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(54) Title: ANTI-MYOSTATIN ANTIBODIES, POLYPEPTIDES CONTAINING VARIANT FC REGIONS, AND METHODS OF USE

(57) Abstract: The disclosure provides anti-myostatin antibodies and methods of making and using the same. Nucleic acids encoding the anti-myostatin antibodies and host cells comprising the nucleic acids are also provided. The disclosure also provides polypeptides containing a variant Fc region and methods of making and using the same. Nucleic acids encoding the polypeptides and host cells comprising the nucleic acids are also provided.



Description

Title of Invention: ANTI-MYOSTATIN ANTIBODIES, POLYPEPTIDES CONTAINING VARIANT FC REGIONS, AND METHODS OF USE

Technical Field

[0001] The present invention relates to anti-myostatin antibodies and methods of using the same. The present invention also relates to polypeptides containing variant Fc regions and methods of using the same.

Background Art

[0002] Myostatin, also referred to as growth differentiation factor-8 (GDF8), is a secreted protein and is a member of the transforming growth factor-beta (TGF-beta) superfamily of proteins. Members of this superfamily possess growth-regulatory and morphogenetic properties (see, e.g., NPL1, NPL2, and PTL1). Myostatin is expressed primarily in the developing and adult skeletal muscle and functions as a negative regulator of muscle growth. Systemic overexpression of myostatin in adult mice leads to muscle wasting (see, e.g., NPL3) while, conversely, a myostatin knockout mouse is characterized by hypertrophy and hyperplasia of the skeletal muscle resulting in two- to threefold greater muscle mass than their wild type littermates (see, e.g., NPL4).

[0003] Like other members of the TGF-beta family, myostatin is synthesized as a large precursor protein containing an N-terminal propeptide domain, and a C-terminal domain considered as the active molecule (see, e.g., NPL5; PTL2). Two molecules of myostatin precursor are covalently linked via a single disulfide bond present in the C-terminal growth factor domain. Active mature myostatin (disulfide-bonded homodimer consisting of the C-terminal growth factor domain) is liberated from myostatin precursor through multiple steps of proteolytic processing. In the first step of the myostatin activation pathway, a peptide bond between the N-terminal propeptide domain and the C-terminal growth factor domain, Arg266-Asp267, is cleaved by a furin-type proprotein convertase in both chains of the homodimeric precursor. But the resulting three peptides (two propeptides and one mature myostatin (i.e., a disulfide-bonded homodimer consisting of the growth factor domains)) remain associated, forming a noncovalent inactive complex that is referred to as "latent myostatin." Mature myostatin can then be liberated from latent myostatin through degradation of the propeptide. Members of the bone morphogenetic protein 1 (BMP1) family of metalloproteinases cleave a single peptide bond within the propeptide, Arg98-Asp99, with concomitant release of mature, active myostatin, a homodimer (see, e.g., NPL6). Moreover, the latent myostatin can be activated in vitro by dissociating the complex

with either acid or heat treatment as well (see, e.g., NPL7).

[0004] Myostatin exerts its effects through a transmembrane serine/threonine kinase heterotetramer receptor family, activation of which enhances receptor transphosphorylation, leading to the stimulation of serine/threonine kinase activity. It has been shown that the myostatin pathway involves an active myostatin dimer binding to the activin receptor type IIB (ActRIIB) with high affinity, which then recruits and activates the transphosphorylation of the low affinity receptor, the activin-like kinase 4 (ALK4) or activin-like kinase 5 (ALK5). It has also been shown that the proteins Smad 2 and Smad 3 are subsequently activated and form complexes with Smad 4, which are then translocated to the nucleus for the activation of target gene transcription. It has been demonstrated that ActRIIB is able to mediate the influence of myostatin in vivo, as expression of a dominant negative form of ActRIIB in mice mimics myostatin gene knockout (see, e.g., NPL8).

[0005] A number of disorders or conditions are associated with muscle wasting (i.e., loss of or functional impairment of muscle tissue), such as muscular dystrophy (MD; including Duchenne muscular dystrophy), amyotrophic lateral sclerosis (ALS), muscle atrophy, organ atrophy, frailty, congestive obstructive pulmonary disease (COPD), sarcopenia, and cachexia resulting from cancer or other disorders, as well as renal disease, cardiac failure or disease, and liver disease. Patients will benefit from an increase in muscle mass and/or muscle strength; however, there are presently limited treatments available for these disorders. Thus, due to its role as a negative regulator of skeletal muscle growth, myostatin becomes a desirable target for therapeutic or prophylactic intervention for such disorders or conditions, or for monitoring the progression of such disorders or conditions. In particular, agents that inhibit the activity of myostatin may be therapeutically beneficial.

[0006] Inhibition of myostatin expression leads to both muscle hypertrophy and hyperplasia (NPL9). Myostatin negatively regulates muscle regeneration after injury and lack of myostatin in myostatin null mice results in accelerated muscle regeneration (see, e.g., NPL10). Anti-myostatin (GDF8) antibodies described in, e.g., PTL3, PTL4, PTL5, PTL6, and PTL7, and PTL8, PTL9, and PTL10 have been shown to bind to myostatin and inhibit myostatin activity in vitro and in vivo, including myostatin activity associated with the negative regulation of skeletal muscle mass. Myostatin-neutralizing antibodies increase body weight, skeletal muscle mass, and muscle size and strength in the skeletal muscle of wild type mice (see, e.g., NPL11) and the mdx mice, a model for muscular dystrophy (see, e.g., NPL12; NPL13). However, these prior art antibodies are all specific for mature myostatin but not for latent myostatin, and the strategies described for inhibiting myostatin activity have utilized antibodies that can bind to and neutralize mature myostatin.

[0007] Antibodies are drawing attention as pharmaceuticals since they are highly stable in blood and have few side effects (see, e.g., NPL14 and NPL15). Almost all therapeutic antibodies currently on the market are antibodies of the human IgG1 subclass. One of the known functions of IgG class antibodies is antibody-dependent cell-mediated cytotoxicity (hereinafter denoted as ADCC activity) (see, e.g., NPL16). For an antibody to exhibit ADCC activity, the antibody Fc region must bind to an Fc gamma receptor (hereinafter denoted as Fc gamma R) which is an antibody-binding receptor present on the surface of effector cells such as killer cells, natural killer cells, and activated macrophages.

[0008] In humans, the Fc gamma RIa (CD64A), Fc gamma RIIa (CD32A), Fc gamma RIIb (CD32B), Fc gamma RIIIa (CD16A), and Fc gamma RIIIb (CD16B) isoforms have been reported as the Fc gamma R protein family, and the respective allotypes have also been reported (see, e.g., NPL17). Fc gamma RIa, Fc gamma RIIa, and Fc gamma RIIIa are called activating Fc gamma R since they have immunologically active functions, and Fc gamma RIIb is called inhibitory Fc gamma R since it has immunosuppressive functions (see, e.g., NPL18).

[0009] In the binding between the Fc region and Fc gamma R, several amino acid residues in the antibody hinge region and CH2 domain, and a sugar chain attached to Asn at position 297 (EU numbering) bound to the CH2 domain have been shown to be important (see, e.g., NPL19, NPL20, and NPL21]). Various variants having Fc gamma R-binding properties, mainly antibodies with mutations introduced into these sites, have been studied so far; and Fc region variants having higher binding activities towards activating Fc gamma R have been obtained (see, e.g., PTL11, PTL12, PTL13, and PTL14).

[0010] When an activating Fc gamma R is cross-linked with an immune complex, it phosphorylates immunoreceptor tyrosine-based activating motifs (ITAMs) contained in the intracellular domain or FcR common gamma-chain (an interaction partner), activates a signal transducer SYK, and triggers an inflammatory immune response by initiating an activation signal cascade (see, e.g., NPL22).

[0011] Fc gamma RIIb is the only Fc gamma R expressed on B cells (see, e.g., NPL23). Interaction of the antibody Fc region with Fc gamma RIIb has been reported to suppress the primary immune response of B cells (see, e.g., NPL24). Furthermore, it is reported that when Fc gamma RIIb on B cells and B cell receptor (BCR) are cross-linked via an immune complex in blood, B cell activation and antibody production by B cells is suppressed (see, e.g., NPL25). In this immunosuppressive signal transduction mediated by BCR and Fc gamma RIIb, the immunoreceptor tyrosine-based inhibitory motif (ITIM) contained in the intracellular domain of Fc gamma RIIb is necessary (see, e.g., NPL26 and NPL27). When ITIM is phosphorylated upon signaling, SH2-containing

inositol polyphosphate 5-phosphatase (SHIP) is recruited, transduction of other activating Fc gamma R signal cascades is inhibited, and inflammatory immune response is suppressed (see, e.g., NPL28). Furthermore, aggregation of Fc gamma RIIb alone has been reported to transiently suppress calcium influx due to BCR cross-linking and B cell proliferation in a BCR-independent manner without inducing apoptosis of IgM-producing B cells (see, e.g., NPL29).

[0012] Fc gamma RIIb is also expressed on dendritic cells, macrophages, activated neutrophils, mast cells, and basophils. Fc gamma RIIb inhibits the functions of activating Fc gamma R such as phagocytosis and release of inflammatory cytokines in these cells, and suppresses inflammatory immune responses (see, e.g., NPL30).

[0013] The importance of immunosuppressive functions of Fc gamma RIIb has been elucidated so far through studies using Fc gamma RIIb knockout mice. There are reports that in Fc gamma RIIb knockout mice, humoral immunity is not appropriately regulated (see, e.g., NPL31), sensitivity towards collagen-induced arthritis (CIA) is increased (see, e.g., NPL32), lupus-like symptoms are presented, and Goodpasture's syndrome-like symptoms are presented (see, e.g., NPL33).

[0014] Additionally, regulatory inadequacy of Fc gamma RIIb has been reported to be related to human autoimmune diseases. For example, the relationship between genetic polymorphism in the transmembrane region and promoter region of Fc gamma RIIb, and the frequency of development of systemic lupus erythematosus (SLE) (see, e.g., NPL34, NPL35, NPL36, NPL37, and NPL38), and decrease of Fc gamma RIIb expression on the surface of B cells in SLE patients (see, e.g., NPL39 and NPL40) have been reported.

[0015] From mouse models and clinical findings as such, Fc gamma RIIb is considered to play the role of controlling autoimmune diseases and inflammatory diseases through involvement in particular with B cells, and it is a promising target molecule for controlling autoimmune diseases and inflammatory diseases.

[0016] IgG1, mainly used as a commercially available therapeutic antibody, is known to bind not only to Fc gamma RIIb, but also strongly to activating Fc gamma R (see, e.g., NPL41). It may be possible to develop therapeutic antibodies having greater immunosuppressive properties compared with those of IgG1, by utilizing an Fc region with enhanced Fc gamma RIIb binding, or improved Fc gamma RIIb-binding selectivity compared with activating Fc gamma R. For example, it has been suggested that the use of an antibody having a variable region that binds to BCR and an Fc with enhanced Fc gamma RIIb binding may inhibit B cell activation (see, e.g., NPL42). It has been reported that crosslinking Fc gamma RIIb on B cells and IgE bound to a B-cell receptor suppresses differentiation of B cells into plasma cells, which as a result causes suppression of IgE production; and in human PBMC-transplanted mice, human IgG

and IgM concentrations are maintained whereas the human IgE concentration is decreased (see, e.g., NPL43). Besides IgE, it has been reported that when Fc gamma RIIb and CD79b which is a constituent molecule of a B-cell receptor complex are cross-linked by an antibody, B cell proliferation is suppressed in vitro, and arthritis symptoms are alleviated in the collagen arthritis model (see, e.g., NPL44).

[0017] Besides B cells, it has been reported that crosslinking of Fc epsilon RI and Fc gamma RIIb on mast cells using molecules, in which the Fc portion of an IgG with enhanced Fc gamma RIIb binding is fused to the Fc portion of IgE that binds to an IgE receptor Fc epsilon RI, causes phosphorylation of Fc gamma RIIb, thereby suppressing Fc epsilon RI-dependent calcium influx. This suggests that inhibition of degranulation via Fc gamma RIIb stimulation is possible by enhancing Fc gamma RIIb binding (see, e.g., NPL45).

[0018] Accordingly, an antibody having an Fc with improved Fc gamma RIIb-binding activity is suggested to be promising as a therapeutic agent for inflammatory diseases such as an autoimmune disease.

[0019] Furthermore, it has been reported that activation of macrophages and dendritic cells via Toll-like receptor 4 due to LPS stimulation is suppressed in the presence of an antibody-antigen immune complex, and this effect is also suggested to be actions of the immune complex via Fc gamma RIIb (see, e.g., NPL46 and NPL47). Therefore, use of antibodies with enhanced Fc gamma RIIb binding is expected to enable enhancement of TLR-mediated activation signal-suppressing actions; thus such antibodies have been suggested as being promising as therapeutic agents for inflammatory diseases such as autoimmune diseases.

[0020] Additionally, mutants with enhanced Fc gamma RIIb binding have been suggested to be promising therapeutic agents for cancer, as well as therapeutic agents for inflammatory diseases such as autoimmune diseases. So far, Fc gamma RIIb has been found to play an important role in the agonistic activity of agonist antibodies against the anti-TNF receptor superfamily. Specifically, it has been suggested that interaction with Fc gamma RIIb is required for the agonistic activity of antibodies against CD40, DR4, DR5, CD30, and CD137, which are included in the TNF receptor family (see, e.g., NPL48, NPL49, NPL50, NPL51, NPL52, NPL53 and NPL54). NPL55 shows that the use of antibodies with enhanced Fc gamma RIIb binding enhances the anti-tumor effect of anti-CD40 antibodies. Accordingly, antibodies with enhanced Fc gamma RIIb are expected to have an effect of enhancing agonistic activity of agonist antibodies including antibodies against the anti-TNF receptor superfamily.

[0021] In addition, it has been shown that cell proliferation is suppressed when using an antibody that recognizes Kit, a type of receptor tyrosine kinase (RTK), to crosslink Fc gamma RIIb and Kit on Kit-expressing cells. Similar effects have been reported even

in cases where this Kit is constitutively activated and has mutations that cause oncogenesis (see, e.g., NPL56). Therefore, it is expected that use of antibodies with enhanced Fc gamma RIIb binding may enhance inhibitory effects on cells expressing RTK having constitutively activated mutations.

[0022] Antibodies having an Fc with improved Fc gamma RIIb-binding activity have been reported (see, e.g., NPL57). In this Literature, Fc gamma RIIb-binding activity was improved by adding alterations such as S267E/L328F, G236D/S267E, and S239D/S267E to an antibody Fc region. Among them, the antibody introduced with the S267E/L328F mutation most strongly binds to Fc gamma RIIb, and maintains the same level of binding to Fc gamma RIa and Fc gamma RIIa type H in which a residue at position 131 of Fc gamma RIIa is His as that of a naturally-occurring IgG1. However, another report shows that this alteration enhances the binding to Fc gamma RIIa type R in which a residue at position 131 of Fc gamma RIIa is Arg several hundred times to the same level of Fc gamma RIIb binding, which means the Fc gamma RIIb-binding selectivity is not improved in comparison with type-R Fc gamma RIIa (see, e.g., PTL15).

[0023] Only the effect of enhancing Fc gamma RIIa binding and not the enhancement of Fc gamma RIIb binding is considered to have influence on cells such as platelets which express Fc gamma RIIa but do not express Fc gamma RIIb (see, e.g., NPL58). For example, the group of patients who were administered bevacizumab, an antibody against VEGF, is known to have an increased risk for thromboembolism (see, e.g., NPL59). Furthermore, thromboembolism has been observed in a similar manner in clinical development tests of antibodies against the CD40 ligand, and the clinical study was discontinued (see, e.g., NPL60). In both cases of these antibodies, later studies using animal models and such have suggested that the administered antibodies aggregate platelets via Fc gamma RIIa binding on the platelets, and form blood clots (see, e.g., NPL61 and NPL62). In systemic lupus erythematosus which is an autoimmune disease, platelets are activated via an Fc gamma RIIa-dependent mechanism, and platelet activation has been reported to correlate with the severity of symptoms (see, e.g., NPL63). Administering an antibody with enhanced Fc gamma RIIa binding to such patients who already have a high risk for developing thromboembolism will increase the risk for developing thromboembolism, thus is extremely dangerous.

[0024] Furthermore, antibodies with enhanced Fc gamma RIIa binding have been reported to enhance macrophage-mediated antibody dependent cellular phagocytosis (ADCP) (see, e.g., NPL64). When antigens to be bound by the antibodies are phagocytized by macrophages, antibodies themselves are considered to be also phagocytized at the same time. When antibodies are administered as pharmaceuticals, it is supposed that peptide fragments derived from the administered antibodies are likely to be also

presented as an antigen, thereby increasing the risk of production of antibodies against therapeutic antibodies (anti-therapeutic antibodies). More specifically, enhancing Fc gamma RIIa binding will increase the risk of production of antibodies against the therapeutic antibodies, and this will remarkably decrease their value as pharmaceuticals. Furthermore, Fc gamma RIIb on dendritic cells have been suggested to contribute to peripheral tolerance by inhibiting dendritic cell activation caused by immune complexes formed between antigens and antibodies, or by suppressing antigen presentation to T cells via activating Fc gamma receptors (see, e.g., NPL65). Since Fc gamma RIIa is also expressed on dendritic cells, when antibodies having an Fc with enhanced selective binding to Fc gamma RIIb are used as pharmaceuticals, antigens are not readily presented by dendritic cells and such due to enhanced selective binding to Fc gamma RIIb, and risk of anti-drug antibody production can be relatively decreased. Such antibodies may be useful in that regard as well.

[0025] More specifically, the value as pharmaceuticals will be considerably reduced when Fc gamma RIIa binding is enhanced, which leads to increased risk of thrombus formation via platelet aggregation and increased risk of anti-therapeutic antibody production due to an increased immunogenicity.

[0026] From such a viewpoint, the aforementioned Fc variant with enhanced Fc gamma RIIb binding shows significantly enhanced type-R Fc gamma RIIa binding compared with that of a naturally-occurring IgG1. Therefore, its value as a pharmaceutical for patients carrying type-R Fc gamma RIIa is considerably reduced. Types H and R of Fc gamma RIIa are observed in Caucasians and African-Americans with approximately the same frequency (see, e.g., NPL66 and NPL67). Therefore, when this Fc variant was used for treatment of autoimmune diseases, the number of patients who can safely use it while enjoying its effects as a pharmaceutical will be limited.

