tumor volume (mm³)
2000
1500
1000
500
0
7
11
14
18
21
25
Days post tumor inoculation
Vehicle control
383-hulgG4m2
383-hulgG4m40
383-hulgG2m20
383-hulgG2m40
383-hulgG1m2
383-hulgG1m40
383-mulgG2aDANA

FIG. 7B


Vehicle control
383-hulgG2m20
383-hulgG2
383-hulgG1m2
383-hulgG4m2
383-hulgG2m40
383-hulgG4m40
383-hulgG1m40
Serum ALT (U/L)
1500
1000
500
0

SEQUENCE LISTING

<110> LYVGEN BIOPHARMA CO., LTD.
LYVGEN BIOPHARMA (SUZHOU) CO., LTD.

<120> ANTI-CD40 BINDING MOLECULES HAVING ENGINEERED FC DOMAINS AND THERAPEUTIC USES THEREOF

<130> 112238-0032-70004WO1

<140> PCT/IB2019/001135
<141> 2019-09-27

<150> PCT/CN2018/108285
<151> 2018-09-28

<160> 215

<170> PatentIn version 3.5

<210> 1
<211> 237
<212> PRT
<213> Homo sapiens

<400> 1

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 2
<211> 233
<212> PRT

<213> Homo sapiens

<400> 2

```
Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1               5                  10                  15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
```

165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 3
<211> 234
<212> PRT
<213> Homo sapiens

<400> 3

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 4
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 4

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 5
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 5

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 6
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 6

```
Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1               5                  10                  15


Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
            20                  25                  30


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


Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
    50                  55                  60


Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65                  70                  75                  80


Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
                85                  90                  95


Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
            100                 105                 110


Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
        115                 120                 125


Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
    130                 135                 140
```

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 7
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 7

Val Asp Lys Lys Val Glu Pro Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 8
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 8

Val Asp Lys Lys Val Glu Pro Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln

115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 9
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 9

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
            20   25   30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
        35   40   45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Glu Lys
    50   55   60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65   70   75   80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
                85   90   95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
            100   105   110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
        115   120   125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
    130   135   140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145   150   155   160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
                165   170   175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
            180   185   190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln

195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 10
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 10

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 11
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 11

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 12
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 12

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 13
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 13

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser His Glu Asp Pro Glu Glu Lys Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 14
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 14

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 15
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 15

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Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1               5                  10                  15


Pro Pro Cys Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro
            20                  25                  30


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        35                  40                  45


Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
    50                  55                  60


Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65                  70                  75                  80


Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
                85                  90                  95


His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            100                 105                 110


Lys Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
        115                 120                 125


Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
    130                 135                 140
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Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 16
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 16

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

35 40 45

Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 17
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 17

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
20 25 30

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Glu Lys Phe
50 55 60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65 70 75 80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
85 90 95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
100 105 110

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

115 120 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
130 135 140

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 18
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 18

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
            20   25   30

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

Thr Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe
    50   55   60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65   70   75   80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
                85   90   95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
            100   105   110

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
        115   120   125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
    130   135   140

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145   150   155   160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
                165   170   175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
            180   185   190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln

195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 19
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 19

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
20 25 30

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
50 55 60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65 70 75 80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
85 90 95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
100 105 110

Ser Asn Lys Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
115 120 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
130 135 140

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 20
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 20

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
20 25 30

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

Thr Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe
50 55 60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65 70 75 80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
85 90 95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
100 105 110

Ser Asn Lys Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
115 120 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
130 135 140

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 21
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 21

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 22
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 22

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 23
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 23

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 24
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 24

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Val Asp Lys Thr Val Glu Arg Lys Ser Cys Asp Lys Thr His Thr Cys
1               5                  10                  15


Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
            20                  25                  30


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


Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
    50                  55                  60


Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65                  70                  75                  80


Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr
                85                  90                  95


Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
            100                 105                 110


Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
        115                 120                 125


Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
    130                 135                 140
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Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 25
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 25

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

35 40 45

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 26
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 26

Val Asp Lys Thr Val Glu Arg Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln

115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 27
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 27

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser His Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val

195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 28
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 28

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 29
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 29

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Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1               5                  10                  15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    50                  55                  60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

Gly Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
        115                 120                 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175
```

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 30
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 30

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 31
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 31

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Val Ser Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 32
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 32

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser His Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 33
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 33

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Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1               5                  10                  15


Pro Ala Pro Pro Val Ala Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
            20                  25                  30


Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
        35                  40                  45


Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    50                  55                  60


Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65                  70                  75                  80


Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
                85                  90                  95


Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
            100                 105                 110


Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
        115                 120                 125


Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    130                 135                 140
```