[0027] Furthermore, in dendritic cells deficient in Fc gamma RIIb or dendritic cells in which the interaction between Fc gamma RIIb and the antibody Fc portion is inhibited by an anti-Fc gamma RIIb antibody, dendritic cells have been reported to mature (see, e.g., NPL68 and NPL69). This report suggests that Fc gamma RIIb is actively suppressing maturation of dendritic cells in a steady state where inflammation and such are not taking place and activation does not take place. Fc gamma RIIa is expressed on the dendritic cell surface in addition to Fc gamma RIIb; therefore, even if binding to inhibitory Fc gamma RIIb is enhanced and if binding to activating Fc gamma R such as Fc gamma RIIa is also enhanced, maturation of dendritic cells may be promoted as a result. More specifically, improving not only the Fc gamma RIIb-binding activity but also the ratio of Fc gamma RIIb-binding activity relative to Fc gamma RIIa-binding activity is considered to be important in providing antibodies with an immunosuppressive action.

- [0028] Therefore, when considering the generation of a pharmaceutical that utilizes the Fc gamma RIIb binding-mediated immunosuppressive action, there is a need for an Fc variant that not only has enhanced Fc gamma RIIb-binding activity, but also has binding to both Fc gamma RIIa types H and R allotypes, which is maintained at a similar level or is weakened to a lower level than that of a naturally-occurring IgG1.
- [0029] Meanwhile, cases where amino acid alterations were introduced into the Fc region to increase the Fc gamma RIIb-binding selectivity have been reported so far (see, e.g., NPL70). However, all variants said to have improved Fc gamma RIIb selectivity as reported in this literature showed decreased Fc gamma RIIb binding compared with that of a naturally-occurring IgG1. Therefore, it is considered to be difficult for these variants to actually induce an Fc gamma RIIb-mediated immunosuppressive reaction more strongly than IgG1.
- [0030] Furthermore, since Fc gamma RIIb plays an important role in the agonist antibodies mentioned above, enhancing their binding activity is expected to enhance the agonistic activity. However, when Fc gamma RIIa binding is similarly enhanced, unintended activities such as ADCC activity and ADCP activity will be exhibited, and this may cause side effects. Also from such viewpoint, it is preferable to be able to selectively enhance Fc gamma RIIb-binding activity.
- [0031] From these results, in producing therapeutic antibodies to be used for treating autoimmune diseases and cancer utilizing Fc gamma RIIb, it is important that compared with those of a naturally-occurring IgG, the activities of binding to both Fc gamma RIIa allotypes are maintained or decreased, and Fc gamma RIIb binding is enhanced. However, Fc gamma RIIb shares 93% sequence identity in the extracellular region with that of Fc gamma RIIa which is one of the activating Fc gamma Rs, and they are very similar structurally. There are allotypes of Fc gamma RIIa, H type and R type, in which the amino acid at position 131 is His (type H) or Arg (type R), and yet each of them reacts differently with the antibodies (see, e.g., NPL71). Therefore, the difficult problem may be producing an Fc region variant with enhanced selective Fc gamma RIIb binding as compared to each allotype of Fc gamma RIIa, which involves distinguishing highly homologous sequences between Fc gamma RIIa and Fc gamma RIIb. In spite of those difficulties, several Fc region variants have been identified so far, which has selective binding activity to Fc gamma RIIb as compared to Fc gamma RIIa, by conducting comprehensive amino acid modification analysis in the Fc region (see, e.g., PTL16, PTL17, PTL18, PTL19 and PTL20).
- [0032] There has been a report on an Fc region variant with binding selectivity for Fc gamma RIIb in relation to human Fc gamma R so far, whereas there has been no report on an Fc region variant with binding selectivity for Fc gamma RIIb in relation to monkey Fc gamma R. Owing to the absence of such an Fc variant, the effects of the Fc

variant selectively binding to Fc gamma RIIb have not been thoroughly tested yet in monkey.

[0033] Apart from the above, it is reported that by modifying the charge of amino acid residues which may be exposed on the surface of an antibody so as to increase or decrease the isoelectric point (pI) of the antibody, it is possible to regulate the half-life of the antibody in blood (see, e.g., PTL21 and PTL22). They show that it is possible to prolong the plasma half-life of an antibody by reducing the antibody's pI and vice versa.

[0034] Further, it is reported that incorporation of an antigen into cells can be promoted by modifying the charge of specified amino acid residues particularly in its CH3 domain to increase the antibody's pI (see, e.g., PTL23). Also, it has been reported that modifying the charge of amino acid residues in the constant region (mainly CH1 domain) of an antibody to reduce pI can prolong the half-life of the antibody in plasma (see, e.g., PTL24).

Citation List

Patent Literature

- [0035] [PTL1] US Patent No. 5,827,733
[PTL2] WO 1994/021681
[PTL3] US Patent No. 6,096,506
[PTL4] US Patent No. 7,261,893
[PTL5] US Patent No. 7,320,789
[PTL6] US Patent No. 7,807,159
[PTL7] US Patent No. 7,888,486
[PTL8] WO 2005/094446
[PTL9] WO 2007/047112
[PTL10] WO 2010/070094
[PTL11] WO 2000/042072
[PTL12] WO 2006/019447
[PTL13] WO 2004/099249
[PTL14] WO 2004/029207
[PTL15] US Appl. Publ. No. US2009/0136485
[PTL16] WO 2012/115241
[PTL17] WO 2013/047752
[PTL18] WO 2013/125667
[PTL19] WO 2014/030728
[PTL20] WO 2014/163101
[PTL21] WO 2007/114319

[PTL22] WO 2009/041643

[PTL23] WO 2014/145159

[PTL24] WO 2012/016227

Non Patent Literature

- [0036] [NPL1] Kingsley et al., *Genes Dev.* 8(2):133-146 (1994)
- [NPL2] Hoodless et al., *Curr. Top. Microbiol. Immunol.* 228:235-272 (1998)
- [NPL3] Zimmers et al., *Science* 296(5572):1486-1488 (2002)
- [NPL4] McPherron et al., *Nature* 387(6628):83-90 (1997)
- [NPL5] McPherron and Lee, *Proc. Natl. Acad. Sci. USA* 94(23):12457-12461 (1997)
- [NPL6] Szlama et al., *FEBS J* 280(16):3822-3839 (2013)
- [NPL7] Lee, *PloS One* 3(2):e1628 (2008)
- [NPL8] Lee, *Proc. Natl. Acad. Sci. USA* 98(16):9306-9311 (2001)
- [NPL9] McPherron et al., *Nature* 387(6628):83-90 (1997)
- [NPL10] McCroskery et al., *J Cell Sci.* 118(15):3531-3541 (2005)
- [NPL11] Whittemore et al., *Biochem. Biophys. Res. Commun.* 300(4):965-971 (2003)
- [NPL12] Bogdanovich et al., *Nature* 420(6914):418-421 (2002)
- [NPL13] Wagner., *Ann. Neurol.* 52(6):832-836 (2002)
- [NPL14] Reichert et al., *Nat. Biotechnol.* 23:1073-1078 (2005)
- [NPL15] Pavlou et al., *Eur. J. Pharm. Biopharm.* 59:389-396 (2005)
- [NPL16] Clark et al., *Chem. Immunol.* 65:88-110 (1997)
- [NPL17] Jefferis et al., *Immunol. Lett.* 82:57-65 (2002)
- [NPL18] Smith et al., *Nat. Rev. Immunol.* 10:328-343 (2010)
- [NPL19] Radaev et al., *J. Biol. Chem.* 276:16478-16483 (2001)
- [NPL20] Greenwood et al., *Eur. J. Immunol.* 23:1098-1104 (1993)
- [NPL21] Morgan et al., *Immunology* 86:319-324 (1995)
- [NPL22] Nimmerjahn et al., *Nat. Rev. Immunol.* 8:34-47 (2008)
- [NPL23] Amigorena et al., *Eur. J. Immunol.* 19:1379-1385 (1989)
- [NPL24] Sinclair, *J. Exp. Med.* 129:1183-1201 (1969)
- [NPL25] Heyman, *Immunol. Lett.* 88:157-161 (2003)
- [NPL26] Amigorena et al., *Science* 256:1808-1812 (1992)
- [NPL27] Muta et al., *Nature* 368:70-73 (1994)
- [NPL28] Ravetch, *Science* 290:84-89 (2000)
- [NPL29] Fournier et al., *J. Immunol.* 181:5350-5359 (2008)
- [NPL30] Smith et al., *Nat. Rev. Immunol.* 10:328-343 (2010)
- [NPL31] *J. Immunol.* 163:618-622 (1999)
- [NPL32] Yuasa et al., *J. Exp. Med.* 189:187-194 (1999)

- [NPL33] Nakamura et al., *J. Exp. Med.* 191:899-906 (2000)
- [NPL34] Blank, *Hum. Genet.* 117:220-227 (2005)
- [NPL35] Olferiev et al., *J. Biol. Chem.* 282:1738-1746 (2007)
- [NPL36] Chen et al., *Arthritis Rheum.* 54:3908-3917 (2006)
- [NPL37] Floto et al., *Nat. Med.* 11:1056-1058 (2005)
- [NPL38] Li et al., *J. Immunol.* 176:5321-5328 (2006)
- [NPL39] Mackay et al., *J. Exp. Med.* 203:2157-2164 (2006)
- [NPL40] Yang et al., *J. Immunol.* 178:3272-3280 (2007)
- [NPL41] Bruhns et al., *Blood* 113:3716-3725 (2009)
- [NPL42] Chu et al., *Mol. Immunol.* 45:3926-3933 (2008)
- [NPL43] Chu et al., *J. Allergy Clin. Immunol.* 129:1102-1115 (2012)
- [NPL44] Veri et al., *Arthritis Rheum.* 62:1933-1943 (2010)
- [NPL45] Cemerski et al., *Immunol. Lett.* 143:34-43 (2012)
- [NPL46] Wenink et al., *J. Immunol.* 183:4509-4520 (2009)
- [NPL47] Zhang et al., *J. Immunol.* 182:554-562 (2009)
- [NPL48] Ravetch, *Science* 333:1030-1034 (2011)
- [NPL49] Wilson et al., *Cancer Cell* 19:101-113 (2011)
- [NPL50] Kohrt et al., *J. Clin. Invest.* 122:1066-1075 (2012)
- [NPL51] Xu et al., *J. Immunol.* 171:562-568 (2003)
- [NPL52] Zhang et al., *Blood* 108:705-710 (2006)
- [NPL53] Chuntharapai et al., *J. Immunol.* 166:4891-4898 (2001)
- [NPL54] Ravetch et al., *Proc. Natl. Acad. Sci. USA* 109:10966-10971 (2012)
- [NPL55] Ravetch, *Science* 333:1030-1034 (2011)
- [NPL56] Cemerski et al., *Immunol. Lett.* 143:28-33 (2002)
- [NPL57] Chu et al., *Mol. Immunol.* 45:3926-3933 (2008)
- [NPL58] Smith et al., *Nat. Rev. Immunol.* 10:328-343 (2010)
- [NPL59] Scappaticci et al., *J. Natl. Cancer. Inst.* 99:1232-1239 (2007)
- [NPL60] *Arthritis Rheum.* 48:719-727 (2003)
- [NPL61] Meyer et al., *J. Thromb. Haemost.* 7:171-181 (2008)
- [NPL62] Robles-Carrillo et al., *J. Immunol.* 185:1577-1583 (2010)
- [NPL63] Duffau et al., *Sci. Transl. Med.* 2:47ra63 (2010)
- [NPL64] Richards et al., *Mol. Cancer Ther.* 7:2517-2527 (2008)
- [NPL65] Desai et al., *J. Immunol.* 178:6217-6226 (2007)
- [NPL66] Salmon et al., *J. Clin. Invest.* 97:1348-1354 (1996)
- [NPL67] Manger et al., *Arthritis Rheum.* 41:1181-1189 (1998)
- [NPL68] Boruchov et al., *J. Clin. Invest.* 115:2914-2923 (2005)
- [NPL69] Dhodapkar et al., *Proc. Natl. Acad. Sci. USA* 102:2910-2915 (2005)
- [NPL70] Armour et al., *Mol. Immunol.* 40:585-593 (2003)

[NPL71] Warmerdam et al., J. Exp. Med. 172:19-25 (1990)

[Summary of Invention]

[0037]

The invention provides anti-myostatin antibodies and methods of using the same. The invention also provides proteins containing a variant Fc region and methods of using the same.

[0037a]

In a first aspect, the present invention provides an isolated antibody that binds to latent myostatin, wherein the antibody inhibits activation of myostatin, wherein the antibody blocks the spontaneous release of mature myostatin from latent myostatin, and wherein the antibody binds to the same epitope as an antibody comprising the VH sequence of SEQ ID NO: 12 and the VL sequence of SEQ ID NO: 14.

[0037b]

In a second aspect, the present invention provides an isolated nucleic acid encoding the antibody of the first aspect.

[0037c]

In a third aspect, the present invention provides a host cell comprising the nucleic acid of the second aspect.

[0037d]

In a fourth aspect, the present invention provides a method of producing an anti-myostatin antibody comprising:

- (a) culturing the host cell of the third aspect so that the antibody is produced; or
- (b) immunizing an animal against a polypeptide, wherein the polypeptide comprises the region corresponding to amino acids at positions 21 to 100 of myostatin propeptide (SEQ ID NO: 78).

[0037e]

In a fifth aspect, the present invention provides a pharmaceutical formulation comprising the antibody of the first aspect and a pharmaceutically acceptable carrier.

[0037f]

In a sixth aspect, the present invention provides an anti-myostatin antibody produced by the method of the fourth aspect.

[0038]

In some embodiments, an isolated anti-myostatin antibody of the present invention binds to latent myostatin. In further embodiments, the antibody binds to an epitope within a fragment

consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78). In some embodiments, an isolated anti-myostatin antibody of the present invention inhibits activation of myostatin. In further embodiments, the antibody blocks the release of mature myostatin from latent myostatin. In further embodiments, the antibody blocks the proteolytic release of mature myostatin. In further embodiments, the antibody blocks the spontaneous release of mature myostatin. In further embodiments, the antibody does not bind to mature myostatin. In further embodiments, the antibody binds to the same epitope as an antibody described in Table 13. In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 13. In further embodiments, the antibody binds to the same epitope as an antibody described in Table 2a. In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 2a. In further embodiments, the antibody binds to the same epitope as an antibody described in Table 11a. . In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 11a. In further embodiments, the antibody binds to the same epitope as an antibody described in Table 2a, 11a, or 13. In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 2a, 11a, or 13.

[0039]

In some embodiments, an isolated anti-myostatin antibody of the present invention binds to latent myostatin with higher affinity at neutral pH than at acidic pH. In some embodiments, the anti-myostatin antibody binds to latent myostatin with higher affinity at pH7.4 than at pH5.8. In some embodiments, an isolated anti-myostatin antibody of the present invention binds to a polypeptide fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78) with higher affinity at pH7.4 than at pH5.8. In some embodiments, the antibody binds to the same myostatin epitope as an antibody described in Table 13 with a higher affinity at neutral pH than at acidic pH. In additional embodiments, an anti-myostatin antibody binds to the same

epitope as an antibody described in Table 13 with a higher affinity at pH7.4 than at pH5.8. In further embodiments, the antibody binds to the same epitope as an antibody

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comprising a VH and a VL pair described in Table 13 with a higher affinity at pH7.4 than at pH5.8. In some embodiments, the antibody binds to the same myostatin epitope as an antibody described in Table 2a with a higher affinity at neutral pH than at acidic pH. In some embodiments, the antibody binds to the same myostatin epitope as an antibody described in Table 2a with a higher affinity at pH7.4 than at pH5.8. In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 2a with a higher affinity at pH7.4 than at pH5.8. In additional embodiments, an anti-myostatin antibody binds to the same epitope as an antibody described in Table 11a with a higher affinity at neutral pH than at acidic pH. In further embodiments, the antibody binds to the same myostatin epitope as an antibody described in Table 11a with a higher affinity at pH7.4 than at pH5.8. In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 11a with a higher affinity at pH7.4 than at pH5.8. In additional embodiments, an anti-myostatin antibody binds to the same epitope as an antibody described in Table 2a, 11a, or 13 with a higher affinity at neutral pH than at acidic pH. In further embodiments, the antibody binds to the same myostatin epitope as an antibody described in Table 2a, 11a, or 13 with a higher affinity at pH7.4 than at pH5.8. In further embodiments, the antibody binds to the same epitope as an antibody comprising a VH and a VL pair described in Table 2a, 11a, or 13 with a higher affinity at pH7.4 than at pH5.8.

[0040] In some embodiments, an isolated anti-myostatin antibody of the present invention competes for binding latent myostatin with an antibody provided herein. In some embodiments, an isolated anti-myostatin antibody of the present invention competes for binding latent myostatin with an antibody described in Table 13. In some embodiments, an isolated anti-myostatin antibody of the present invention competes for binding latent myostatin with an antibody comprising a VH and VL pair described in Table 13. In some embodiments, the antibody competes for binding latent myostatin with an antibody described in Table 2a. In some embodiments, an isolated anti-myostatin antibody of the present invention competes for binding latent myostatin with an antibody comprising a VH and VL pair described in Table 2a. In some embodiments, the antibody competes for binding latent myostatin with an antibody described in Table 11a. In some embodiments, an isolated anti-myostatin antibody of the present invention competes for binding latent myostatin with an antibody comprising a VH and VL pair described in Table 11a. In additional embodiments, an anti-myostatin antibody competes for binding latent myostatin with an antibody described in Table 2a, 11a, or 13. In additional embodiments, an anti-myostatin antibody competes for binding latent myostatin with an antibody comprising a VH and VL pair described in Table 2a, 11a, or 13. In further embodiments, the anti-myostatin

antibody binds to latent myostatin with a higher affinity at neutral pH than at acidic pH. In further embodiments, the anti-myostatin antibody binds to latent myostatin with a higher affinity at pH7.4 than at pH5.8. In further embodiments, the anti-myostatin antibody binds to a polypeptide fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78) with higher affinity at pH7.4 than at pH5.8. Methods for assessing the ability of an antibody to compete with a reference antibody for binding latent myostatin are described herein and known in the art.

[0041] In some embodiments, an isolated anti-myostatin antibody of the present invention is a monoclonal antibody. In some embodiments, an isolated anti-myostatin antibody of the present invention is a human, humanized, or chimeric antibody. In some embodiments, an isolated anti-myostatin antibody of the present invention is an antibody fragment that binds to myostatin. In some embodiments, an isolated anti-myostatin antibody of the present invention is an antibody fragment that binds to latent myostatin. In some embodiments, an isolated anti-myostatin antibody of the present invention is an antibody fragment that binds to a polypeptide fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78). In some embodiments, an isolated anti-myostatin antibody of the present invention is a full length IgG antibody.

[0042] In some embodiments, a anti-myostatin antibody of the invention comprises:

(a) (i) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128), (ii) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131), and (iii) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127);

(b) (i) a HVR-H1 comprising the amino acid sequence X₁X₂DIS, wherein X₁ is S or H, X₂ is Y, T, D or E (SEQ ID NO: 126), (ii) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127), and (iii) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128);

(c) (i) a HVR-H1 comprising the amino acid sequence X₁X₂DIS, wherein X₁ is S or H, X₂ is Y, T, D or E (SEQ ID NO: 126), (ii) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127), (iii) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128), (iv) a HVR-L1 comprising the amino acid sequence X₁X₂SQX₃VX₄X₅X₆NWLS, wherein X₁ is Q or T, X₂ is S or T, X

₃ is S or E, X₄ is Y or F, X₅ is D or H, X₆ is N, D, A or E (SEQ ID NO: 129); (v) a HVR-L2 comprising the amino acid sequence WAX₁TLAX₂, wherein X₁ is S or E, X₂ is S, Y, F or W (SEQ ID NO: 130); and (vi) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131);

(d) (i) a HVR-L1 comprising the amino acid sequence X₁X₂SQX₃VX₄X₅X₆NWLS, wherein X₁ is Q or T, X₂ is S or T, X₃ is S or E, X₄ is Y or F, X₅ is D or H, X₆ is N, D, A or E (SEQ ID NO: 129); (ii) a HVR-L2 comprising the amino acid sequence WAX₁TLAX₂, wherein X₁ is S or E, X₂ is S, Y, F or W (SEQ ID NO: 130); and (iii) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131). In some embodiments the antibody of (b) further comprises a heavy chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 132-134; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 135-136; FR3 comprising the amino acid sequence of SEQ ID NO: 137; and FR4 comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, the antibody of (d), further comprises a light chain variable domain framework FR1 comprising the amino acid sequence of SEQ ID NO: 139; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 140-141; FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 142-143; and FR4 comprising the amino acid sequence of SEQ ID NO: 144.

[0043] In some embodiments, an isolated anti-myostatin antibody of the present invention comprises (a) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128), (b) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131), and (c) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127).

[0044] In some embodiments, an isolated anti-myostatin antibody of the present invention comprises (a) a HVR-H1 comprising the amino acid sequence X₁X₂DIS, wherein X₁ is S or H, X₂ is Y, T, D or E (SEQ ID NO: 126), (b) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127), and (c) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128). In further embodiments, the antibody comprises a heavy chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 132-134; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 135-136; FR3 comprising the amino acid sequence of SEQ ID NO: 137; and FR4 comprising the amino acid sequence of SEQ ID NO: 138. In further embodiments, the antibody addi-

tionally comprises (a) a HVR-L1 comprising the amino acid sequence $X_1X_2SQX_3VX_4X_5X_6NWLS$, wherein X_1 is Q or T, X_2 is S or T, X_3 is S or E, X_4 is Y or F, X_5 is D or H, X_6 is N, D, A or E (SEQ ID NO: 129); (b) a HVR-L2 comprising the amino acid sequence WAX_1TLAX_2 , wherein X_1 is S or E, X_2 is S, Y, F or W (SEQ ID NO: 130); and (c) a HVR-L3 comprising the amino acid sequence $AGGYGGGX_1YA$, wherein X_1 is L or R (SEQ ID NO: 131).

[0045] In some embodiments, an isolated anti-myostatin antibody of the present invention comprises (a) a HVR-L1 comprising the amino acid sequence $X_1X_2SQX_3VX_4X_5X_6NWLS$, wherein X_1 is Q or T, X_2 is S or T, X_3 is S or E, X_4 is Y or F, X_5 is D or H, X_6 is N, D, A or E (SEQ ID NO: 129); (b) a HVR-L2 comprising the amino acid sequence WAX_1TLAX_2 , wherein X_1 is S or E, X_2 is S, Y, F or W (SEQ ID NO: 130); and (c) a HVR-L3 comprising the amino acid sequence $AGGYGGGX_1YA$, wherein X_1 is L or R (SEQ ID NO: 131). In a further embodiment, the antibody further comprises a light chain variable domain framework FR1 comprising the amino acid sequence of SEQ ID NO: 139; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 140-141; FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 142-143; and FR4 comprising the amino acid sequence of SEQ ID NO: 144.

[0046] In some embodiments, an isolated anti-myostatin antibody of the present invention comprises a heavy chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 132-134; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 135-136; FR3 comprising the amino acid sequence of SEQ ID NO: 137; and FR4 comprising the amino acid sequence of SEQ ID NO: 138. In some embodiments, an isolated anti-myostatin antibody of the present invention comprises a light chain variable domain framework FR1 comprising the amino acid sequence of SEQ ID NO: 139; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 140-141; FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 142-143; and FR4 comprising the amino acid sequence of SEQ ID NO: 144.

[0047] In some embodiments, an isolated anti-myostatin antibody of the present invention comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 15, 31, 35-38, and 96-99; or (c) a VH sequence as in (a) and a VL sequence as in (b). In further embodiments, the antibody comprises a VH sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95. In further embodiments, the antibody comprises a VL sequence of any one of SEQ ID NOs: 15, 31, 35-38, and 96-99. In some embodiments, the antibody comprises a VH sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95. In further embodiments, the antibody comprises a

VH sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95; and a VL sequence of any one of SEQ ID NOs: 15, 31, 35-38, and 96-99.

[0048] The invention also provides isolated nucleic acids encoding an anti-myostatin antibody of the present invention. The invention also provides host cells comprising a nucleic acid of the present invention. The invention also provides a method of producing an antibody comprising culturing a host cell of the present invention so that the antibody is produced.

[0049] In some aspects the invention provides a method of producing an anti-myostatin antibody comprising: (a) culturing a host cell of the present invention so that the antibody is produced; or (b) immunizing an animal against a polypeptide, wherein the polypeptide comprises the region corresponding to amino acids at positions 21 to 100 of myostatin propeptide (SEQ ID NO: 78).

[0050] The invention further provides a method of producing an anti-myostatin antibody. In some embodiments, the method comprises immunizing an animal against a polypeptide, wherein the polypeptide comprises the region corresponding to amino acids at positions 21-100 of myostatin propeptide (SEQ ID NO: 78).

[0051] The invention also provides a pharmaceutical formulation comprising an anti-myostatin antibody of the present invention and a pharmaceutically acceptable carrier.

[0052] The invention provides polypeptides comprising variant Fc regions and methods of making and using the same.

[0053] In one embodiment, the invention provides Fc gamma RIIb-binding polypeptides comprising variant Fc regions and methods of using the same. In some embodiments, a variant Fc region with enhanced Fc gamma RIIb-binding activity of the present invention comprises at least one amino acid alteration in a parent Fc region. In further embodiments, the ratio of [KD value of the parent Fc region for monkey Fc gamma RIIb]/[KD value of the variant Fc region for monkey Fc gamma RIIb] is 2.0 or greater. In further embodiments, the ratio of [KD value of the parent Fc region for monkey Fc gamma RIIIa]/[KD value of the variant Fc region for monkey Fc gamma RIIIa] is 0.5 or smaller. In further embodiments, the ratio of [KD value of the parent Fc region for human Fc gamma RIIb]/[KD value of the variant Fc region for human Fc gamma RIIb] is 2.0 or greater. In further embodiments, the ratio of [KD value of the parent Fc region for human Fc gamma RIIIa]/[KD value of the variant Fc region for human Fc gamma RIIIa] is 0.5 or smaller. In further embodiments, the ratio of [KD value of the parent Fc region for human Fc gamma RIIa (type H)]/[KD value of the variant Fc region for human Fc gamma RIIa (type H)] is 5.0 or smaller. In further embodiments, the ratio of [KD value of the parent Fc region for human Fc gamma RIIa (type R)]/[KD value of the variant Fc region for human Fc gamma RIIa (type R)] is 5.0 or smaller. In another embodiment, the KD value of the variant Fc region for monkey Fc gamma RIIb is

1.0x10⁻⁶ M or smaller. In another embodiment, the KD value of the variant Fc region for monkey Fc gamma RIIIa is 5.0x10⁻⁷ M or greater. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIb is 2.0x10⁻⁶ M or smaller. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIIa is 1.0x10⁻⁶ M or greater. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIa (type H) is 1.0x10⁻⁷ M or greater. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIa (type R) is 2.0x10⁻⁷ M or greater.

- [0054] In some embodiments, a variant Fc region with enhanced Fc gamma RIIb-binding activity of the present invention comprises at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 236, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering.
- [0055] In further embodiments, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least two amino acid alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: (i) position 231, 232, 233, 234, 235, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396; (ii) position: 231, 232, 235, 239, 268, 295, 298, 326, 330, and 396; or (iii) position 268, 295, 326, and 330; according to EU numbering.
- [0056] In further embodiments, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least two amino acid alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering.
- [0057] In further embodiments, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least two amino acid alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 235, 239, 268, 295, 298, 326, 330, and 396, according to EU numbering.
- [0058] In further embodiments, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least two amino acid alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 268, 295, 326, and 330 according to EU numbering.
- [0059] In some embodiments, a variant Fc region with enhanced Fc gamma RIIb-binding activity of the present invention comprises at least one amino acid selected from the

group consisting of: (a) Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 231; (b) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 232; (c) Asp at position 233; (d) Trp, Tyr at position 234; (e) Trp at position 235; (f) Ala, Asp, Glu, His, Ile, Leu, Met, Asn, Gln, Ser, Thr, Val at position 236; (g) Asp, Tyr at position 237; (h) Glu, Ile, Met, Gln, Tyr at position 238; (i) Ile, Leu, Asn, Pro, Val at position 239; (j) Ile at position 264; (k) Phe at position 266; (l) Ala, His, Leu at position 267; (m) Asp, Glu at position 268; (n) Asp, Glu, Gly at position 271; (o) Leu at position 295; (p) Leu at position 298; (q) Glu, Phe, Ile, Leu at position 325; (r) Thr at position 326; (s) Ile, Asn at position 327; (t) Thr at position 328; (u) Lys, Arg at position 330; (v) Glu at position 331; (w) Asp at position 332; (x) Asp, Ile, Met, Val, Tyr at position 334; and (y) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 396; according to EU numbering.

[0060] In further embodiments, the variant Fc region with enhanced Fc gamma RIIB-binding activity comprises at least one amino acid selected from the group consisting of: (a) Gly, Thr at position 231; (b) Asp at position 232; (c) Trp at position 235; (d) Asn, Thr at position 236; (e) Val at position 239; (f) Asp, Glu at position 268; (g) Leu at position 295; (h) Leu at position 298; (i) Thr at position 326; (j) Lys, Arg at position 330, and (k) Lys, Met at position 396; according to EU numbering.

[0061] In another embodiment, the invention provides a polypeptide comprising an isoelectric point (pI)-increased variant Fc region and a method of using the same. In some embodiments, a polypeptide comprising a variant Fc region with increased pI comprises at least two amino acid alterations in a parent Fc region. In further embodiments, each of the amino acid alterations increases the isoelectric point (pI) of the variant Fc region compared with that of the parent Fc region. In further embodiments, the amino acid can be exposed on the surface of the variant Fc region. In further embodiments, a polypeptide comprises the variant Fc region and an antigen-binding domain. In further embodiments, antigen-binding activity of the antigen-binding domain changes according to ion concentration conditions. In further embodiments, the variant Fc region with increased pI of the present invention comprises at least two amino acid alterations of at least two positions selected from the group consisting of: 285, 311, 312, 315, 318, 333, 335, 337, 341, 342, 343, 384, 385, 388, 390, 399, 400, 401, 402, 413, 420, 422, and 431 according to EU numbering. In further embodiments, the variant Fc region with increased pI comprises Arg or Lys at each of the positions selected.

[0062] In some embodiments, a variant Fc region of the present invention comprises amino acid alterations described in Tables 14-30.

[0063] In some embodiments, a polypeptide comprises a variant Fc region of the present

invention. In further embodiments, the parent Fc region is derived from human IgG1. In further embodiments, the polypeptide is an antibody. In further embodiments, the polypeptide is an Fc fusion protein.

[0064] The invention provides a polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 229-381.

[0065] The invention also provides isolated nucleic acid encoding the polypeptide comprising a variant Fc region of the present invention. The invention also provides a host cell comprising the nucleic acid of the present invention. The invention also provides a method of producing a polypeptide comprising a variant Fc region comprising culturing the host of the present invention so that the polypeptide is produced.

[0066] The invention further provides a pharmaceutical formulation comprising the polypeptide comprising a variant Fc region of the present invention and a pharmaceutically acceptable carrier.

[0067] Specifically, the present invention relates to:

[1] An isolated antibody that binds to latent myostatin, wherein the antibody inhibits activation of myostatin.

[2] The antibody of [1], wherein the antibody:

(a) blocks the release of mature myostatin from latent myostatin;

(b) blocks the proteolytic release of mature myostatin;

(c) blocks the spontaneous release of mature myostatin; or

(d) does not bind to mature myostatin; or binds to an epitope within a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78).

[3] The antibody of [1] or [2], wherein the antibody competes for binding latent myostatin with, or binds the same epitope as, an antibody comprising a VH and VL pair described in Tables 2a, 11a, or 13.

[4] The antibody of any one of [1] to [3], which binds to latent myostatin with higher affinity at neutral pH than at acidic pH, or which binds to latent myostatin with higher affinity at pH7.4 than at pH5.8.

[5] The antibody of any one of [1] to [4], which is (a) a monoclonal antibody, (b) a human, humanized, or chimeric antibody; (c) a full length IgG antibody or (d) an antibody fragment that binds to myostatin.

[6] The antibody of any one of [1] to [5], wherein the antibody comprises :

(a) (i) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128), (ii) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131), and (iii) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M

or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127);

(b) (i) a HVR-H1 comprising the amino acid sequence X₁X₂DIS, wherein X₁ is S or H, X₂ is Y, T, D or E (SEQ ID NO: 126), (ii) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127), and (iii) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128);

(c) (i) a HVR-H1 comprising the amino acid sequence X₁X₂DIS, wherein X₁ is S or H, X₂ is Y, T, D or E (SEQ ID NO: 126), (ii) a HVR-H2 comprising the amino acid sequence IISX₁AGX₂X₃YX₄X₅X₆WAKX₇, wherein X₁ is Y or H, X₂ is S or K, X₃ is T, M or K, X₄ is Y or K, X₅ is A, M or E, X₆ is S or E, X₇ is G or K (SEQ ID NO: 127), (iii) a HVR-H3 comprising the amino acid sequence GVPAX₁SX₂GGDX₃, wherein X₁ is Y or H, X₂ is T or H, X₃ is L or K (SEQ ID NO: 128), (iv) a HVR-L1 comprising the amino acid sequence X₁X₂SQX₃VX₄X₅X₆NWLS, wherein X₁ is Q or T, X₂ is S or T, X₃ is S or E, X₄ is Y or F, X₅ is D or H, X₆ is N, D, A or E (SEQ ID NO: 129); (v) a HVR-L2 comprising the amino acid sequence WAX₁TLAX₂, wherein X₁ is S or E, X₂ is S, Y, F or W (SEQ ID NO: 130); and (vi) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131); or

(d) (i) a HVR-L1 comprising the amino acid sequence X₁X₂SQX₃VX₄X₅X₆NWLS, wherein X₁ is Q or T, X₂ is S or T, X₃ is S or E, X₄ is Y or F, X₅ is D or H, X₆ is N, D, A or E (SEQ ID NO: 129); (ii) a HVR-L2 comprising the amino acid sequence WAX₁TLAX₂, wherein X₁ is S or E, X₂ is S, Y, F or W (SEQ ID NO: 130); and (iii) a HVR-L3 comprising the amino acid sequence AGGYGGGX₁YA, wherein X₁ is L or R (SEQ ID NO: 131).

[7] The antibody of [6](b), further comprising a heavy chain variable domain framework FR1 comprising the amino acid sequence of any one of SEQ ID NOs: 132-134; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 135-136; FR3 comprising the amino acid sequence of SEQ ID NO: 137; and FR4 comprising the amino acid sequence of SEQ ID NO: 138.

[8] The antibody of [6](d), further comprising a light chain variable domain framework FR1 comprising the amino acid sequence of SEQ ID NO: 139; FR2 comprising the amino acid sequence of any one of SEQ ID NOs: 140-141; FR3 comprising the amino acid sequence of any one of SEQ ID NOs: 142-143; and FR4 comprising the amino acid sequence of SEQ ID NO: 144.

[9] The antibody of any one of [1] to [5], comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 15, 31, 35-38, and 96-99; or (c) a

VH sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95, and a VL sequence of any one of SEQ ID NOs: 15, 31, 35-38, and 96-99.

[10] An isolated nucleic acid encoding the antibody of any one of [1] to [9].

[11] A host cell comprising the nucleic acid of [10].

[12] A method of producing an anti-myostatin antibody comprising:

(a) culturing the host cell of [11] so that the antibody is produced; or

(b) immunizing an animal against a polypeptide, wherein the polypeptide comprises the region corresponding to amino acids at positions 21 to 100 of myostatin propeptide (SEQ ID NO: 78).

[13] A pharmaceutical formulation comprising the antibody of any one of [1] to [9] and a pharmaceutically acceptable carrier.

[14] A polypeptide comprising a variant Fc region comprising at least one amino acid alteration in a parent Fc region, wherein the ratio of [KD value of the parent Fc region for monkey Fc gamma RIIb]/[KD value of the variant Fc region for monkey Fc gamma RIIb] is 2.0 or greater, and the ratio of [KD value of the parent Fc region for monkey Fc gamma RIIIa]/[KD value of the variant Fc region for monkey Fc gamma RIIIa] is 0.5 or smaller.

[15] The polypeptide of [14], further wherein the ratio of [KD value of the parent Fc region for human Fc gamma RIIb]/[KD value of the variant Fc region for human Fc gamma RIIb] is 2.0 or greater, and the ratio of [KD value of the parent Fc region for human Fc gamma RIIIa]/[KD value of the variant Fc region for human Fc gamma RIIIa] is 0.5 or smaller.

[16] The polypeptide of [15], further wherein the ratio of [KD value of the parent Fc region for human Fc gamma RIIa (type H)]/[KD value of the variant Fc region for human Fc gamma RIIa (type H)] is 5.0 or smaller.

[17] The polypeptide of [16], further wherein the ratio of [KD value of the parent Fc region for human Fc gamma RIIa (type R)]/[KD value of the variant Fc region for human Fc gamma RIIa (type R)] is 5.0 or smaller.

[18] The polypeptide of [14], wherein the KD value of the variant Fc region for monkey Fc gamma RIIb is 1.0×10^{-6} M or smaller, and the KD value of the variant Fc region for monkey Fc gamma RIIIa is 5.0×10^{-7} M or greater.

[19] The polypeptide of [15], wherein the KD value of the variant Fc region for human Fc gamma RIIb is 2.0×10^{-6} M or smaller, and the KD value of the variant Fc region for human Fc gamma RIIIa is 1.0×10^{-6} M or greater.

[20] The polypeptide of [16], wherein the KD value of the variant Fc region for human Fc gamma RIIa (type H) is 1.0×10^{-7} M or greater.

[21] The polypeptide of [17], wherein the KD value of the variant Fc region for human Fc gamma RIIa (type R) is 2.0×10^{-7} M or greater.