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 34
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 34

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

```
        35                  40                  45

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
    50                  55                  60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65                  70                  75                  80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
                85                  90                  95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe
            100                 105                 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
        115                 120                 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
    130                 135                 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145                 150                 155                 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
                165                 170                 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
            180                 185                 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
        195                 200                 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
    210                 215                 220
```

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 35
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 35

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe
100 105 110

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg

115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 36
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 36

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20   25   30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35   40   45

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
    50   55   60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65   70   75   80

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
                85   90   95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
            100   105   110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
        115   120   125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130   135   140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145   150   155   160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165   170   175

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180   185   190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe

195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 37
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 37

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 38
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38

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Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1               5                  10                  15

Pro Ala Pro Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
            100                 105                 110

Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175
```

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 39
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 39

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 40
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 40

Val Asp Lys Arg Val Glu Ser Lys Ser Cys Asp Lys Thr His Thr Pro
1 5 10 15

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
20 25 30

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
35 40 45

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
50 55 60

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
65 70 75 80

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
85 90 95

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
100 105 110

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
115 120 125

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
130 135 140

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
145 150 155 160

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
165 170 175

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
180 185 190

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
195 200 205

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
210 215 220

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230 235

<210> 41
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 41

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 42
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 42

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Val Asp Lys Arg Val Glu Ser Lys Cys Cys Val Glu Pro Pro Cys Pro
1               5                  10                  15

Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
            20                  25                  30

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

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
    50                  55                  60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65                  70                  75                  80

Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
                85                  90                  95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
            100                 105                 110

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
        115                 120                 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
    130                 135                 140
```

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230 235

<210> 43
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 44
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg

115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 45
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn

195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 46
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 47
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Phe Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 48
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Phe Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 49
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Val Ser Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe
100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 50
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 51
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 51

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
35 40 45

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe
100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 52
<211> 231
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
20 25 30

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

35 40 45

Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
50 55 60

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
65 70 75 80

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
85 90 95

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe
100 105 110

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
115 120 125

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
130 135 140

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
145 150 155 160

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
165 170 175

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
180 185 190

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
195 200 205

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
210 215 220

Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 53
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
100 105 110

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro

115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 54
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20   25   30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35   40   45

Val Val Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr
    50   55   60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65   70   75   80

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85   90   95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100   105   110

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115   120   125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
    130   135   140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145   150   155   160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165   170   175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            180   185   190

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val

195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 55
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 56
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Phe Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 57
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Phe Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 58
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 58

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
100 105 110

Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 59
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 60
<211> 67
<212> PRT
<213> Homo sapiens

<400> 60

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
35 40 45

Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
50 55 60

Ala Pro Ile
65

<210> 61
<211> 63
<212> PRT
<213> Homo sapiens

<400> 61

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
    50   55   60

<210> 62
<211> 64
<212> PRT
<213> Homo sapiens

<400> 62

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys
1   5   10   15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            20   25   30

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
        35   40   45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 63
<211> 62
<212> PRT
<213> Mus musculus

<400> 63

Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile
1   5   10   15

Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Thr Cys
            20   25   30

Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp

35 40 45

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile
50 55 60

<210> 64
<211> 68
<212> PRT
<213> Mus musculus

<400> 64

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
1 5 10 15

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

Ile Phe Pro Pro Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro
35 40 45

Asp Val Gln Ile Ser Trp Phe Lys Cys Lys Val Asn Asn Lys Asp Leu
50 55 60

Pro Ala Pro Ile
65

<210> 65
<211> 64
<212> PRT
<213> Homo sapiens

<400> 65

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            20   25   30

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
        35   40   45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 66
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 66

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65   70   75   80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 Ala Val
260 265 270

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
        275   280   285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
    290   295   300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu
305   310   315   320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
                325   330   335

Ser 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 Gln 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 Glu 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 Leu Gly Lys

450

<210> 67
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 67

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 Ala Val
260 265 270

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser
325 330 335

Ser 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 Gln 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 Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 68
<211> 453
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 68

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145                 150                 155                 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala
225 230 235 240

Leu Gly Ala 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 Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Ala Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
325 330 335

Ser 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 Gln 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 Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 69
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 69

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr

20 25 30

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Ala
225 230 235 240

Ala 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 Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser
325 330 335

Ser 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 Gln 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 Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 70
<211> 67
<212> PRT
<213> Homo sapiens

<400> 70

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
35 40 45

Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
50 55 60

Ala Pro Ile

65

<210> 71
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
50 55 60

<210> 72
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 72

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
        35   40   45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
    50   55   60