[22] The polypeptide of any one of [14] to [21], wherein the variant Fc region comprises at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 236, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering.

[23] The polypeptide of [22], wherein the variant Fc region comprises at least two amino acid alterations comprising:

(a) one amino acid alteration at position 236, and

(b) at least one amino acid alteration of at least one position selected from the group consisting of:

(i) position 231, 232, 233, 234, 235, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396;

(ii) position: 231, 232, 235, 239, 268, 295, 298, 326, 330, and 396; or

(iii) position 268, 295, 326, and 330;

according to EU numbering.

[24] The polypeptide according to [22] or [23], wherein the variant Fc region comprises at least one amino acid selected from the group consisting of:

(a) Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 231,

(b) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 232,

(c) Asp at position 233,

(d) Trp, Tyr at position 234,

(e) Trp at position 235,

(f) Ala, Asp, Glu, His, Ile, Leu, Met, Asn, Gln, Ser, Thr, Val at position 236,

(g) Asp, Tyr at position 237,

(h) Glu, Ile, Met, Gln, Tyr at position 238,

(i) Ile, Leu, Asn, Pro, Val at position 239,

(j) Ile at position 264,

(k) Phe at position 266,

(l) Ala, His, Leu at position 267,

(m) Asp, Glu at position 268,

(n) Asp, Glu, Gly at position 271,

(o) Leu at position 295,

(p) Leu at position 298,

(q) Glu, Phe, Ile, Leu at position 325,

(r) Thr at position 326,

(s) Ile, Asn at position 327,

(t) Thr at position 328,
(u) Lys, Arg at position 330,
(v) Glu at position 331,
(w) Asp at position 332,
(x) Asp, Ile, Met, Val, Tyr at position 334, and
(y) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 396;
according to EU numbering.

[25] The polypeptide according to [24], wherein the variant Fc region comprises at least one amino acid selected from the group consisting of:

(a) Gly, Thr at position 231,
(b) Asp at position 232,
(c) Trp at position 235,
(d) Asn, Thr at position 236,
(e) Val at position 239,
(f) Asp, Glu at position 268,
(g) Leu at position 295,
(h) Leu at position 298,
(i) Thr at position 326,
(j) Lys, Arg at position 330, and
(k) Lys, Met at position 396;
according to EU numbering.

[26] A polypeptide comprising a variant Fc region comprising at least two amino acid alterations in a parent Fc region, wherein each of the amino acid alterations increases the isoelectric point (pI) of the variant Fc region compared with that of the parent Fc region.

[27] The polypeptide of [26], wherein the amino acid alterations are exposed on the surface of the variant Fc region.

[28] The polypeptide of [26] or [27], further comprising an antigen-binding domain.

[29] The polypeptide of [28] wherein antigen-binding activity of the antigen-binding domain changes according to ion concentration conditions.

[30] The polypeptide of any one of [26] to [29], wherein the variant Fc region comprises at least two amino acid alterations of at least two positions selected from the group consisting of: 285, 311, 312, 315, 318, 333, 335, 337, 341, 342, 343, 384, 385, 388, 390, 399, 400, 401, 402, 413, 420, 422, and 431, according to EU numbering.

[31] The polypeptide of [30], wherein the variant Fc region comprises Arg or Lys at each of the positions selected.

[32] A polypeptide comprising a variant Fc region comprising amino acid alterations

described in Tables 14-30.

[33] The polypeptide of any one of [14] to [32], wherein the parent Fc region is derived from human IgG1.

[34] The polypeptide of any one of [14] to [33] wherein the polypeptide is an antibody or an Fc fusion protein.

[35] A polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 229-381.

[36] An isolated nucleic acid encoding the polypeptide of any one of [14] to [35].

[37] A host cell comprising the nucleic acid of [36].

[38] A method of producing a polypeptide comprising a variant Fc region, the method comprising culturing the host cell of [37] so that the polypeptide is produced.

[39] A pharmaceutical formulation comprising the polypeptide of any one of [14] to [35] and a pharmaceutically acceptable carrier.

Brief Description of Drawings

- [0068] [fig.1]Figure 1 illustrates inhibition of proteolytic activation of latent myostatin by anti-latent myostatin antibody, as described in Example 3. The activity of active myostatin released from latent myostatin by BMP1 protease was measured in the presence of anti-latent myostatin antibody, using HEK Blue Assay.
- [fig.2]Figure 2 illustrates inhibition of spontaneous activation of latent myostatin by anti-latent myostatin antibody, as described in Example 4. The activity of active myostatin released from latent myostatin by 37 degrees C incubation was measured in the presence of anti-latent myostatin antibody, using HEK Blue Assay.
- [fig.3]Figure 3 illustrates binding of anti-latent myostatin antibody to propeptide domain, as described in Example 5.
- [fig.4]Figure 4 illustrates Western Blot analysis against myostatin propeptide, as described in Example 6. Proteolytic cleavage of myostatin propeptide by BMP1 was assessed in the presence and absence of anti-latent myostatin antibody.
- [fig.5]Figures 5A-5C illustrate BIACORE (registered trademark) sensorgrams of anti-latent myostatin antibody MST1032-G1m towards human latent myostatin (A), cynomolgus monkey latent myostatin (B), and mouse latent myostatin (C), as described in Example 7.
- [fig.6]Figure 6 illustrates inhibition of proteolytic and spontaneous activation of latent myostatin by humanized anti-latent myostatin antibody, as described in Example 8. The activity of active myostatin released from latent myostatin by BMP1 protease (proteolytic) or by 37 degrees C incubation without BMP1 (spontaneous) was measured in the presence of anti-latent myostatin antibody, using HEK Blue Assay.
- [fig.7]Figure 7 illustrates BIACORE (registered trademark) sensorgrams of histidine

substituted variants of anti-latent myostatin antibody, as described in Example 9. The antibody/antigen complexes were allowed to dissociate at pH7.4, followed by additional dissociation at pH5.8 (pointed by an arrow) to assess the pH-dependent interactions. Antibodies tested in this experiment are: Ab001 (black solid curve), Ab002 (black short-dashed curve), Ab003 (black dotted curve), Ab004 (gray short-dashed curve), Ab005 (gray solid curve), Ab006 (gray long-dashed curve), and Ab007 (black long-dashed curve).

[fig.8]Figure 8 illustrates inhibition of proteolytic and spontaneous activation of latent myostatin by pH-dependent anti-latent myostatin antibodies, as described in Example 11. The activity of active myostatin released from latent myostatin by BMP1 protease (proteolytic) or by 37 degrees C incubation without BMP1 (spontaneous) was measured in the presence of anti-latent myostatin antibodies, using HEK Blue Assay. Antibodies MS1032LO01-SG1, MS1032LO02-SG1, MS1032LO03-SG1, and MS1032LO04-SG1 are described respectively as MSLO-01, MSLO-02, MSLO-03, and MSLO-04 in the Figure. Comparable inhibition of proteolytic and spontaneous activation of latent myostatin to MS1032LO00-SG1 was achieved by MS1032LO01-SG1, MS1032LO02-SG1, MS1032LO03-SG1, and MS1032LO04-SG1.

[fig.9]Figures 9A-9F illustrate BIACORE (registered trademark) sensorgrams of pH-dependent anti-latent myostatin antibody, as described in Example 12. Kinetic parameters of MST1032-SG1 (A), MS1032LO00-SG1 (B), MS1032LO01-SG1 (C), MS1032LO02-SG1 (D), MS1032LO03-SG1 (E), and MS1032LO04-SG1 (F), were measured at neutral pH and acidic pH.

[fig.10]Figure 10 illustrates the time course of plasma myostatin concentration after intravenous administration of an anti-myostatin antibody in mice, as described in Example 13. The effects of Fc gamma R-mediated cellular uptake of antibody/antigen complexes on myostatin clearance in vivo was assessed by comparing anti-myostatin antibodies with Fc gamma R binding (MS1032LO00-SG1) and anti-myostatin antibodies with abolished Fc gamma R binding (MS1032LO00-F760).

[fig.11]Figure 11 illustrates the time course of plasma myostatin concentration after intravenous administration of an anti-myostatin antibody in mice, as described in Example 14. The effects of pH-dependent binding of anti-myostatin antibody on myostatin clearance in vivo was assessed by comparing pH-dependent anti-myostatin antibody (MS1032LO01-SG1 or MS1032LO01-F760) and non pH-dependent anti-myostatin antibody (MS1032LO00-SG1 or MS1032LO00-F760).

[fig.12]Figure 12 illustrates binding activity of anti-latent myostatin antibody MST1032 to latent myostatin and GDF11, as described in Example 16.

[fig.13]Figure 13 illustrates the inhibitory activity of anti-latent myostatin antibody

MST1032 against proteolytic and spontaneous activation of GDF11, as described in Example 17. The activity of active GDF11 released by BMP1 protease (proteolytic) or by 37 degrees C incubation without BMP1 (spontaneous) was measured in the presence of anti-latent myostatin antibody, using HEK Blue Assay.

[fig.14]Figure 14 illustrates inhibition of proteolytic activation of latent myostatin by anti-latent myostatin antibody, as described in Example 19. The activity of active myostatin released from latent myostatin by BMP1 protease was measured in the presence of anti-latent myostatin antibody, using HEK Blue Assay.

[fig.15]Figure 15 illustrates the time course of plasma myostatin concentration after intravenous administration of anti-latent myostatin antibodies in mice, as described in Example 20. The effects of pH dependency on myostatin clearance in vivo was assessed by comparing non-pH dependent anti-latent myostatin antibody (MS1032LO00-SG1) and different pH-dependent anti-latent myostatin antibodies (MS1032LO01-SG1, MS1032LO06-SG1, MS1032LO11-SG1, MS1032LO18-SG1, MS1032LO19-SG1, MS1032LO21-SG1 and MS1032LO25-SG1).

[fig.16]Figures 16A and 16B illustrate the time course of plasma myostatin concentration after intravenous administration of anti-latent myostatin antibodies in cynomolgus monkey, as described in Example 21. (A) The effect of pH-dependency and Fc engineering on myostatin clearance in vivo was assessed by comparing non pH-dependent anti-latent myostatin antibody (MS1032LO00-SG1) and pH-dependent anti-latent myostatin antibodies with Fc engineering (MS1032LO06-SG1012, MS1032LO06-SG1016, MS1032LO06-SG1029, MS1032LO06-SG1031, MS1032LO06-SG1033, MS1032LO06-SG1034). (B) The effect of Fc engineering on myostatin clearance in vivo was assessed by comparing anti-latent myostatin antibodies (MS1032LO19-SG1079, MS1032LO19-SG1071, MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081, and MS1032LO19-SG1077).

[fig.17]Figure 17 illustrates inhibitory activity on latent myostatin activation by anti-latent myostatin antibodies, as described in Example 22. The amounts of mature myostatin released from latent myostatin by BMP1 protease were measured in the presence of anti-latent myostatin antibodies (MST1032, MST1504, MST1538, MST1551, MST1558, MST1572, and MST1573).

[fig.18A]Figure 18A illustrates a schematic diagram of latent myostatin fragments of 100 amino acid each, designed for epitope mapping of anti-latent myostatin antibodies, as described in Example 22.

[fig.18B]Figure 18B illustrates Western blotting analysis against GST tagged human latent myostatin fragments (GST-hMSTN) by an anti-GST antibody, as described in Example 22. Each lane indicates: 1, GST-hMSTN 1-100aa; 2, GST-hMSTN 21-120aa; 3, GST-hMSTN 41-140aa; 4, GST-hMSTN 61-160aa; 5, GST-hMSTN 81-180aa; 6,

GST-hMSTN 101-200aa; 7, GST-hMSTN 121-220aa; 8, GST-hMSTN 141-241aa; 9, GST control.

[fig.18C]Figure 18C illustrates Western blotting analysis against GST tagged human latent myostatin fragments (GST-hMSTN) by anti-latent myostatin antibodies (MST1032, MST1538, MST1572, and MST1573), as described in Example 22. Each lane indicates: 1, GST-hMSTN 1-100aa; 2, GST-hMSTN 21-120aa; 3, GST-hMSTN 41-140aa; 4, GST-hMSTN 61-160aa; 5, GST-hMSTN 81-180aa; 6, GST-hMSTN 101-200aa; 7, GST-hMSTN 121-220aa; 8, GST-hMSTN 141-241aa; 9, GST control; 10, human latent myostatin (100ng).

[fig.18D]Figure 18D illustrates summarized results of Western blotting analysis and deduced epitope positions for anti-latent myostatin antibodies (MST1032, MST1538, MST1572, and MST1573), as described in Example 22.

[fig.19]Figure 19 illustrates an alignment of amino acid sequences of cynomolgus (cyno) Fc gamma RIIa1, Fc gamma RIIa2, Fc gamma RIIa3, Fc gamma RIIb, human Fc gamma RIIaH, Fc gamma RIIaR, and Fc gamma RIIb. Squared regions indicate putative residues which interact with Fc domain.

[fig.20]Figure 20 illustrates the time course of total myostatin concentration in plasma after intravenous administration of an anti-myostatin antibody with an Fc gamma RIIb-enhanced Fc variant in all human Fc gamma R transgenic mice, as described in Example 24. The effects of Fc gamma RIIb-enhanced Fc variants on antigen elimination through human Fc gamma RIIb were evaluated.

[fig.21]Figure 21 illustrates the time course of antibody concentration in plasma after intravenous administration of an anti-myostatin antibody with an Fc gamma RIIb-enhanced Fc variant in all human Fc gamma R transgenic mice, as described in Example 24. The effects of Fc gamma RIIb-enhanced Fc variants on antibody pharmacokinetics were evaluated.

[fig.22]Figures 22A and 22B illustrate the time course of plasma myostatin concentration after intravenous administration of anti-latent myostatin antibodies in cynomolgus monkey, as described in Example 25. (A) The effect of pH-dependency and Fc engineering on myostatin clearance in vivo was assessed by comparing non pH-dependent anti-latent myostatin antibody (MS1032LO00-SG1) and pH-dependent anti-latent myostatin antibodies with Fc engineering (MS1032LO06-SG1012, MS1032LO06-SG1016, MS1032LO06-SG1029, MS1032LO06-SG1031, MS1032LO06-SG1033, MS1032LO06-SG1034). (B) The effect of Fc engineering on myostatin clearance in vivo was assessed by comparing anti-latent myostatin antibodies (MS1032LO19-SG1079, MS1032LO19-SG1071, MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081, and MS1032LO19-SG1077).

[fig.23A]Figure 23A illustrates the time course of total myostatin concentration in

plasma after intravenous administration of an anti-myostatin antibody with a pI-increased Fc variant in human FcRn transgenic mice, as described in Example 26. The effects of pI-increased Fc variants on antigen elimination were evaluated.

[fig.23B]Figure 23B illustrates the time course of antibody concentration in plasma after intravenous administration of an anti-myostatin antibody with a pI-increased Fc variant in human FcRn transgenic mice, as described in Example 26. The effects of pI-increased Fc variants on antibody pharmacokinetics were evaluated.

[fig.24A]Figure 24A illustrates the time course of total myostatin concentration in plasma after intravenous administration of an anti-myostatin antibody with a pI-increased Fc variant in human FcRn transgenic mice, as described in Example 26. The effects of pI-increased Fc variants on antigen elimination were evaluated. In this assay, an excess of human normal immunoglobulin were co-administered with the anti-myostatin antibody in order to mimic the situation of human plasma.

[fig.24B]Figure 24B illustrates the time course of antibody concentration in plasma after intravenous administration of an anti-myostatin antibody with a pI-increased Fc variant in human FcRn transgenic mice, as described in Example 26. The effects of pI-increased Fc variants on antibody pharmacokinetics were evaluated. In this assay, an excess of human normal immunoglobulin were co-administered with the anti-myostatin antibody in order to mimic the situation of human plasma.

[fig.25]Figure 25 illustrates the time course of total myostatin concentration in plasma after intravenous administration of an anti-myostatin antibody with an Fc gamma RIIb-enhanced Fc variant in human Fc gamma RIIb transgenic mice, as described in Example 27. The effects of Fc gamma RIIb-enhanced Fc variants on antigen elimination through human Fc gamma RIIb were evaluated.

[fig.26]Figure 26 illustrates the time course of antibody concentration in plasma after intravenous administration of an anti-myostatin antibody with an Fc gamma RIIb-enhanced Fc variant in human Fc gamma RIIb transgenic mice, as described in Example 27. The effects of Fc gamma RIIb-enhanced Fc variants on antibody pharmacokinetics were evaluated.

[fig.27]Figure 27 illustrates results of cell imaging analysis of anti-myostatin antibodies with an Fc gamma RIIb-enhanced Fc variant, as described in Example 29. Each antibody was complexed with fluorescence-labelled myostatin and intracellular uptake of the antigen-antibody complex into cells expressing human Fc gamma RIIb was measured.

Description of Embodiments

[0069] The techniques and procedures described or referenced herein are generally well understood and commonly employed using conventional methodology by those skilled in

the art, such as, for example, the widely utilized methodologies described in Sambrook et al., *Molecular Cloning: A Laboratory Manual* 3d edition (2001) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (F.M. Ausubel, et al., eds., (2003)); the series *Methods in Enzymology* (Academic Press, Inc.): *PCR 2: A Practical Approach* (M.J. MacPherson, B.D. Hames and G.R. Taylor eds. (1995)), Harlow and Lane, eds. (1988) *Antibodies, A Laboratory Manual*, and *Animal Cell Culture* (R.I. Freshney, ed. (1987)); *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; *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); *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); and *Cancer: Principles and Practice of Oncology* (V.T. DeVita et al., eds., J.B. Lippincott Company, 1993).

[0070] I. DEFINITIONS

Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton et al., *Dictionary of Microbiology and Molecular Biology* 2nd ed., J. Wiley & Sons (New York, N.Y. 1994), and March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure* 4th ed., John Wiley & Sons (New York, N.Y. 1992), provide one skilled in the art with a general guide to many of the terms used in the present application. All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

[0071] For purposes of interpreting this specification, the following definitions will apply and whenever appropriate, terms used in the singular will also include the plural and vice versa. It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting. In the event that any definition set forth below conflicts with any document incorporated herein by

reference, the definition set forth below shall control.

[0072] An "acceptor human framework" for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0073] "Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0074] An "affinity matured" antibody refers to an antibody with one or more alterations in one or more hypervariable regions (HVRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

[0075] The terms "anti-myostatin antibody" and "an antibody that binds to myostatin" refer to an antibody that is capable of binding myostatin with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting myostatin. In one embodiment, the extent of binding of an anti-myostatin antibody to an unrelated, non-myostatin protein is less than about 10% of the binding of the antibody to myostatin as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to myostatin has a dissociation constant (Kd) of 1 micro M or less, 100 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, 0.01 nM or less, or 0.001 nM or less (e.g., 10^{-8} M or less, e.g., from 10^{-8} M to 10^{-13} M, e.g., from 10^{-9} M to 10^{-13} M). In certain embodiments, an anti myostatin antibody binds to an epitope of myostatin that is conserved among myostatin from different species.