<210> 73
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73

Lys Lys Val Glu Pro Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
            20   25   30

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        35   40   45

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
    50   55   60

<210> 74
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 74

Lys Lys Val Glu Pro Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
20 25 30

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
35 40 45

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
50 55 60

<210> 75
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 75

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Glu Lys Phe
35 40 45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
50 55 60

<210> 76
<211> 64

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 76

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Thr Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe
35 40 45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
50 55 60

<210> 77
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
35 40 45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile
50 55 60

<210> 78
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Thr Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe
35 40 45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile
50 55 60

<210> 79
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val
            20   25   30

Val Val Asp Val Ser His Glu Asp Pro Glu Glu Lys Phe Asn Trp Tyr
        35   40   45

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
    50   55   60

<210> 80
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1   5   10   15

Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val
            20   25   30

Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35   40   45

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
    50   55   60

<210> 81
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 81

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile
50 55 60

<210> 82
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 82

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile
50 55 60

<210> 83
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 83

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Glu Lys Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
50 55 60

<210> 84
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 84

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn

35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
50 55 60

<210> 85
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 85

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile
50 55 60

<210> 86
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 86

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Glu His Glu Asp Pro Glu Val Lys Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile
50 55 60

<210> 87
<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 87

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
1 5 10 15

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
20 25 30

Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
35 40 45

Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
50 55 60

Ile
65

<210> 88

<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 88

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
1 5 10 15

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
20 25 30

Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
35 40 45

Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro
50 55 60

Ile
65

<210> 89
<211> 63
<212> PRT
<213> Homo sapiens

<400> 89

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn

35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 90
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 90

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val Asp
20 25 30

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys Lys
35 40 45

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55

<210> 91
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 91

Lys Thr Val Glu Arg Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
1 5 10 15

Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
            20   25   30

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe
        35   40   45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
    50   55   60

<210> 92
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 92

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1   5   10   15

Pro Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
            20   25   30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        35   40   45

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
    50   55   60

<210> 93
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 93

Lys Thr Val Glu Arg Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

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

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 94
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 94

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

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

Val Asp Val Ser His Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr Lys
35 40 45

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 95
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

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

Val Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys
35 40 45

Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 96
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 96

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

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

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys
        35   40   45

Cys Lys Val Ser Asn Lys Gly Phe Pro Ala Pro Ile
    50   55   60

<210> 97
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 97

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1   5   10   15

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

Val Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys
        35   40   45

Cys Lys Val Ser Asn Lys Gly Phe Pro Ala Pro Ile
    50   55   60

<210> 98
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 98

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Glu Val Ser Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val Asp
20 25 30

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys Lys
35 40 45

Val Ser Asn Lys Gly Phe Pro Ala Pro Ile
50 55

<210> 99
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 99

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val Asp
20 25 30

Val Ser His Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr Lys Cys Lys
35 40 45

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55

<210> 100
<211> 58
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 100

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val Asp
20 25 30

Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys Lys
35 40 45

Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55

<210> 101
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 101

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val Asp
20 25 30

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys Lys
35 40 45

Val Ser Asn Lys Gly Phe Pro Ala Pro Ile
50 55

<210> 102
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 102

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val Asp
20 25 30

Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys Lys
35 40 45

Val Ser Asn Lys Gly Phe Pro Ala Pro Ile
50 55

<210> 103
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 103

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val

20 25 30

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55

<210> 104
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 104

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55

<210> 105
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 105

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
1 5 10 15

Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Phe Pro Ala Pro Ile
50 55

<210> 106
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 106

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55

<210> 107

<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 107

Lys Arg Val Glu Ser Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
1 5 10 15

Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
20 25 30

Pro Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln
35 40 45

Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser
50 55 60

Ile
65

<210> 108
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 108

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        35   40   45

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 109
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 109

Lys Arg Val Glu Ser Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
            20   25   30

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
        35   40   45

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

<210> 110
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 110

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
20 25 30

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp
35 40 45

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

<210> 111
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 111

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55

<210> 112
<211> 61

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 112

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55 60

<210> 113
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 113

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
20 25 30

Val Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
35 40 45

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

<210> 114
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 114

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
20 25 30

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
35 40 45

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

<210> 115
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 115

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
            20   25   30

Val Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
        35   40   45

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

<210> 116
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 116

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Glu Val Ser Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
            20   25   30

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
        35   40   45

Lys Val Ser Asn Lys Gly Phe Pro Ser Ser Ile
    50   55

<210> 117
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 117

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55

<210> 118
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 118

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55

<210> 119
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 119

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys
35 40 45

Lys Val Ser Asn Lys Gly Phe Pro Ser Ser Ile
50 55

<210> 120
<211> 59
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 120

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val Val
20 25 30

Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys Cys

35 40 45

Lys Val Ser Asn Lys Gly Phe Pro Ser Ser Ile
50 55

<210> 121
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 121

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val
20 25 30

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys
35 40 45

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55 60

<210> 122
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 122

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
            20   25   30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Glu Gln Phe Asn Trp Tyr
        35   40   45

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 123
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 123

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1   5   10   15

Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
            20   25   30

Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        35   40   45

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 124
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 124

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Gly Phe Pro Ser Ser Ile
50 55 60

<210> 125
<211> 61
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 125

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val
20 25 30

Val Val Asp Val Glu Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
35 40 45

Lys Cys Lys Val Ser Asn Lys Gly Phe Pro Ser Ser Ile
50 55 60

<210> 126
<211> 60
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 126

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Leu Pro Ser Val Phe Leu Phe Pro Pro Thr Cys Val Val
20 25 30

Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Lys
35 40 45

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55 60

<210> 127
<211> 62
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 127

Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
20 25 30

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
35 40 45

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

<210> 128
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 128

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 129
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 129

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

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

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

Tyr Thr 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 Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ile Phe Pro Leu
85 90 95

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

<210> 130

<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 130

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

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

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

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

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

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

Ala Arg Arg Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ala

<210> 131
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 131

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

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

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

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

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

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

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

<210> 132
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 132

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly Ala

1 5 10 15

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

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

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

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

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

Thr Lys Gly Val Ile Thr Thr Leu Val Ala Gly Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 133
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 133

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

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

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

Tyr Phe Val Asp Arg Leu Leu Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Arg His Ser Leu Lys Ile Ser Gly Met Gln Pro
65 70 75 80

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

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

<210> 134
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 134

Glu Val Gln Ile Leu Glu Thr Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

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

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

Ala Gln Ile Arg Asn Lys Asn Tyr Asn Tyr Ala Thr Tyr Tyr Thr Glu
50 55 60

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

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

Tyr Cys Thr Ser Tyr Tyr Tyr Asp Gly Phe Ala Asp Tyr Phe Asp Tyr
100 105 110

Trp Gly Gln Gly Val Met Val Thr Val Ser Ser
115 120

<210> 135
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 135

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

Glu Lys Ile Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Ser Asn
20 25 30

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

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

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Gly Thr Met Glu
65 70 75 80

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

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

<210> 136
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 136

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

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

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

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

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

Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr Tyr Tyr Cys

85 90 95

Ala Leu Pro Phe Leu Gly Trp Gly Gly Ala Asn Trp Ile Ala His Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 137
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 137

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

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

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Glu Pro Pro Lys Leu Leu Ile
35 40 45

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

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

Glu Asp Val Ala Thr Tyr Phe Cys Met Gln His Asn Val Arg Arg Thr
85 90 95

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

<210> 138
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 138

Glu Val His Ile Leu Glu Thr Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Gly Leu Ser Cys Thr Thr Ser Gly Phe Asn Phe Asn Asp Tyr
20 25 30