[0076] The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal an-

tibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0077] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, F(ab')₂; diabodies; linear antibodies; single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments.

[0078] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay, and/or conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay. An exemplary competition assay is provided herein.

[0079] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0080] The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively.

[0081] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, adriamycin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed below.

[0082] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

[0083] An "effective amount" of an agent, e.g., a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired

therapeutic or prophylactic result.

[0084] The term "epitope" includes any determinant capable of being bound by an antibody. An epitope is a region of an antigen that is bound by an antibody that targets that antigen, and includes specific amino acids that directly contact the antibody. Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics. Generally, antibodies specific for a particular target antigen will preferentially recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules.

[0085] "Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. In some embodiments, an FcR is a native human FcR. In some embodiments, an FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc gamma RI, Fc gamma RII, and Fc gamma RIII subclasses, including allelic variants and alternatively spliced forms of those receptors. Fc gamma RII receptors include Fc gamma RIIA (an "activating receptor") and Fc gamma RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc gamma RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc gamma RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (See, e.g., Daeron, *Annu. Rev. Immunol.* 15:203-234 (1997).) FcRs are reviewed, for example, in Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991); Capel et al., *Immunomethods* 4:25-34 (1994); and de Haas et al., *J. Lab. Clin. Med.* 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein.

[0086] The term "Fc receptor" or "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)) and regulation of homeostasis of immunoglobulins. Methods of measuring binding to FcRn are known (see, e.g., Ghetie and Ward., *Immunol. Today* 18(12):592-598 (1997); Ghetie et al., *Nature Biotechnology* 15(7):637-640 (1997); Hinton et al., *J. Biol. Chem.* 279(8):6213-6216 (2004); WO 2004/92219 (Hinton et al.). Binding to human FcRn in vivo and serum half life of human FcRn high affinity binding polypeptides can be assayed, e.g., in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides with a variant Fc region are administered. WO 2000/42072 (Presta) describes antibody variants with improved or diminished binding to FcRs. See also, e.g., Shields et al., *J. Biol. Chem.* 9(2):6591-6604 (2001).

- [0087] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In one embodiment, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.
- [0088] The term "Fc region-comprising antibody" refers to an antibody that comprises an Fc region. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody. Accordingly, a composition comprising an antibody having an Fc region according to this invention can comprise an antibody with K447, with all K447 removed, or a mixture of antibodies with and without the K447 residue.
- [0089] "Framework" or "FR" refers to variable domain residues other than hypervariable region (HVR) residues. The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR and FR sequences generally appear in the following sequence in VH (or VL):
FR1-H1(L1)-FR2-H2(L2)-FR3-H3(L3)-FR4.
- [0090] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.
- [0091] A "functional Fc region" possesses an "effector function" of a native sequence Fc region. Exemplary "effector functions" include C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding domain (e.g., an antibody variable domain) and can be assessed using various assays as disclosed, for example, in definitions herein.
- [0092] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant

progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0093] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0094] A "human consensus framework" is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3. In one embodiment, for the VL, the subgroup is subgroup kappa I as in Kabat et al., *supra*. In one embodiment, for the VH, the subgroup is subgroup III as in Kabat et al., *supra*.

[0095] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0096] The term "hypervariable region" or "HVR" as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence ("complementarity determining regions" or "CDRs") and/or form structurally defined loops ("hypervariable loops") and/or contain the antigen-contacting residues ("antigen contacts"). Generally, antibodies comprise six HVRs: three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). Exemplary HVRs herein include: (a) hypervariable loops occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987)); (b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, NIH, Bethesda, MD (1991)); (c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al., *J. Mol. Biol.* 262:

732-745 (1996)); and (d) combinations of (a), (b), and/or (c), including HVR amino acid residues 46-56 (L2), 47-56 (L2), 48-56 (L2), 49-56 (L2), 26-35 (H1), 26-35b (H1), 49-65 (H2), 93-102 (H3), and 94-102 (H3).

- [0097] Unless otherwise indicated, HVR residues and other residues in the variable domain (e.g., FR residues) are numbered herein according to Kabat et al., *supra*.
- [0098] An "immunoconjugate" is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.
- [0099] An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual or subject is a human.
- [0100] An "isolated" antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, e.g., Flatman et al., *J. Chromatogr. B* 848:79-87 (2007).
- [0101] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.
- [0102] "Isolated nucleic acid encoding an anti-myostatin antibody" refers to one or more nucleic acid molecules encoding antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.
- [0103] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used

in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0104] A "naked antibody" refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical formulation.

[0105] "Native antibodies" refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain.

[0106] A "native sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

[0107] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0108] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any al-

gorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the US Copyright Office, Washington D.C., 20559, where it is registered under US Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0109] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows: 100 times the fraction X/Y; where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0110] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0111] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0112] The term "myostatin", as used herein, may refer to any native myostatin from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats). Unless otherwise indicated, the term "myostatin" refers to a human myostatin protein having the amino acid sequence shown in SEQ ID NO: 1 and containing the terminal propeptide domain of human myostatin as shown in SEQ ID NO: 75 or 78. The term encompasses "full-length", unprocessed myostatin as well as

any form of myostatin that results from processing in the cell. The term also encompasses naturally occurring variants of myostatin, e.g., splice variants or allelic variants. The amino acid sequence of an exemplary human myostatin (promyostatin) is shown in SEQ ID NO: 1. The amino acid sequence of an exemplary C-terminal growth factor domain of human myostatin is shown in SEQ ID NO: 2. The amino acid sequence of an exemplary N-terminal propeptide domain of human myostatin is shown in SEQ ID NO: 75 or 78. Active mature myostatin is a disulfide-bonded homodimer consisting of two C-terminal growth factor domains. Inactive latent myostatin is a non-covalently-associated complex of two propeptides and the mature myostatin. As disclosed herein, the antibodies of the invention bind inactive latent myostatin, but do not bind the mature active myostatin homodimer. In some embodiments, the antibodies of the invention bind an epitope within a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO:78), but do not bind the mature active myostatin homodimer. The amino acid sequence of an exemplary cynomolgus monkey and murine myostatin (promyostatin) are shown in SEQ ID NO: 3 and 5, respectively. The amino acid sequence of an exemplary C-terminal growth factor domain of cynomolgus monkey and murine myostatin are shown in SEQ ID NO: 4 and 6, respectively. The amino acid sequence of an exemplary N-terminal propeptide domain of cynomolgus monkey and murine myostatin are shown in SEQ ID NO: 76 or 79, and 77 or 80, respectively. GDF-11 (BMP-11) is a closely related molecule to myostatin, both of which are members of TGF-beta superfamily. Similarly to myostatin, GDF11 is synthesized as a precursor polypeptide first, and then cleaved into an N-terminal prodomain and C-terminal mature GDF11. The amino acid sequence of human GDF11 (precursor) is shown in SEQ ID NO: 81. The amino acid sequence of C-terminal mature human GDF11 is shown in SEQ ID NO: 82. The amino acid sequence of an N-terminal prodomain of human GDF11 is shown in SEQ ID NO: 83 or 84. Amino acid sequences of SEQ ID NOS: 1, 3, 5, 78, 79, 80, 81, and 84 include a signal sequence. Amino acids 1-24 of them correspond to it and they are removed during processing in the cell.

[0113] As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to

slow the progression of a disease.

[0114] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al., *Kuby Immunology*, 6th ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991).

[0115] A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification (alteration), preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g., from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

[0116] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors".

[0117] II. COMPOSITIONS AND METHODS

In one aspect, the invention is based, in part, on anti-myostatin antibodies and uses thereof. In certain embodiments, antibodies that bind to myostatin are provided. Antibodies of the invention are useful, e.g., for the diagnosis or treatment of a disease.

[0118] In another aspect, the invention is based, in part, on polypeptides comprising variant Fc regions and uses thereof. In one embodiment, polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity are provided. In another embodiment, polypeptides comprising variant Fc regions with increased pI are provided. In particular embodiments, the polypeptides of the invention are antibodies.

Polypeptides comprising a variant Fc region of the invention are useful, e.g., for the diagnosis or treatment of diseases.

[0119] A. Exemplary Anti-myostatin Antibodies and Polypeptides comprising variant Fc regions

In one aspect, the invention provides isolated antibodies that bind to myostatin. In certain embodiments, an anti-myostatin antibody of the present invention binds to latent myostatin. In further embodiments, an anti-myostatin antibody of the present invention binds to the myostatin propeptide (human: SEQ ID NO: 75 or 78; cynomolgus monkey: SEQ ID NO: 76 or 79; mouse: SEQ ID NO: 77 or 80). In further embodiments, the antibody binds to an epitope within a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78). Propeptide is contained in latent myostatin as one of the components, as described above. In certain embodiments, an anti-myostatin antibody of the present invention inhibits activation of myostatin. In certain embodiments, the anti-myostatin antibody blocks the release of mature myostatin from latent myostatin. It has been reported that mature myostatin is released via proteolytic and non-proteolytic processes from latent myostatin. The anti-myostatin antibody of the present invention may block the proteolytic and/or non-proteolytic release of mature myostatin from latent myostatin. In certain embodiments, the anti-myostatin antibody blocks the proteolytic cleavage of latent myostatin. In certain embodiments, the anti-myostatin antibody blocks access of a protease to latent myostatin (especially, to the proteolytic cleavage site (Arg98-Asp99) of latent myostatin). In further embodiments, the protease may be a BMP1/TLD family metalloprotease such as BMP1, TED, tolloid-like protein-1 (TLL-1), or tolloid-like protein-2 (TLL-2). In another embodiment, the anti-myostatin antibody blocks the non-proteolytic release of mature myostatin from latent myostatin. The non-proteolytic release as used herein means a spontaneous release of mature myostatin from latent myostatin, which is not accompanied by the proteolytic cleavage of latent myostatin. The non-proteolytic release includes, for example, a release of mature myostatin by incubating latent myostatin e.g., at 37 degrees C in the absence of a protease that cleaves the latent myostatin. In certain embodiments, the anti-myostatin antibody of the present invention does not bind to mature myostatin. In some embodiments, the anti-myostatin antibody binds to the same epitope as an antibody described in Table 2a. In some embodiments, the anti-myostatin antibody competes for binding latent myostatin with an antibody described in Table 2a. In additional embodiments, an anti-myostatin antibody competes for binding latent myostatin with an antibody comprising a VH and VL pair described in Table 2a. In some embodiments, the anti-myostatin antibody competes for binding a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78) with an antibody described in Table 2a. In further em-

bodiments, the anti-myostatin antibody binds to the same epitope as an antibody described in Table 11a or 13. In some embodiments, the anti-myostatin antibody competes for binding latent myostatin with an antibody described in Table 11a or 13. In some embodiments, the anti-myostatin antibody competes for binding a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78) with an antibody described in Table 11a or 13.

[0120] In some embodiments, an anti-myostatin antibody of the present invention binds to latent myostatin and inhibits the activation of myostatin. In further embodiments, the antibody: (a) blocks the release of mature myostatin from latent myostatin; (b) blocks the proteolytic release of mature myostatin; (c) blocks the spontaneous release of mature myostatin; or (d) does not bind to mature myostatin; or binds to an epitope within a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78). In further embodiments, the antibody competes for binding latent myostatin with, or binds the same epitope as, an antibody comprising a VH and VL pair described in Tables 2a, 11a, or 13. In further embodiments, the antibody binds to latent myostatin with higher affinity at neutral pH (e.g., pH7.4) than at acidic pH (e.g., pH5.8). In further embodiments, the antibody is (a) a monoclonal antibody, (b) a human, humanized, or chimeric antibody; (c) a full length IgG antibody or (d) an antibody fragment that binds to latent myostatin or myostatin propeptide.

[0121] In another embodiment, an anti-myostatin antibody of the present invention does not bind to GDF11. In certain embodiments, an anti-myostatin antibody of the present invention does not inhibit activation of GDF11. In certain embodiments, the anti-myostatin antibody does not block the release of mature GDF11 from latent GDF11. The anti-myostatin antibody of the present invention does not block either proteolytic or non-proteolytic release of mature GDF11 from latent GDF11. In certain embodiments, the anti-myostatin antibody does not block the proteolytic cleavage of latent GDF11. In certain embodiments, the anti-myostatin antibody does not block access of a protease to latent GDF11 (especially, to the proteolytic cleavage site of latent GDF11). In further embodiments, the protease may be a BMP1/TLD family metalloprotease such as BMP1, TED, tolloid-like protein-1 (TLL-1), or tolloid-like protein-2 (TLL-2). The non-proteolytic release as used herein means a spontaneous release of mature GDF11 from latent GDF11, which is not accompanied by the proteolytic cleavage of latent GDF11. The non-proteolytic release includes, for example, a release of mature GDF11 by incubating latent GDF11 e.g., at 37 degrees C in the absence of a protease that cleaves the latent GDF11. Most of the anti-myostatin antibodies known to date were not specific for myostatin. These antibodies have high affinity for other members of the TGF-beta superfamily, such as GDF11 and neutralize the biological activities of them. GDF11 plays an important role during em-

bryogenesis, and is responsible for homeotic transformation of the axial skeleton. Homozygous GDF11 knockout mice are perinatal lethal, mice with one wild type copy of the GDF11 gene are viable but have skeletal defects. Since GDF11 plays an important role during embryogenesis, an antagonist that inhibits GDF11 poses theoretical safety risks that could present either as toxicity in treated patients or as reproductive toxicity in, e.g., women of childbearing potential. Thus, there is a need for specific inhibition of myostatin activity in treatments of myostatin-associated disorders, particularly in women with childbearing potential.

[0122] In another aspect, the invention provides anti-myostatin antibodies that exhibit pH-dependent binding characteristics. As used herein, the expression "pH-dependent binding" means that the antibody exhibits "reduced binding to myostatin at acidic pH as compared to its binding at neutral pH" (for purposes of the present disclosure, both expressions may be used interchangeably). For example, antibodies "with pH-dependent binding characteristics" include antibodies that bind to myostatin with higher affinity at neutral pH than at acidic pH. In certain embodiments, the antibodies of the present invention bind to myostatin with at least 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or more times higher affinity at neutral pH than at acidic pH. In some embodiments, the antibodies bind to myostatin (e.g., latent myostatin or propeptide myostatin) with higher affinity at pH7.4 than at pH5.8. In further embodiments, the antibodies bind to myostatin with at least 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or more times higher affinity at pH7.4 than at pH5.8.

[0123] When an antigen is a soluble protein, the binding of an antibody to the antigen can result in an extended half-life of the antigen in plasma (i.e., reduced clearance of the antigen from plasma), since the antibody can have a longer half-life in plasma than the antigen itself and may serve as a carrier for the antigen. This is due to the recycling of the antigen-antibody complex by FcRn through the endosomal pathway in cell (Roopenian, *Nat. Rev. Immunol.* 7(9): 715-725 (2007)). However, an antibody with pH-dependent binding characteristics, which binds to its antigen in neutral extracellular environment while releasing the antigen into acidic endosomal compartments following its entry into cells, is expected to have superior properties in terms of antigen neutralization and clearance relative to its counterpart that binds in a pH-independent manner (Igawa et al., *Nature Biotechnol.* 28(11):1203-1207 (2010); Devanaboyina et al., *mAbs* 5(6):851-859 (2013); WO 2009/125825).

[0124] The "affinity" of an antibody for myostatin, for purposes of the present disclosure, is expressed in terms of the KD of the antibody. The KD of an antibody refers to the equilibrium dissociation constant of an antibody-antigen interaction. The greater the

KD value is for an antibody binding to its antigen, the weaker its binding affinity is for that particular antigen. Accordingly, as used herein, the expression "higher affinity at neutral pH than at acidic pH" (or the equivalent expression "pH-dependent binding") means that the KD of the antibody binding to myostatin at acidic pH is greater than the KD of the antibody binding to myostatin at neutral pH. For example, in the context of the present invention, an antibody is considered to bind to myostatin with higher affinity at neutral pH than at acidic pH if the KD of the antibody binding to myostatin at acidic pH is at least 2 times greater than the KD of the antibody binding to myostatin at neutral pH. Thus, the present invention includes antibodies that bind to myostatin at acidic pH with a KD that is at least 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or more times greater than the KD of the antibody binding to myostatin at neutral pH. In another embodiment, the KD value of the antibody at neutral pH can be 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less. In another embodiment, the KD value of the antibody at acidic pH can be 10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, or greater.

[0125] In further embodiments an antibody is considered to bind to myostatin (e.g., latent myostatin or propeptide myostatin) with a higher affinity at neutral pH than at acidic pH if the KD of the antibody binding to myostatin at pH5.8 is at least 2 times greater than the KD of the antibody binding to myostatin at pH7.4. In some embodiments the provided antibodies bind to myostatin at pH5.8 with a KD that is at least 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or more times greater than the KD of the antibody binding to myostatin at pH7.4. In another embodiment, the KD value of the antibody at pH7.4 can be 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less. In another embodiment, the KD value of the antibody at pH5.8 can be 10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, or greater.

[0126] The binding properties of an antibody for a particular antigen may also be expressed in terms of the kd of the antibody. The kd of an antibody refers to the dissociation rate constant of the antibody with respect to a particular antigen and is expressed in terms of reciprocal seconds (i.e., sec^{-1}). An increase in kd value signifies weaker binding of an antibody to its antigen. The present invention therefore includes antibodies that bind to myostatin with a higher kd value at acidic pH than at neutral pH. The present invention includes antibodies that bind to myostatin at acidic pH with a kd that is at least 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or more times greater than the kd of the antibody binding to myostatin at neutral pH. In another embodiment, the kd value of the antibody at neutral pH can be 10^{-2} 1/s, 10^{-3} 1/s, 10^{-4} 1/s, 10^{-5} 1/s, 10^{-6} 1/s, or less. In another embodiment, the kd value of the antibody at acidic pH can be 10^{-3} 1/s, 10^{-2} 1/s, 10^{-1} 1/s, or greater. The invention also includes antibodies that bind to myostatin (e.g., latent myostatin or

propeptide myostatin) with a higher k_d value at pH5.8 than at pH7.4. The invention includes antibodies that bind to myostatin at pH5.8 with a k_d that is at least 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or more times greater than the k_d of the antibody binding to myostatin at pH7.4. In another embodiment, the k_d value of the antibody at pH7.4 can be 10^{-2} 1/s, 10^{-3} 1/s, 10^{-4} 1/s, 10^{-5} 1/s, 10^{-6} 1/s, or less. In another embodiment, the k_d value of the antibody at pH5.8 can be 10^{-3} 1/s, 10^{-2} 1/s, 10^{-1} 1/s, or greater.