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

Ala Gln Ile Arg Asn Gly Asn Tyr Asp Tyr Ala Ala Tyr Tyr Ala Glu
50 55 60

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

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

Tyr Cys Thr Ser Tyr Tyr Tyr Asp Gly His Phe Asp Tyr Phe Asp Asn
100 105 110

Trp Gly His Gly Val Met Val Thr Val Ser Ser
115 120

<210> 139
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 139

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

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

Leu Asn Trp Tyr Gln Gln Lys Phe Gly Glu Ala Pro Lys Leu Leu Ile
35 40 45

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

Ser Glu Ser Gly Thr Val Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

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

<210> 140
<211> 215
<212> PRT
<213> Homo sapiens

<400> 140

```
His Arg Arg Leu Asp Lys Ile Glu Asp Glu Arg Asn Leu His Glu Asp
1               5                  10                  15

Phe Val Phe Met Lys Thr Ile Gln Arg Cys Asn Thr Gly Glu Arg Ser
            20                  25                  30

Leu Ser Leu Leu Asn Cys Glu Glu Ile Lys Ser Gln Phe Glu Gly Phe
        35                  40                  45

Val Lys Asp Ile Met Leu Asn Lys Glu Glu Thr Lys Lys Glu Asn Ser
    50                  55                  60

Phe Glu Met Gln Lys Gly Asp Gln Asn Pro Gln Ile Ala Ala His Val
65                  70                  75                  80

Ile Ser Glu Ala Ser Ser Lys Thr Thr Ser Val Leu Gln Trp Ala Glu
                85                  90                  95

Lys Gly Tyr Tyr Thr Met Ser Asn Asn Leu Val Thr Leu Glu Asn Gly
            100                 105                 110

Lys Gln Leu Thr Val Lys Arg Gln Gly Leu Tyr Tyr Ile Tyr Ala Gln
        115                 120                 125

Val Thr Phe Cys Ser Asn Arg Glu Ala Ser Ser Gln Ala Pro Phe Ile
    130                 135                 140

Ala Ser Leu Cys Leu Lys Ser Pro Gly Arg Phe Glu Arg Ile Leu Leu
145                 150                 155                 160

Arg Ala Ala Asn Thr His Ser Ser Ala Lys Pro Cys Gly Gln Gln Ser
                165                 170                 175
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Ile His Leu Gly Gly Val Phe Glu Leu Gln Pro Gly Ala Ser Val Phe
180 185 190

Val Asn Val Thr Asp Pro Ser Gln Val Ser His Gly Thr Gly Phe Thr
195 200 205

Ser Phe Gly Leu Leu Lys Leu
210 215

<210> 141
<211> 277
<212> PRT
<213> Homo sapiens

<400> 141

Met Val Arg Leu Pro Leu Gln Cys Val Leu Trp Gly Cys Leu Leu Thr
1 5 10 15

Ala Val His Pro Glu Pro Pro Thr Ala Cys Arg Glu Lys Gln Tyr Leu
20 25 30

Ile Asn Ser Gln Cys Cys Ser Leu Cys Gln Pro Gly Gln Lys Leu Val
35 40 45

Ser Asp Cys Thr Glu Phe Thr Glu Thr Glu Cys Leu Pro Cys Gly Glu
50 55 60

Ser Glu Phe Leu Asp Thr Trp Asn Arg Glu Thr His Cys His Gln His
65 70 75 80

Lys Tyr Cys Asp Pro Asn Leu Gly Leu Arg Val Gln Gln Lys Gly Thr
85 90 95

Ser Glu Thr Asp Thr Ile Cys Thr Cys Glu Glu Gly Trp His Cys Thr
100 105 110

Ser Glu Ala Cys Glu Ser Cys Val Leu His Arg Ser Cys Ser Pro Gly
115 120 125

Phe Gly Val Lys Gln Ile Ala Thr Gly Val Ser Asp Thr Ile Cys Glu
130 135 140

Pro Cys Pro Val Gly Phe Phe Ser Asn Val Ser Ser Ala Phe Glu Lys
145 150 155 160

Cys His Pro Trp Thr Ser Cys Glu Thr Lys Asp Leu Val Val Gln Gln
165 170 175

Ala Gly Thr Asn Lys Thr Asp Val Val Cys Gly Pro Gln Asp Arg Leu
180 185 190

Arg Ala Leu Val Val Ile Pro Ile Ile Phe Gly Ile Leu Phe Ala Ile
195 200 205

Leu Leu Val Leu Val Phe Ile Lys Lys Val Ala Lys Lys Pro Thr Asn
210 215 220

Lys Ala Pro His Pro Lys Gln Glu Pro Gln Glu Ile Asn Phe Pro Asp
225 230 235 240

Asp Leu Pro Gly Ser Asn Thr Ala Ala Pro Val Gln Glu Thr Leu His
245 250 255

Gly Cys Gln Pro Val Thr Gln Glu Asp Gly Lys Glu Ser Arg Ile Ser
260 265 270

Val Gln Glu Arg Gln
275

<210> 142
<211> 232
<212> PRT
<213> Mus musculus

<400> 142

Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile
1 5 10 15

Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro
20 25 30

Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val
35 40 45

Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val
50 55 60

Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln
65 70 75 80

Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala
100 105 110

Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro
115 120 125

Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala
130 135 140

Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu

145 150 155 160

Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr
165 170 175

Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr
180 185 190

Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe
195 200 205

Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys
210 215 220

Ser Leu Ser His Ser Pro Gly Lys
225 230

<210> 143
<211> 238
<212> PRT
<213> Mus musculus

<400> 143

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
1 5 10 15

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

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
35 40 45

Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val
50 55 60

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
65 70 75 80

Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala
85 90 95

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
100 105 110

Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser
115 120 125

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
130 135 140

Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val
145 150 155 160

Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
165 170 175

Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp
180 185 190

Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp
195 200 205

Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His
210 215 220

Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
225 230 235

<210> 144
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 144

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Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile
1               5                  10                  15


Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro
            20                  25                  30


Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val
        35                  40                  45


Val Ala Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val
    50                  55                  60


Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln
65                  70                  75                  80


Phe Ala Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln
                85                  90                  95


Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala
            100                 105                 110


Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro
        115                 120                 125


Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala
    130                 135                 140
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Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu
145 150 155 160

Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr
165 170 175

Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr
180 185 190

Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe
195 200 205

Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys
210 215 220

Ser Leu Ser His Ser Pro Gly Lys
225 230

<210> 145
<211> 238
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 145

Val Asp Lys Lys Ile Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro
1 5 10 15

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

Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro
35 40 45

Ile Val Thr Cys Val Val Val Ala Val Ser Glu Asp Asp Pro Asp Val
    50   55   60

Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr
65   70   75   80

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

Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys
            100   105   110

Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser
        115   120   125

Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro
    130   135   140

Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val
145   150   155   160

Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly
                165   170   175

Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp
            180   185   190

Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp
        195   200   205

Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His
    210   215   220

Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
225 230 235

<210> 146
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 146

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

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

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

Tyr Thr 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 Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ile Phe 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

Phe Asn Arg Gly Glu Cys
210

<210> 147
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 147

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Leu Leu 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

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> 148
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 148

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Leu Leu 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 Glu 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

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> 149
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 149

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 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 Phe Arg
290 295 300

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
325 330 335

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

Thr Leu Pro Pro Ser Arg 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 Met
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> 150

<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 150

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


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


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


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


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125


Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
    130                 135                 140
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Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 Glu His 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 Phe Arg
290 295 300

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe Pro Ala Pro Ile Glu

325 330 335

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

Thr Leu Pro Pro Ser Arg 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 Met
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> 151
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 151

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

180 185 190

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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

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> 152
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 152

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225 230 235 240

Leu 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

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser
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 Gln Glu Glu Met 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 Arg Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 153
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 153

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225 230 235 240

Leu Gly 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 Gln
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 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 Gly Leu Pro Ser Ser 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 Gln 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 Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu 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

Leu Gly Lys
450

<210> 154
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 154

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225 230 235 240

Leu 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 Gln
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 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 Gly Leu Pro Ser Ser 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 Gln 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 Arg Leu Thr Val
405 410 415

Asp Lys Ser Arg Trp Gln Glu 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

Leu Gly Lys
450

<210> 155

<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 155

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

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

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

Tyr Thr 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 Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ile Phe Pro Leu
85 90 95

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

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

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

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

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

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

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

Phe Asn Arg Asn Glu Cys
210

<210> 156
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 156

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

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

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

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

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Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
    130                 135                 140

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
145                 150                 155                 160

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
                165                 170                 175

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
            180                 185                 190

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
        195                 200                 205

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
    210                 215                 220

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
225                 230                 235                 240
```