[0127] In certain instances, a "reduced binding to myostatin at acidic pH as compared to its binding at neutral pH" is expressed in terms of the ratio of the KD value of the antibody binding to myostatin at acidic pH to the KD value of the antibody binding to myostatin at neutral pH (or vice versa). For example, an antibody may be regarded as exhibiting "reduced binding to myostatin at acidic pH as compared to its binding at neutral pH", for purposes of the present invention, if the antibody exhibits an acidic/neutral KD ratio of 2 or greater. In certain embodiments, the pH5.8/pH7.4 KD ratio for an anti-myostatin antibody of the present invention is 2 or greater. In certain exemplary embodiments, the acidic/neutral KD ratio for an antibody of the present invention can be 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or greater. In another embodiment, the KD value of the antibody at neutral pH can be 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less. In another embodiment, the KD value of the antibody at acidic pH can be 10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, or greater. In further instances an antibody may be regarded as exhibiting "reduced binding to myostatin (e.g., latent myostatin) at acidic pH as compared to its binding at neutral pH", if the antibody exhibits an pH5.8/pH7.4 KD ratio of 2 or greater. In certain exemplary embodiments, the pH5.8/pH7.4 KD ratio for the antibody can be 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or greater. In another embodiment, the KD value of the antibody at pH7.4 can be 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, or less. In another embodiment, the KD value of the antibody at pH5.8 can be 10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, or greater.

[0128] In certain instances, a "reduced binding to myostatin at acidic pH as compared to its binding at neutral pH" is expressed in terms of the ratio of the k_d value of the antibody binding to myostatin at acidic pH to the k_d value of the antibody binding to myostatin at neutral pH (or vice versa). For example, an antibody may be regarded as exhibiting "reduced binding to myostatin at acidic pH as compared to its binding at neutral pH", for purposes of the present invention, if the antibody exhibits an acidic/neutral k_d ratio of 2 or greater. In certain exemplary embodiments, the pH5.8/pH7.4 k_d ratio for an antibody of the present invention is 2 or greater. In certain exemplary embodiments, the acidic/neutral k_d ratio for an antibody of the present invention can be 2, 3, 5, 10,

15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or greater. In another embodiment, the k_d value of the antibody at neutral pH can be 10^{-2} 1/s, 10^{-3} 1/s, 10^{-4} 1/s, 10^{-5} 1/s, 10^{-6} 1/s, or less. In another embodiment, the k_d value of the antibody at acidic pH can be 10^{-3} 1/s, 10^{-2} 1/s, 10^{-1} 1/s, or greater. In certain exemplary embodiments, the pH5.8/pH7.4 k_d ratio for an antibody of the present invention can be 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 400, 1000, 10000, or greater. In another embodiment, the k_d value of the antibody at pH7.4 can be 10^{-2} 1/s, 10^{-3} 1/s, 10^{-4} 1/s, 10^{-5} 1/s, 10^{-6} 1/s, or less. In another embodiment, the k_d value of the antibody at pH5.8 can be 10^{-3} 1/s, 10^{-2} 1/s, 10^{-1} 1/s, or greater.

[0129] As used herein, the expression "acidic pH" means a pH of 4.0 to 6.5. The expression "acidic pH" includes pH values of any one of 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, and 6.5. In particular aspects, the "acidic pH" is 5.8.

[0130] As used herein, the expression "neutral pH" means a pH of 6.7 to about 10.0. The expression "neutral pH" includes pH values of any one of 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, and 10.0. In particular aspects, the "neutral pH" is 7.4.

[0131] KD values, and k_d values, as expressed herein, may be determined using a surface plasmon resonance-based biosensor to characterize antibody-antigen interactions. (See, e.g., Example 7, herein.) KD values, and k_d values can be determined at 25 degrees C or 37 degrees C.

[0132] In certain embodiments, an anti-myostatin antibody of the present invention binds to myostatin from more than one species. In further embodiments, the anti-myostatin antibody binds to myostatin from a human and non-human animal. In further embodiments, the anti-myostatin antibody binds to myostatin from human, mouse, and monkey (e.g., cynomolgus, rhesus macaque, marmoset, chimpanzee, or baboon).

[0133] In certain embodiments, an anti-myostatin antibody of the present invention binds to latent myostatin from more than one species. In further embodiments, the anti-myostatin antibody binds to latent myostatin from a human and non-human animal. In further embodiments, the anti-myostatin antibody binds to latent myostatin from human, mouse, and monkey.

[0134] In certain embodiments, an anti-myostatin antibody of the present invention binds to propeptide myostatin from more than one species. In further embodiments, the anti-myostatin antibody binds to propeptide myostatin from a human and non-human animal. In further embodiments, the anti-myostatin antibody binds to propeptide myostatin from human, mouse, and monkey.

[0135] In a further aspect, the invention provides an anti-myostatin antibody that forms an

immune complex (i.e. antigen-antibody complex) with myostatin. In certain embodiments, two or more anti-myostatin antibodies bind to two or more myostatin molecules to form an immune complex. This is possible because myostatin exists as a homodimer containing two myostatin molecules while an antibody has two antigen-binding sites. The anti-myostatin antibody may bind to the same epitope on a myostatin molecule or may bind to different epitopes on a myostatin molecule, much like a bispecific antibody. Generally speaking, when two or more antibodies form an immune complex with two or more antigens, the resulting immune complex can strongly bind to Fc receptors existing on cell surfaces due to avidity effects through the Fc regions of the antibodies in the complex and can then be taken up into the cell with high efficiency. Thus, the above-mentioned anti-myostatin antibody capable of forming an immune complex containing two or more anti-myostatin antibodies and two or more myostatin molecules can lead to a rapid clearance of myostatin from plasma in a living body, via the strong binding to Fc receptors due to avidity effects.

[0136] Furthermore, an antibody with pH-dependent binding characteristics is thought to have superior properties in terms of antigen neutralization and clearance relative to its counterpart that binds in a pH-independent manner (Igawa et al., *Nature Biotech.* 28(11):1203-1207 (2010); Devanaboyina et al. *mAbs* 5(6):851-859 (2013); WO 2009/125825). Therefore, an antibody having both properties above, that is, an antibody which has pH-dependent binding characteristics and which forms an immune complex containing two or more antibodies with two or more antigens, is expected to have even more superior properties for highly accelerated elimination of antigens from plasma (WO 2013/081143).

[0137] In another aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114-115, 126; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124, 129; (e) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125, 130; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131.

[0138] In another aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69; (e) a HVR-L2 comprising

the amino acid sequence of any one of SEQ ID NOs: 70-72; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0139] In one aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six hypervariable regions (HVRs) selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 114-115; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 116-120; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 122-124; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 125; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0140] In another aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In another aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74.

[0141] In another aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 126; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 127; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 129; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 130; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131.

[0142] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114-115, 126; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128. In one embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128. In another em-

bodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128 and HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131. In a further embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128, HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131, and HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127. In a further embodiment, the antibody comprises (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114-115, 126; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127; and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128.

[0143] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60; and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64. In one embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64. In another embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64 and HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74. In a further embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, and HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60. In a further embodiment, the antibody comprises (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60; and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64.

[0144] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 114-115; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 116-120; and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121. In one embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121. In another embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121 and HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74. In a further embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121, HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, and HVR-H2

comprising the amino acid sequence of any one of SEQ ID NOs: 116-120. In a further embodiment, the antibody comprises (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 114-115; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 116-120; and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121.

[0145] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58; and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63. In one embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63. In another embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63 and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In a further embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63, HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74, and HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58. In a further embodiment, the antibody comprises (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58; and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63.

[0146] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 126; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 127; and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128. In one embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128. In another embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128 and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131. In a further embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128, HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131, and HVR-H2 comprising the amino acid sequence of SEQ ID NO: 127. In a further embodiment, the antibody comprises (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 126; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 127; and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128.

[0147] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124, 129; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125, 130; and

(c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124, 129; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125, 130; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131.

[0148] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0149] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 122-124; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 125; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 122-124; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 125; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0150] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (c) a

HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74.

[0151] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 129; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 130; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 129; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 130; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO 131.

[0152] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114,115,126 (ii) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127, and (iii) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124, 129, (ii) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125, 130 and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131.

[0153] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, (ii) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, and (iii) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, (ii) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0154] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 114-115, (ii) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 116-120, and (iii) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 122-124, (ii) a HVR-L2 comprising the amino acid sequence of SEQ

ID NO: 125, and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0155] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114, (ii) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58, and (iii) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122, (ii) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71, and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114, (ii) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58, and (iii) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123, (ii) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71, and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74.

[0156] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 126, (ii) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 127, and (iii) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 129, (ii) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 130, and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131.

[0157] In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114-115, 126; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124, 129; (e) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125, 130; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131.

[0158] In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114-115; (b) a

HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124; (e) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0159] In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 114-115; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 116-120; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 121; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 122-124; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 125; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0160] In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74.

[0161] In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 126; (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 127; (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 128; (d) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 129; (e) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 130; and (f) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131.

[0162] In certain embodiments, any one or more amino acids of an anti-myostatin antibody as provided above are substituted at the following HVR positions: (a) in HVR-H1 (SEQ ID NO: 55), at positions 1, and 2; (b) in HVR-H2 (SEQ ID NO: 58), at positions 4, 7, 8, 10, 11, 12, and 16; (c) in HVR-H3 (SEQ ID NO: 61), at positions 5, 7, and 11; (d) in HVR-L1 (SEQ ID NO: 65), at positions 1, 2, 5, 7, 8, and 9; (e) in HVR-L2 (SEQ ID NO: 70), at positions 3, and 7; and (f) in HVR-L3 (SEQ ID NO: 73), at position 8.

[0163] In certain embodiments, the one or more amino acid substitutions of an anti-

myostatin antibody are conservative substitutions, as provided herein. In certain embodiments, any one or more of the following substitutions may be made in any combination: (a) in HVR-H1 (SEQ ID NO: 55), S1H; Y2T, D, or E; (b) in HVR-H2 (SEQ ID NO: 58), Y4H; S7K; T8M or K; Y10K; A11M or E; S12E; G16K; (c) in HVR-H3 (SEQ ID NO: 61), Y5H; T7H; L11K; (d) in HVR-L1 (SEQ ID NO: 65), Q1T; S2T; S5E; Y7F; D8H; N9D or A or E; (e) in HVR-L2 (SEQ ID NO: 70), S3E; S7Y, F or W; and (f) in HVR-L3 (SEQ ID NO: 73), L8R.

[0164] All possible combinations of the above substitutions are encompassed by the consensus sequences of SEQ ID NOs: 126, 127, 128, 129, 130, and 131 for HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3, respectively.

[0165] In any of the above embodiments, an anti-myostatin antibody can be humanized. In one embodiment, an anti-myostatin antibody comprises HVRs as in any of the above embodiments, and further comprises an acceptor human framework, e.g., a human immunoglobulin framework or a human consensus framework. In another embodiment, an anti-myostatin antibody comprises HVRs as in any of the above embodiments, and further comprises a VH or VL comprising an FR sequence. In a further embodiment, the anti-myostatin antibody comprises the following heavy chain and/or light chain variable domain FR sequences: For the heavy chain variable domain, the FR1 comprises the amino acid sequence of any one of SEQ ID NOs: 132-134, FR2 comprises the amino acid sequence of any one of SEQ ID NOs: 135-136, FR3 comprises the amino acid sequence of SEQ ID NO: 137, FR4 comprises the amino acid sequence of SEQ ID NO: 138. For the light chain variable domain, FR1 comprises the amino acid sequence of SEQ ID NO: 139, FR2 comprises the amino acid sequence of any one of SEQ ID NOs: 140-141, FR3 comprises the amino acid sequence of any one of SEQ ID NOs: 142-143, FR4 comprises the amino acid sequence of SEQ ID NO: 144.

[0166] In one aspect, the invention provides an anti-myostatin antibody comprising at least one, two, three, four, five, or six HVRs selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 157-162; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 163-168; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 175-180; (e) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 181-186; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192.

[0167] In one aspect, the invention provides an antibody comprising at least one, at least two, or all three VH HVR sequences selected from (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 157-162; (b) a HVR-H2 comprising

the amino acid sequence of any one of SEQ ID NOs: 163-168; and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174. In one embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174. In another embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174 and HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192. In a further embodiment, the antibody comprises a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174, HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192, and a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 163-168. In a further embodiment, the antibody comprises (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 157-162; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 163-168; and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174.

[0168] In another aspect, the invention provides an antibody comprising at least one, at least two, or all three VL HVR sequences selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 175-180; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 181-186; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192. In one embodiment, the antibody comprises (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 175-180; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 181-186; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192.

[0169] In another aspect, an antibody of the invention comprises (a) a VH domain comprising at least one, at least two, or all three VH HVR sequences selected from (i) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 157-162, (ii) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 163-168, and (iii) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174; and (b) a VL domain comprising at least one, at least two, or all three VL HVR sequences selected from (i) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 175-180, (ii) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 181-186, and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192.

[0170] In another aspect, the invention provides an antibody comprising (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 157-162; (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 163-168; (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 169-174; (d) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs:

175-180; (e) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 181-186; and (f) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 187-192.

[0171] In another aspect, an anti-myostatin antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 13, 16-30, and 32-34. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in any one of SEQ ID NOs: 13, 16-30, and 32-34, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64.

[0172] In another aspect, an anti-myostatin antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, 114-115, 126, (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, 116-120, 127, and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64, 121, 128.

[0173] In another aspect, an anti-myostatin antibody comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 13, 16-30, 32, 33, and 34. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 13, 16-30, 32, 33 and 34. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in any one of SEQ ID NOs: 13, 16-30, 32, 33, and 34, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55-57, (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58-60, and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61-64.

[0174] In another aspect, an anti-myostatin antibody comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 86-95. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 86-95. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in any one of SEQ ID NOs: 86-95, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 114-115, 126, (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 116-120, 127, and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 121, 128.

[0175] In another aspect, an anti-myostatin antibody comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 86. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%

identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 86. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in SEQ ID NO: 86, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114, (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58, and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63. In another aspect, an anti-myostatin antibody comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 92. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 92. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in SEQ ID NO: 92, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of SEQ ID NO: 114, (b) a HVR-H2 comprising the amino acid sequence of SEQ ID NO: 58, and (c) a HVR-H3 comprising the amino acid sequence of SEQ ID NO: 63.

[0176] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VL having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 15, 31, 35-38, and 96-99. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 15, 31, 35-38, and 96-99. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VL sequence in any one of SEQ ID NOs: 15, 31, 35-38, and

96-99, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69, 122-124, 129; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72, 125, 130; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74, 131.

[0177] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VL having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 15, 31, 35, 36, 37, and 38. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 15, 31, 35, 36, 37, and 38. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VL sequence in any one of SEQ ID NOs: 15, 31, 35, 36, 37, and 38, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65-69; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70-72; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73-74.

[0178] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VL having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 96-99. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 96-99. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs. Optionally, the anti-myostatin antibody comprises the VL sequence in any one of SEQ ID NOs: 96-99, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 122-124, 129; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs:

125, 130; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 131.

[0179] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VL having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 96. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 96. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs. Optionally, the anti-myostatin antibody comprises the VL sequence in SEQ ID NO: 96, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 122; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74. In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VL having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 97. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 97. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs. Optionally, the anti-myostatin antibody comprises the VL sequence in SEQ ID NO: 97, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) a HVR-L1 comprising the amino acid sequence of SEQ ID NO: 123; (b) a HVR-L2 comprising the amino acid sequence of SEQ ID NO: 71; and (c) a HVR-L3 comprising the amino acid sequence of SEQ ID NO: 74.

[0180] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 13, 16-30, 32-34, and 86-95 and any one of SEQ ID NOs: 15, 31, 35-38, and 96-99, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 13, 16-30, 32-34, and

86-95 and any one of SEQ ID NOs: 15, 31, 35-38, and 96-99, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 86-95 and any one of SEQ ID NOs: 96-99, respectively, including post-translational modifications of those sequences.

[0181] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 13, 16-30, and 32-34 and any one of SEQ ID NOs: 15, 31, and 35-38, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 13, 16-30, and 32-34 and any one of SEQ ID NOs: 15, 31, and 35-38, respectively, including post-translational modifications of those sequences.

[0182] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 86-95 and any one of SEQ ID NOs: 96-99, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 86-95 and any one of SEQ ID NOs: 96-99, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 86-95 and any one of SEQ ID NOs: 96-99, respectively, including post-translational modifications of those sequences. In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO: 86 and SEQ ID NO: 96, respectively, including post-translational modifications of those sequences. In one embodiment, the antibody comprises the VH and VL sequences in SEQ ID NO: 92 and SEQ ID NO: 97, respectively, including post-translational modifications of those sequences.

[0183] In another aspect, an anti-myostatin antibody comprises a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 12, 145-150. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain em-

bodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 12, 145-150. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VH sequence in any one of SEQ ID NOs: 12, 145-150, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) a HVR-H1 comprising the amino acid sequence of any one of SEQ ID NOs: 55, 157-162, (b) a HVR-H2 comprising the amino acid sequence of any one of SEQ ID NOs: 58, 163-168, and (c) a HVR-H3 comprising the amino acid sequence of any one of SEQ ID NOs: 61, 169-174.

[0184] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a light chain variable domain (VL) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 14, 151-156. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-myostatin antibody comprising that sequence retains the ability to bind to myostatin. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in any one of SEQ ID NOs: 14, 151-156. In certain embodiments, the substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-myostatin antibody comprises the VL sequence in any one of SEQ ID NOs: 14, 151-156, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from (a) a HVR-L1 comprising the amino acid sequence of any one of SEQ ID NOs: 65, 175-180; (b) a HVR-L2 comprising the amino acid sequence of any one of SEQ ID NOs: 70, 181-186; and (c) a HVR-L3 comprising the amino acid sequence of any one of SEQ ID NOs: 73, 187-192.

[0185] In another aspect, an anti-myostatin antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In one embodiment, the antibody comprises the VH and VL sequences in any one of SEQ ID NOs: 12, 145-150 and any one of SEQ ID NOs: 14, 151-156, respectively, including post-translational modifications of those sequences.

[0186] In certain embodiments, an anti-myostatin antibody of the present invention comprises a VH as in any of the embodiments provided above and a heavy chain constant region comprising the amino acid sequence of any one of SEQ ID NOs: 7, 9, 11, 193, 195-198, 227, 228, 229-381. In certain embodiments, an anti-myostatin

antibody of the present invention comprises a VL as in any of the embodiments provided above, and a light chain constant region comprising the amino acid sequence of any one of SEQ ID NOs: 8 and 10.

[0187] In a further aspect, the invention provides an antibody that binds to the same epitope as an anti-myostatin antibody provided herein. In a further aspect, the invention provides an antibody that binds to the same epitope as an antibody described in Table 2a. In a further aspect, the invention provides an antibody that binds to the same epitope as an antibody described in Tables 11a or 13. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of myostatin propeptide consisting of amino acids 21-100 of SEQ ID NO: 78. Alternatively, the antibody binds a myostatin propeptide fragment consisting of amino acids 21-80, 41-100, 21-60, 41-80, 61-100, 21-40, 41-60, 61-80, or 81-100, of SEQ ID NO: 78.

[0188] In a further aspect of the invention, an anti-myostatin antibody according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human antibody. In one embodiment, an anti-myostatin antibody is an antibody fragment, e.g., a Fv, Fab, Fab', scFv, diabody, or F(ab')₂ fragment. In another embodiment, the antibody is a full length IgG antibody, e.g., an intact IgG1 or IgG4 antibody or other antibody class or isotype as defined herein.

[0189] In a further aspect, an anti-myostatin antibody according to any of the above embodiments may incorporate any of the features, singly or in combination, as described in Sections 1-7 below.

[0190] 1. Antibody Affinity

In certain embodiments, an antibody provided herein has a dissociation constant (K_d) of 1 micro M or less, 100 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, 0.01 nM or less, or 0.001 nM or less (e.g., 10⁻⁸ M or less, e.g., from 10⁻⁸ M to 10⁻¹³ M, e.g., from 10⁻⁹ M to 10⁻¹³ M).

[0191] In one embodiment, K_d is measured by a radiolabeled antigen binding assay (RIA). In one embodiment, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (¹²⁵I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen et al., J. Mol. Biol. 293:865-881 (1999)). To establish conditions for the assay, MICROTITER (registered trademark) multi-well plates (Thermo Scientific) are coated overnight with 5 micro g/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH9.6), and subsequently blocked with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23 degrees C). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [¹²⁵I]-antigen are mixed with serial dilutions of a

Fab of interest (e.g., consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta et al., *Cancer Res.* 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (e.g., about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (e.g., for one hour). The solution is then removed and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20 (registered trademark)) in PBS. When the plates have dried, 150 micro l/well of scintillant (MICROSCINT-20™; Packard) is added, and the plates are counted on a TOPCOUNT™ gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

[0192] According to another embodiment, K_d is measured using a BIACORE (registered trademark) surface plasmon resonance assay. For example, an assay using a BIACORE (registered trademark)-2000 or a BIACORE (registered trademark)-3000 (BIACORE (registered trademark), Inc., Piscataway, NJ) is performed at 25 degrees C with immobilized antigen CM5 chips at ~10 response units (RU). In one embodiment, carboxymethylated dextran biosensor chips (CM5, BIACORE (registered trademark), Inc.) are activated with N-ethyl-N'- (3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH4.8, to 5 micro g/ml (~0.2 micro M) before injection at a flow rate of 5 micro l/minute to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetic measurements, two-fold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20™) surfactant (PBST) at 25 degrees C at a flow rate of approximately 25 micro l/min. Association rates (k_{on}) and dissociation rates (k_{off}) are calculated using a simple one-to-one Langmuir binding model (BIACORE (registered trademark) Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (K_d) is calculated as the ratio k_{off}/k_{on} . See, e.g., Chen et al., *J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds $10^6 \text{ M}^{-1} \text{ s}^{-1}$ by the surface plasmon resonance assay above, then the on-rate can be determined using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation = 295 nm; emission = 340 nm, 16 nm band-pass) at 25 degrees C of a 20 nM anti-antigen antibody (Fab form) in PBS, pH7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophotometer (Aviv Instruments) or a 8000-series SLM-AMINCO™ spectrophotometer (ThermoSpectronic) with a stirred cuvette.

[0193] 2. Antibody Fragments

In certain embodiments, an antibody provided herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, F(ab')₂, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al. *Nat. Med.* 9:129-134 (2003). For a review of scFv fragments, see, e.g., Pluckthun, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also, WO 1993/16185; and US Patent Nos. 5,571,894 and 5,587,458. For discussion of Fab and F(ab')₂ fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see US Patent No. 5,869,046.

[0194] Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., *Nat. Med.* 9:129-134 (2003); and Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., *Nat. Med.* 9:129-134 (2003).

[0195] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; see, e.g., US Patent No. 6,248,516).

[0196] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g., *E. coli* or phage), as described herein.

[0197] 3. Chimeric and Humanized Antibodies

In certain embodiments, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, e.g., in US Patent No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[0198] In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which HVRs, e.g., CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some

embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the HVR residues are derived), e.g., to restore or improve antibody specificity or affinity.

- [0199] Humanized antibodies and methods of making them are reviewed, e.g., in Almagro, *Front. Biosci.* 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); US Patent Nos. 5, 821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing "resurfacing"); Dall'Acqua et al., *Methods* 36:43-60 (2005) (describing "FR shuffling"); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).
- [0200] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, e.g., Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al., *Proc. Natl. Acad. Sci. USA* 89:4285 (1992); and Presta et al. *J. Immunol.* 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).
- [0201] 4. Human Antibodies
- In certain embodiments, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5:368-374 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).
- [0202] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, *Nat. Biotech.* 23:1117-1125 (2005). See also, e.g., US Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; US Patent No. 5,770,429 describing HuMab

(registered trademark) technology; US Patent No. 7,041,870 describing K-M MOUSE (registered trademark) technology, and US Patent Application Publication No. US 2007/0061900, describing VelociMouse (registered trademark) technology). Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

[0203] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor *J. Immunol.*, 133:3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., *J. Immunol.* 147:86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., *Proc. Natl. Acad. Sci. USA* 103:3557-3562 (2006). Additional methods include those described, for example, in US Patent No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyixue* 26(4):265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology* 20(3):927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clinical Pharmacology* 27(3):185-191 (2005).

[0204] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

[0205] 5. Library-Derived Antibodies

Antibodies of the invention may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. For example, a variety of methods are known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (2000); O'Brien et al., ed., Human Press, Totowa, NJ, 2001) and further described, e.g., in the Mc-Cafferty et al., *Nature* 348:552-554; Clackson et al., *Nature* 352:624-628 (1991); Marks et al., *J. Mol. Biol.* 222:581-597 (1992); Marks and Bradbury, in *Methods in Molecular Biology* 248:161-175 (Lo, ed., Human Press, Totowa, NJ, 2003); Sidhu et al., *J. Mol. Biol.* 338(2):299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5):1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34):12467-12472 (2004); and Lee et al., *J. Immunol. Methods* 284(1-2): 119-132 (2004).

[0206] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage

libraries, which can then be screened for antigen-binding phage as described in Winter et al., *Ann. Rev. Immunol.* 12:433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al., *EMBO J.* 12:725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement in vitro, as described by Hoogenboom and Winter, *J. Mol. Biol.* 227:381-388 (1992). Patent publications describing human antibody phage libraries include, for example: US Patent No. 5,750,373, and US Publ. Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360.

[0207] Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

[0208] 6. Multispecific Antibodies

In certain embodiments, an antibody provided herein is a multispecific antibody, e.g., a bispecific antibody. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In certain embodiments, one of the binding specificities is for myostatin and the other is for any other antigen. In certain embodiments, bispecific antibodies may bind to two different epitopes of myostatin. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express myostatin. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.

[0209] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see, Milstein and Cuello, *Nature* 305:537 (1983)), WO 1993/08829, and Traunecker et al., *EMBO J.* 10: 3655 (1991)), and "knob-in-hole" engineering (see, e.g., US Patent No. 5,731,168). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/089004A1); cross-linking two or more antibodies or fragments (see, e.g., US Patent No. 4,676,980, and Brennan et al., *Science*, 229:81 (1985)); using leucine zippers to produce bi-specific antibodies (see, e.g., Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (see, e.g., Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see, e.g., Gruber et al.,

J. Immunol. 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al., J. Immunol. 147:60 (1991).

[0210] Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (see, e.g., US 2006/0025576A1).

[0211] The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising an antigen binding site that binds to myostatin as well as another, different antigen (see, US 2008/0069820, for example).

[0212] 7. Antibody Variants

In certain embodiments, amino acid sequence variants of the antibodies provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, e.g., antigen-binding.

[0213] a. Substitution, Insertion, and Deletion Variants

In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions." More substantial changes are provided in Table 1 under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, e.g., retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

[0214]

[Table 1]

Original Residue	Exemplary Substitutions	Preferred Substitution
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[0215] Amino acids may be grouped according to common side-chain properties: (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile; (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; (3) acidic: Asp, Glu; (4) basic: His, Lys, Arg; (5) residues that influence chain orientation: Gly, Pro; and (6) aromatic: Trp, Tyr, Phe. Non-conservative substitutions will entail exchanging a member of one of these groups for a member of another group.

[0216] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more HVR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (e.g., binding affinity).

[0217] Alterations (e.g., substitutions) may be made in HVRs, e.g., to improve antibody affinity. Such alterations may be made in HVR "hotspots," i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or residues that

contact antigen, with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (e.g., 4-6 residues at a time) are randomized. HVR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[0218] In certain embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may, for example, be outside of antigen contacting residues in the HVRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[0219] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells, *Science* 244:1081-1085 (1989). In this method, a residue or group of target residues (e.g., charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0220] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (e.g., for ADEPT) or a polypeptide which

increases the serum half-life of the antibody.

[0221] b. Glycosylation variants

In certain embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0222] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al., TIBTECH 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[0223] In one embodiment, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e. g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about +/- 3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, e.g., US Publ.Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO 2005/053742; WO 2002/031140; Okazaki et al., J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al., Biotech. Bioeng. 87:614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al., Arch. Biochem. Biophys. 249:533-545 (1986); US Pat Appl No US

2003/0157108 A1, Presta, L; and WO 2004/056312, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al., *Biotech. Bioeng.* 87:614 (2004); Kanda et al., *Biotechnol. Bioeng.* 94(4):680-688 (2006); and WO 2003/085107).

[0224] Antibodies variants are further provided with bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); US Patent No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

[0225] c. Fc region variants

In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

[0226] In certain embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody in vivo is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks Fc gamma R binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express Fc gamma RIII only, whereas monocytes express Fc gamma RI, Fc gamma RII and Fc gamma RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest is described in US Patent No. 5,500,362 (see, e.g., Hellstrom, et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); 5,821,337 (see Bruggemann, et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTI™ non-radioactive cytotoxicity

assay for flow cytometry (CellTechnology, Inc. Mountain View, CA); and CytoTox 96 (registered trademark) non-radioactive cytotoxicity assay (Promega, Madison, WI)). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in an animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al., *J. Immunol. Methods* 202:163 (1996); Cragg et al., *Blood* 101:1045-1052 (2003); and Cragg, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova et al., *Int'l. Immunol.* 18(12):1759-1769 (2006)).

- [0227] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (US Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).
- [0228] Certain antibody variants with improved or diminished binding to FcRs are described. (See, e.g., US Patent No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9(2): 6591-6604 (2001).)
- [0229] In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).
- [0230] In some embodiments, alterations are made in the Fc region that result in altered (i.e., either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in US Patent No. 6,194,551, WO 1999/51642, and Idusogie et al., *J. Immunol.* 164:4178-4184 (2000).
- [0231] Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434 (US Patent No. 7,371,826). See also, Duncan, *Nature* 322:738-40 (1988); US Patent Nos.

5,648,260 and 5,624,821; and WO 1994/29351 concerning other examples of Fc region variants.

[0232] d. Cysteine engineered antibody variants

In certain embodiments, it may be desirable to create cysteine engineered antibodies, e.g., "thioMAbs," in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, e.g., in US Patent No. 7,521,541.

[0233] e. Antibody Derivatives

In certain embodiments, an antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

[0234] In another embodiment, conjugates of an antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam et al., Proc. Natl. Acad. Sci. USA 102:11600-11605 (2005)). The radiation may be of any wavelength, and

includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

[0235] 8. Variant Fc regions

In one aspect, the invention provides an isolated polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity. In some aspects, the polypeptide is an antibody. In some aspects, the polypeptide is an Fc fusion protein. In certain embodiments, the variant Fc region comprises at least one amino acid residue alteration (e.g., substitution) compared to the corresponding sequence in the Fc region of a native or reference variant sequence (sometimes collectively referred to herein as a "parent" Fc region). In certain embodiments, the variant Fc region of the invention has enhanced binding activity for monkey Fc gamma RIIb compared to the parent Fc region. In particular embodiments, the monkey Fc gamma RIIb is cynomolgus monkey Fc gamma RIIb (SEQ ID NO: 223).

[0236] In certain embodiments, the ratio of [KD value of a parent Fc region for monkey Fc gamma RIIb]/[KD value of a variant Fc region for monkey Fc gamma RIIb] can be 2.0 or greater, 3.0 or greater, 4.0 or greater, 5.0 or greater, 6.0 or greater, 7.0 or greater, 8.0 or greater, 9.0 or greater, 10 or greater, 15 or greater, 20 or greater, 25 or greater, 30 or greater, 40 or greater, or 50 or greater. In further embodiments, the variant Fc region has decreased binding activity for monkey Fc gamma RIIIa. In certain embodiments, the ratio of [KD value of a parent Fc region for monkey Fc gamma RIIIa]/[KD value of a variant Fc region for monkey Fc gamma RIIIa] can be 0.50 or smaller, 0.40 or smaller, 0.30 or smaller, 0.20 or smaller, 0.10 or smaller, 0.09 or smaller, 0.08 or smaller, 0.07 or smaller, 0.06 or smaller, 0.05 or smaller, 0.04 or smaller, 0.03 or smaller, 0.02 or smaller, or 0.01 or smaller. In certain embodiments, the monkey Fc gamma RIIb has the sequence of SEQ ID NO:223 (cynomolgus monkey). In certain embodiments, the monkey Fc gamma RIIIa has the sequence of SEQ ID NO:224 (cynomolgus monkey).

[0237] In further embodiments, the variant Fc region has enhanced binding activity for human Fc gamma RIIb. In certain embodiments, the ratio of [KD value of a parent Fc region for human Fc gamma RIIb]/[KD value of a variant Fc region for human Fc gamma RIIb] can be 2.0 or greater, 3.0 or greater, 4.0 or greater, 5.0 or greater, 6.0 or greater, 7.0 or greater, 8.0 or greater, 9.0 or greater, 10 or greater, 15 or greater, 20 or greater, 25 or greater, 30 or greater, 40 or greater, or 50 or greater. In further embodiments, the variant Fc region has decreased binding activity for human Fc gamma RIIIa. In certain embodiments, the ratio of [KD value of a parent Fc region for human Fc gamma RIIIa]/[KD value of a variant Fc region for human Fc gamma RIIIa] can be 0.50 or smaller, 0.40 or smaller, 0.30 or smaller, 0.20 or smaller, 0.10 or smaller, 0.09

or smaller, 0.08 or smaller, 0.07 or smaller, 0.06 or smaller, 0.05 or smaller, 0.04 or smaller, 0.03 or smaller, 0.02 or smaller, or 0.01 or smaller. In certain embodiments, the human Fc gamma RIIb has the sequence of SEQ ID NOS:212, 213, or 214. In certain embodiments, the human Fc gamma RIIIa has the sequence of SEQ ID NO:215, 216, 217, or 218.

[0238] In further embodiments, the variant Fc region has decreased binding activity for human Fc gamma RIIa (type H). In certain embodiments, the ratio of [KD value of a parent Fc region for human Fc gamma RIIa (type H)]/[KD value of a variant Fc region for human Fc gamma RIIa (type H)] can be 5.0 or smaller, 4.0 or smaller, 3.0 or smaller, 2.0 or smaller, 1.0 or smaller, 0.9 or smaller, 0.8 or smaller, 0.7 or smaller, 0.6 or smaller, 0.5 or smaller, 0.4 or smaller, 0.3 or smaller, 0.2 or smaller, or 0.1 or smaller. In further embodiments, the variant Fc region has decreased binding activity for human Fc gamma RIIa (type R). In certain embodiments, the ratio of [KD value of a parent Fc region for human Fc gamma RIIa (type R)]/[KD value of a variant Fc region for human Fc gamma RIIa (type R)] can be 5.0 or smaller, 4.0 or smaller, 3.0 or smaller, 2.0 or smaller, 1.0 or smaller, 0.9 or smaller, 0.8 or smaller, 0.7 or smaller, 0.6 or smaller, 0.5 or smaller, 0.4 or smaller, 0.3 or smaller, 0.2 or smaller, or 0.1 or smaller. In certain embodiments, the human Fc gamma RIIa (type H) has the sequence of SEQ ID NO:211. In certain embodiments, the human Fc gamma RIIa (type R) has the sequence of SEQ ID NO:210.

[0239] In certain embodiments, the ratio of [KD value of a parent Fc region for monkey Fc gamma RIIa]/[KD value of a variant Fc region for monkey Fc gamma RIIa] can be 2.0 or greater, 3.0 or greater, 4.0 or greater, 5.0 or greater, 6.0 or greater, 7.0 or greater, 8.0 or greater, 9.0 or greater, 10 or greater, 15 or greater, 20 or greater, 25 or greater, 30 or greater, 40 or greater, or 50 or greater. In certain embodiments, monkey Fc gamma RIIa is selected from monkey Fc gamma RIIa1 (e.g., cynomolgus Fc gamma RIIa1 (SEQ ID NO:220)), monkey Fc gamma RIIa2 (e.g., cynomolgus Fc gamma RIIa2 (SEQ ID NO:221)), and monkey Fc gamma RIIa3 (e.g., cynomolgus Fc gamma RIIa3 (SEQ ID NO:222)).