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

Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Ala Ile Ser Lys Asp
260 265 270

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

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Ala Ser Thr Phe Arg
290 295 300

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

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

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

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
355 360 365

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

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
385 390 395 400

Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln
405 410 415

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His

420 425 430

Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
435 440 445

Gly Lys
450

<210> 157
<211> 450
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 157

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln
130 135 140

Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro
145 150 155 160

Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
165 170 175

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
180 185 190

Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys
195 200 205

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val
210 215 220

Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val
225 230 235 240

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

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

Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His

275 280 285

Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
290 295 300

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

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

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

Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu
355 360 365

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

Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile
385 390 395 400

Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln
405 410 415

Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His
420 425 430

Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro
435 440 445

Gly Lys
450

<210> 158
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 158

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr

130 135 140

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

Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
165 170 175

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
180 185 190

Ser Val Thr Val Thr Ser Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys
195 200 205

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu
210 215 220

Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala
225 230 235 240

Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
245 250 255

Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
260 265 270

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

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

Tyr Ala Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
305 310 315 320

Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
325 330 335

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

Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr
355 360 365

Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
370 375 380

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

Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
405 410 415

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

Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
435 440 445

Ser Phe Ser Arg Thr Pro Gly Lys
450 455

<210> 159
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 159

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

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

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

Glu Pro Val Thr Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val
165 170 175

His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser
180 185 190

Ser Val Thr Val Thr Ser Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys
195 200 205

Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu
210 215 220

Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala
225 230 235 240

Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile
245 250 255

Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val
260 265 270

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

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

Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln
305 310 315 320

Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp
325 330 335

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

Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr
355 360 365

Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu
370 375 380

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

Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr
405 410 415

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

Ser Cys Ser Val Val His Glu Gly Leu His Asn His His Thr Thr Lys
435 440 445

Ser Phe Ser Arg Thr Pro Gly Lys
450 455

<210> 160
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 160

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 161
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 161

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Ala Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Ala Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 162
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 162

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys

1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 163
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 163

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Thr Cys Val Val Val Ala Val Ser His Glu Asp Pro Glu
35 40 45

Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
50 55 60

Ala Pro Ile
65

<210> 164

<211> 66
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 164

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
20 25 30

Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
35 40 45

Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
50 55 60

Pro Ile
65

<210> 165
<211> 66
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 165

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
20 25 30

Pro Pro Thr Cys Val Val Val Ala Val Ser His Glu Asp Pro Glu Val
        35   40   45

Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    50   55   60

Pro Ile
65

<210> 166
<211> 66
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 166

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1   5   10   15

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
            20   25   30

Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        35   40   45

Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
    50   55   60

Ser Ile
65

<210> 167

<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 167

Val Asp Lys Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
1 5 10 15

Pro Pro Ser Pro Ala Pro Glu Leu Leu Gly Gly Ser Ser Val Phe Leu
20 25 30

Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
35 40 45

Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
50 55 60

Ala Pro Ile
65

<210> 168
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 168

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Ser
1 5 10 15

Pro Pro Ser Pro Ala Pro Pro Val Ala Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
35 40 45

Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
50 55 60

Ala Pro Ile
65

<210> 169
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 169

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 170
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 170

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Ala Ala Ala Ser Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser Ala Glu Asp Pro Glu Val Gln Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55 60

<210> 171
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 171

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55 60

<210> 172
<211> 63
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 172

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Thr
20 25 30

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
35 40 45

Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 173
<211> 62
<212> PRT
<213> Homo sapiens

<400> 173

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Thr Cys
20 25 30

Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
35 40 45

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
50 55 60

<210> 174
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 174

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Thr Cys Val Val Val Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe
35 40 45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
50 55 60

<210> 175
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 175

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            20   25   30

Thr Cys Val Val Val Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe
        35   40   45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 176
<211> 64
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 176

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1   5   10   15

Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro
            20   25   30

Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
        35   40   45

Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50   55   60

<210> 177
<211> 64
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 177

```
Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1               5                  10                  15


Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
            20                  25                  30


Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
        35                  40                  45


Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
    50                  55                  60
```

<210> 178
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 178

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Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1               5                  10                  15


Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
            20                  25                  30


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


Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
    50                  55                  60
```

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65 70 75 80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
85 90 95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
100 105 110

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
115 120 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
130 135 140

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 179
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 179

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Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1               5                  10                  15


Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Pro Ser Val Phe Leu Phe
            20                  25                  30


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


Thr Cys Val Val Val Ala Val Ser His Glu Asp Pro Glu Val Lys Phe
    50                  55                  60


Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65                  70                  75                  80


Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr
                85                  90                  95


Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
            100                 105                 110


Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
        115                 120                 125


Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
    130                 135                 140
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Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 180
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 180

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 181
<211> 236
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 181

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe
20 25 30

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
50 55 60

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
65 70 75 80

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
85 90 95

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
100 105 110

Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
115 120 125

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
130 135 140

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
145 150 155 160

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
165 170 175

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
180 185 190

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
195 200 205

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
210 215 220

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 182
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 182

Val Asp Lys Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser
1 5 10 15

Pro Pro Ser Pro Ala Pro Glu Leu Leu Gly Gly Ser Ser Val Phe Leu

20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 183
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 183

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Ser
1 5 10 15

Pro Pro Ser Pro Ala Pro Pro Val Ala Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys

100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 184
<211> 237
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 184

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1 5 10 15

Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu
20 25 30

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
35 40 45

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
50 55 60

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
65 70 75 80

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
85 90 95

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
100 105 110

Val Ser Asn Lys Ala Leu Pro Ala Ser Ile Glu Lys Thr Ile Ser Lys
115 120 125

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
130 135 140

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
145 150 155 160

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
165 170 175

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly

180 185 190

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
195 200 205

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
210 215 220

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230 235

<210> 185
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 185

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Ala Ala Ala Ser Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser Ala Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 186
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 186

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 187
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 187

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Ala Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Phe Ala Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro
115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165 170 175

Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 188
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 188

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Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1               5                  10                  15


Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30


Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45


Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
    50                  55                  60


Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80


Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95


Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110


Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        115                 120                 125


Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
    130                 135                 140
```

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
180 185 190

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 189
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 189

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
    50   55   60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65   70   75   80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Val
                85   90   95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
            100   105   110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
        115   120   125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
    130   135   140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145   150   155   160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                165   170   175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            180   185   190

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
        195   200   205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
    210   215   220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 190
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 190

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Ala Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 191
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 191

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro

```
            20                  25                  30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
        35                  40                  45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
    50                  55                  60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65                  70                  75                  80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
                85                  90                  95

His Gln Asp Trp Leu Asn Gly Lys Ala Tyr Lys Cys Lys Val Ser Asn
            100                 105                 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
        115                 120                 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
    130                 135                 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145                 150                 155                 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
                165                 170                 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
            180                 185                 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
        195                 200                 205
```

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 192
<211> 234
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 192

Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
20 25 30

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
35 40 45

Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
50 55 60

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
65 70 75 80

Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
85 90 95

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn

100 105 110

Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
115 120 125

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
130 135 140

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
145 150 155 160

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
165 170 175

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
180 185 190

Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
195 200 205

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
210 215 220

Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
225 230

<210> 193
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 193

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Ala Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 194
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 194

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Pro Val Ala 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

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> 195
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 195

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Leu Leu 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

Ala 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

Ala 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> 196
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 196

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 197

<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 197

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


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


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


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


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125


Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140
```

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Pro Val Ala 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

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 Gly Leu

325 330 335

Pro Ser Ser 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> 198
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 198

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Ala
225 230 235 240

Pro Glu Leu Leu Gly Gly Ser Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 199
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 199

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Ser Pro Pro Ser Pro Ala
225 230 235 240

Pro Pro Val Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 200
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 200

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 Ala Val Ser
260 265 270

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala Ser Thr
290 295 300

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Thr 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

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 Met 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> 201
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 201

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Ala
225 230 235 240

Ala Ala Ser 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

Ala Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
290 295 300

Phe 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 Gly Leu Pro Ser Ser
325 330 335

Ile Glu Lys Thr Ile Ser Lys Thr 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

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 Met 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> 202

<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 202

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


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


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


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


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125


Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140
```

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
290 295 300

Phe 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 Gly Leu Pro Ser Ser

325 330 335

Ile Glu Lys Thr Ile Ser Lys Thr 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

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 Met 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> 203
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 203

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Ala
225 230 235 240

Ala Ala 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 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
290 295 300

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Thr 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

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 Met 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> 204
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 204

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 Ala 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 Ala 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

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> 205
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 205

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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

Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser
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 Gln Glu Glu Met 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 Arg Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 206
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 206

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225 230 235 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
245 250 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Val
260 265 270

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Ala 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 Gly Leu Pro Ser
325 330 335

Ser 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 Gln 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 Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 207

<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 207

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


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


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


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


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125


Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
    130                 135                 140
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Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala

325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 208
<211> 452
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 208

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser

180 185 190

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
210 215 220

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
225 230 235 240

Ala 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 Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
275 280 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
290 295 300

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
305 310 315 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
325 330 335

Ile Glu Lys Thr Ile Ser Lys Thr 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

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 Met 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> 209
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 209

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

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

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
130 135 140

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225 230 235 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
245 250 255

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

Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser
325 330 335

Ser 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 Gln 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 Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 210
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 210

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 211
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 211

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
450 455

<210> 212

<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 212

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


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


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


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


Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


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


Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
            100                 105                 110


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
        115                 120                 125


Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
    130                 135                 140
```

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

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr
195 200 205

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
225 230 235 240

Glu 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 Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser

325 330 335

Ser 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 Gln 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 Arg Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Glu 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 Leu Gly Lys
450

<210> 213
<211> 233
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 213

Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
1 5 10 15

Pro Ala Pro Pro Ala Ala Ala Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
50 55 60

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
115 120 125

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
130 135 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu

180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> 214
<211> 456
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 214

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val Cys Ser Tyr
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
145 150 155 160

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

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val
210 215 220

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
225 230 235 240

Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
245 250 255

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val

260 265 270

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
275 280 285

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
290 295 300

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
305 310 315 320

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
325 330 335

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
355 360 365

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
370 375 380

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
385 390 395 400

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
405 410 415

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
420 425 430

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
435 440 445

Ser Leu Ser Leu Ser Pro Gly Lys
    450   455

<210> 215
<211> 67
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 215

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
1   5   10   15

Pro Pro Cys Pro Ala Pro Glu Phe Glu Gly Gly Pro Ser Val Phe Leu
            20   25   30

Phe Pro Pro Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        35   40   45

Val Lys Phe Asn Trp Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    50   55   60

Ala Ser Ile
65