[0240] In another embodiment, the KD value of the variant Fc region for monkey Fc gamma RIIb can be 1.0×10^{-6} M or smaller, 9.0×10^{-7} M or smaller, 8.0×10^{-7} M or smaller, 7.0×10^{-7} M or smaller, 6.0×10^{-7} M or smaller, 5.0×10^{-7} M or smaller, 4.0×10^{-7} M or smaller, 3.0×10^{-7} M or smaller, 2.0×10^{-7} M or smaller, or 1.0×10^{-7} M or smaller. In another embodiment, the KD value of the variant Fc region for monkey Fc gamma RIIIa can be 5.0×10^{-7} M or greater, 6.0×10^{-7} M or greater, 7.0×10^{-7} M or greater, 8.0×10^{-7} M or greater, 9.0×10^{-7} M or greater, 1.0×10^{-6} M or greater, 2.0×10^{-6} M or greater, 3.0×10^{-6} M or greater, 4.0×10^{-6} M or greater, 5.0×10^{-6} M or greater, 6.0×10^{-6} M or greater, 7.0×10^{-6} M or greater, 8.0×10^{-6} M or greater, 9.0×10^{-6} M or greater, or 1.0×10^{-5}

M or greater. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIb can be 2.0×10^{-6} M or smaller, 1.0×10^{-6} M or smaller, 9.0×10^{-7} M or smaller, 8.0×10^{-7} M or smaller, 7.0×10^{-7} M or smaller, 6.0×10^{-7} M or smaller, 5.0×10^{-7} M or smaller, 4.0×10^{-7} M or smaller, 3.0×10^{-7} M or smaller, 2.0×10^{-7} M or smaller, or 1.0×10^{-7} M or smaller. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIIa can be 1.0×10^{-6} M or greater, 2.0×10^{-6} M or greater, 3.0×10^{-6} M or greater, 4.0×10^{-6} M or greater, 5.0×10^{-6} M or greater, 6.0×10^{-6} M or greater, 7.0×10^{-6} M or greater, 8.0×10^{-6} M or greater, 9.0×10^{-6} M or greater, 1.0×10^{-5} M or greater, 2.0×10^{-5} M or greater, 3.0×10^{-5} M or greater, 4.0×10^{-5} M or greater, or 5.0×10^{-5} M or greater. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIa (type H) can be 1.0×10^{-7} M or greater, 2.0×10^{-7} M or greater, 3.0×10^{-7} M or greater, 4.0×10^{-7} M or greater, 5.0×10^{-7} M or greater, 6.0×10^{-7} M or greater, 7.0×10^{-7} M or greater, 8.0×10^{-7} M or greater, 9.0×10^{-7} M or greater, 1.0×10^{-6} M or greater, 2.0×10^{-6} M or greater, 3.0×10^{-6} M or greater, 4.0×10^{-6} M or greater, or 5.0×10^{-6} M or greater. In another embodiment, the KD value of the variant Fc region for human Fc gamma RIIa (type R) can be 2.0×10^{-7} M or greater, 3.0×10^{-7} M or greater, 4.0×10^{-7} M or greater, 5.0×10^{-7} M or greater, 6.0×10^{-7} M or greater, 7.0×10^{-7} M or greater, 8.0×10^{-7} M or greater, 9.0×10^{-7} M or greater, 1.0×10^{-6} M or greater, 2.0×10^{-6} M or greater, 3.0×10^{-6} M or greater, 4.0×10^{-6} M or greater, or 5.0×10^{-6} M or greater.

[0241] In another embodiment, the KD value of the variant Fc region for monkey Fc gamma RIIa can be 1.0×10^{-6} M or smaller, 9.0×10^{-7} M or smaller, 8.0×10^{-7} M or smaller, 7.0×10^{-7} M or smaller, 6.0×10^{-7} M or smaller, 5.0×10^{-7} M or smaller, 4.0×10^{-7} M or smaller, 3.0×10^{-7} M or smaller, 2.0×10^{-7} M or smaller, or 1.0×10^{-7} M or smaller. In certain embodiments, monkey Fc gamma RIIa can be selected from any one of monkey Fc gamma RIIa1, monkey Fc gamma RIIa2, and monkey Fc gamma RIIa3.

[0242] When we develop a pharmaceutical product for the treatment of human diseases, evaluation of its efficacy and safety in monkey are important because of its biological proximity to human. From such viewpoints, a pharmaceutical product to be developed is preferable to have cross-reactivity to both human and monkey in the target binding activity.

[0243] "Fc gamma receptors" (herein, referred to as Fc gamma receptors, Fc gamma R or FcγR) refers to receptors that may bind to the Fc region of IgG1, IgG2, IgG3, and IgG4 monoclonal antibodies, and practically means any member of the family of proteins encoded by the Fc gamma receptor genes. In humans, this family includes Fc gamma RI (CD64) including isoforms Fc gamma RIa, Fc gamma RIb, and Fc gamma RIc; Fc gamma RII (CD32) including isoforms Fc gamma RIIa (including allotypes H131 (type H) and R131 (type R)), Fc gamma RIIb (including Fc gamma RIIb-1 and Fc gamma RIIb-2), and Fc gamma RIIC; and Fc gamma RIII (CD16) including

isoforms Fc gamma RIIIa (including allotypes V158 and F158), and Fc gamma RIIIb (including allotypes Fc gamma RIIIb-NA1 and Fc gamma RIIIb-NA2), and any human Fc gamma Rs, Fc gamma R isoforms or allotypes yet to be discovered, but is not limited thereto. Fc gamma RIIb1 and Fc gamma RIIb2 have been reported as splicing variants of human Fc gamma RIIb. In addition, a splicing variant named Fc gamma RIIb3 has been reported (J Exp Med, 1989, 170: 1369-1385). In addition to these splicing variants, human Fc gamma RIIb includes all splicing variants registered in NCBI, which are NP_001002273.1, NP_001002274.1, NP_001002275.1, NP_001177757.1, and NP_003992.3. Furthermore, human Fc gamma RIIb includes every previously-reported genetic polymorphism, as well as Fc gamma RIIb (Arthritis Rheum. 48:3242-3252 (2003); Kono et al., Hum. Mol. Genet. 14:2881-2892 (2005); and Kyogoju et al., Arthritis Rheum. 46:1242-1254 (2002)), and every genetic polymorphism that will be reported in the future.

- [0244] In Fc gamma RIIa, there are two allotypes, one where the amino acid at position 131 of Fc gamma RIIa is histidine (type H) and the other where the amino acid at position 131 is substituted with arginine (type R) (Warrmerdam, J. Exp. Med. 172:19-25 (1990)).
- [0245] The Fc gamma R includes human, mouse, rat, rabbit, and monkey-derived Fc gamma Rs but is not limited thereto, and may be derived from any organism. Mouse Fc gamma Rs include Fc gamma RI (CD64), Fc gamma RII (CD32), Fc gamma RIII (CD16), and Fc gamma RIII-2 (CD16-2), and any mouse Fc gamma Rs, or Fc gamma R isoforms, but are not limited thereto. Unless otherwise specified, the term "monkey Fc gamma R" or variation thereof, refers to cynomolgus Fc gamma RIIa1 (SEQ ID NO:220), Fc gamma RIIa2 (SEQ ID NO:221), Fc gamma RIIa3 (SEQ ID NO:222), Fc gamma RIIb (SEQ ID NO:223), or Fc gamma RIIIaS (SEQ ID NO:224).
- [0246] The polynucleotide sequence of human Fc gamma RI is set forth in SEQ ID NO: 199 (NM_000566.3); the polynucleotide sequence of human Fc gamma RIIa is set forth in SEQ ID NO: 200 (BC020823.1) or SEQ ID NO:201 (NM_001136219.1); the polynucleotide sequence of human Fc gamma RIIb is set forth in SEQ ID NO: 202 (BC146678.1) or SEQ ID NO:203 (NM_004001.3); the polynucleotide sequence of human Fc gamma RIIIa is set forth in SEQ ID NO: 204 (BC033678.1) or SEQ ID NO:205 (NM_001127593.1); and the polynucleotide sequence of human Fc gamma RIIIb is set forth in SEQ ID NO: 206 (BC128562.1).
- [0247] The amino acid sequence of human Fc gamma RI is set forth in SEQ ID NO: 207 (NP_000557.1); the amino acid sequence of human Fc gamma RIIa is set forth in SEQ ID NO: 208 (AAH20823.1), SEQ ID NO:209, SEQ ID NO:210 or SEQ ID NO:211; the amino acid sequence of human Fc gamma RIIb is set forth in SEQ ID NO: 212 (AAI46679.1), SEQ ID NO: 213 or SEQ ID NO:214; the amino acid sequence of

human Fc gamma RIIIa is set forth in SEQ ID NO: 215 (AAH33678.1), SEQ ID NO:216, SEQ ID NO:217 or SEQ ID NO:218; and the amino acid sequence of human Fc gamma RIIIb is set forth in SEQ ID NO: 219 (AAI28563.1).

[0248] The amino acid sequence of cynomolgus monkey Fc gamma RIIa is set forth in SEQ ID NO: 220 (Fc gamma RIIa1), SEQ ID NO:221 (Fc gamma RIIa2) or SEQ ID NO:222 (Fc gamma RIIa3); the amino acid sequence of cynomolgus Fc gamma RIIb is set forth in SEQ ID NO: 223; and the amino acid sequence of cynomolgus monkey Fc gamma RIIIa is set forth in SEQ ID NO: 224.

[0249] In one aspect, the invention provides polypeptides containing variant Fc regions with enhanced Fc gamma RIIb-binding activity compared to a corresponding reference Fc gamma RIIb-binding polypeptide. In further aspects, the polypeptide of the invention comprises at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 236, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0250] In one aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity comprising at least two amino acid alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0251] In one aspect, the invention provides polypeptides comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity comprising an amino acid alteration at position 236 according to EU numbering.

[0252] In one aspect, the invention provides polypeptides comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity comprising at least two amino acid alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 235, 239, 268, 295, 298, 326, 330, and 396, according to EU numbering. In a further embodiment, the variant Fc region comprises an amino acid alteration of at least one position selected from the group consisting of: 231, 232, 235, 239, 268, 295, 298, 326, 330, and 396, according to EU numbering. In a further embodiment, the

variant Fc region comprises an amino acid alteration of at least one position selected from the group consisting of: 268, 295, 326, and 330, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0253] In another aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity comprising amino acid alterations of any one of the following (1)-(37): (1) positions 231, 236, 239, 268 and 330; (2) positions 231, 236, 239, 268, 295 and 330; (3) positions 231, 236, 268 and 330; (4) positions 231, 236, 268, 295 and 330; (5) positions 232, 236, 239, 268, 295 and 330; (6) positions 232, 236, 268, 295 and 330; (7) positions 232, 236, 268 and 330; (8) positions 235, 236, 268, 295, 326 and 330; (9) positions 235, 236, 268, 295 and 330; (10) positions 235, 236, 268 and 330; (11) positions 235, 236, 268, 330 and 396; (12) positions 235, 236, 268 and 396; (13) positions 236, 239, 268, 295, 298 and 330; (14) positions 236, 239, 268, 295, 326 and 330; (15) positions 236, 239, 268, 295 and 330; (16) positions 236, 239, 268, 298 and 330; (17) positions 236, 239, 268, 326 and 330; (18) positions 236, 239, 268 and 330; (19) positions 236, 239, 268, 330 and 396; (20) positions 236, 239, 268 and 396; (21) positions 236 and 268; (22) positions 236, 268 and 295; (23) positions 236, 268, 295, 298 and 330; (24) positions 236, 268, 295, 326 and 330; (25) positions 236, 268, 295, 326, 330 and 396; (26) positions 236, 268, 295 and 330; (27) positions 236, 268, 295, 330 and 396; (28) positions 236, 268, 298 and 330; (29) positions 236, 268, 298 and 396; (30) positions 236, 268, 326 and 330; (31) positions 236, 268, 326, 330 and 396; (32) positions 236, 268 and 330; (33) positions 236, 268, 330 and 396; (34) positions 236, 268 and 396; (35) positions 236 and 295; (36) positions 236, 330 and 396; and (37) positions 236 and 396, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0254] In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least one amino acid selected from the group consisting of: (a) Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 231; (b) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 232; (c) Asp at position 233; (d) Trp, Tyr at position 234; (e) Trp at position 235; (f) Ala, Asp, Glu, His, Ile, Leu, Met, Asn, Gln, Ser, Thr, Val at position 236; (g) Asp, Tyr at position 237; (h) Glu, Ile, Met, Gln, Tyr at position 238; (i) Ile, Leu, Asn, Pro, Val at position 239; (j) Ile at position 264; (k) Phe at position 266; (l) Ala, His, Leu at position 267; (m) Asp, Glu at position 268; (n)

Asp, Glu, Gly at position 271; (o) Leu at position 295; (p) Leu at position 298; (q) Glu, Phe, Ile, Leu at position 325; (r) Thr at position 326; (s) Ile, Asn at position 327; (t) Thr at position 328; (u) Lys, Arg at position 330; (v) Glu at position 331; (w) Asp at position 332; (x) Asp, Ile, Met, Val, Tyr at position 334; and (y) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 396; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0255] In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least one amino acid alteration (e.g., substitution) selected from the group consisting of: (a) Gly, Thr at position 231; (b) Asp at position 232; (c) Trp at position 235; (d) Asn, Thr at position 236; (e) Val at position 239; (f) Asp, Glu at position 268; (g) Leu at position 295; (h) Leu at position 298; (i) Thr at position 326; (j) Lys, Arg at position 330; and (k) Lys, Met at position 396; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asn at position 236, Glu at position 268, Lys at position 330, and Met at position 396; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asn at position 236, Asp at position 268, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asn at position 236, Asp at position 268, Leu at position 295, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Thr at position 236, Asp at position 268, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asn at position 236, Asp at position 268, Leu at position 295, Thr at position 326, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Trp at position 235, Asn at position 236, Asp at position 268, Leu at position 295, Thr at position 326, and Lys at position 330; according to EU numbering.

[0256] In one aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity comprising an amino acid alteration at position 238 according to EU numbering.

[0257] In one aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity comprising at least one amino acid alteration of at least one position selected from the group consisting of: 234, 238, 250, 264, 267, 307, and 330 according to EU numbering. In further embodiments, the polypeptide comprises at least one amino acid alteration of at least one position selected from the group consisting of: 234, 250, 264, 267, 307, and 330 according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0258] In another aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity comprising amino acid alterations of any one of the following (1)-(9): (1) positions 234, 238, 250, 307 and 330; (2) positions 234, 238, 250, 264, 307 and 330; (3) positions 234, 238, 250, 264, 267, 307 and 330; (4) positions 234, 238, 250, 267, 307 and 330; (5) positions 238, 250, 264, 307 and 330; (6) positions 238, 250, 264, 267, 307 and 330; (7) positions 238, 250, 267, 307 and 330; (8) positions 238, 250 and 307; and (9) positions 238, 250, 307 and 330, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0259] In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises at least one amino acid alteration (e.g., substitution) selected from the group consisting of: (a) Tyr at position 234; (b) Asp at position 238; (c) Val at position 250, (d) Ile at position 264; (e) Ala at position 267; (f) Pro at position 307; and (g) Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asp at position 238; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asp at position 238, Val at position 250, and Pro at position 307; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asp at position 238, Val at position 250, Pro at position 307, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asp at position 238, Val at position 250, Ile at position 264, Pro at position 307, and Lys at position 330; according to EU numbering. In a further em-

bodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asp at position 238, Val at position 250, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Tyr at position 234, Asp at position 238, Val at position 250, Pro at position 307, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Tyr at position 234, Asp at position 238, Val at position 250, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Asp at position 238, Val at position 250, Ile at position 264, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Tyr at position 234, Asp at position 238, Val at position 250, Ile at position 264, Pro at position 307, and Lys at position 330; according to EU numbering. In a further embodiment, the variant Fc region with enhanced Fc gamma RIIb-binding activity comprises amino acid alterations (e.g., substitutions) of: Tyr at position 234, Asp at position 238, Val at position 250, Ile at position 264, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0260] In another aspect, the invention provides isolated polypeptides comprising variant Fc regions with increased isoelectric point (pI). In certain embodiments, a variant Fc region described herein comprises at least two amino acid alterations in a parent Fc region. In certain embodiments, each of the amino acid alterations increases the isoelectric point (pI) of the variant Fc region compared with that of the parent Fc region. They are based on the findings that antigen elimination from plasma can be promoted with an antibody whose pI has been increased by modification of at least two amino acid residues, for example when the antibody is administered in vivo.

[0261] In the present invention, pI may be either a theoretical or an experimentally determined pI. The value of pI can be determined, for example, by isoelectric focusing known to those skilled in the art. The value of a theoretical pI can be calculated, for example, using gene and amino acid sequence analysis software (Genetyx, etc.).

[0262] In one embodiment, the pI value may be increased, for example, at least by 0.01,

0.03, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, or more, at least by 0.6, 0.7, 0.8, 0.9, or more, at least by 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, or more, or at least by 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 3.0 or more, as compared to before modification.

[0263] In certain embodiments, the amino acid for increased pI can be exposed on the surface of the variant Fc region. In the present invention, an amino acid that can be exposed on the surface generally refers to an amino acid residue located on the surface of a polypeptide constituting a variant Fc region. An amino acid residue located on the surface of a polypeptide refers to an amino acid residue whose side chain can be in contact with solvent molecules (which in general are mostly water molecules). However, the side chain does not necessarily have to be wholly in contact with solvent molecules, and when even a portion of the side chain is in contact with the solvent molecules, the amino acid is defined as an "amino acid residue located on the surface". The amino acid residues located on the surface of a polypeptide also include amino acid residues located close to the surface and thereby can have an electric charge influence from another amino acid residue whose side chain, even partly, is in contact with the solvent molecules. Those skilled in the art can prepare a homology model of a polypeptide for example, using commercially available softwares. Alternatively, it is possible to use methods known to those skilled in the art, such as X-ray crystallography. The amino acid residues that can be exposed on the surface are determined, for example, using coordinates from a three-dimensional model using a computer program such as InsightII program (Accelrys). Surface-exposable sites may be determined using algorithms known in the technical field (for example, Lee and Richards (J. Mol. Biol. 55:379-400 (1971)); Connolly (J. Appl. Cryst. 16:548-558 (1983))). Surface-exposable sites can be determined using software suitable for protein modeling and three-dimensional structure information. Software available for such purposes includes, for example, the SYBYL Biopolymer Module software (Tripos Associates). When an algorithm requires a user input size parameter, the "size" of a probe which is used in the calculation may be set to about 1.4 Angstrom or less in radius. Furthermore, methods for determining surface-exposable regions using software for personal computers have been described by Pacios (Comput. Chem. 18(4):377-386 (1994); J. Mol. Model. 1:46-53 (1995)). Based on such information as described above, appropriate amino acid residues located on the surface of a polypeptide that constitutes a variant Fc region can be selected.

[0264] In certain embodiments, a polypeptide comprises both the variant Fc region and an antigen-binding domain. In further embodiments, the antigen is a soluble antigen. In one embodiment, the antigen is present in biological fluids (for example, plasma, interstitial fluid, lymphatic fluid, ascitic fluid, and pleural fluid) of subjects. The antigen may also be a membrane antigen.

[0265] In further embodiments, antigen-binding activity of the antigen-binding domain changes according to ion concentration conditions. In one embodiment, ion concentration is not particularly limited and refers to hydrogen ion concentration (pH) or metal ion concentration. Herein, metal ions refer to ions of group I elements except hydrogen, such as alkaline metals and the copper group elements, group II elements such as alkaline earth metals and zinc group elements, group III elements except boron, group IV elements except carbon and silicon, group VIII elements such as iron group and platinum group elements, elements belonging to subgroup A of groups V, VI, and VII, and metal elements such as antimony, bismuth, and polonium. In the present invention, metal ions include, for example, calcium ion, as described in WO 2012/073992 and WO 2013/125667. In one embodiment, "ion concentration condition" may be a condition that focuses on differences in the biological behavior of an antigen-binding domain between a low ion concentration and a high ion concentration. Furthermore, "antigen-binding activity of an antigen-binding domain changes according to ion concentration conditions" means that the antigen-binding activity of an antigen-binding domain changes between a low ion concentration and a high ion concentration (such an antigen-binding domain is referred to herein as "ion concentration-dependent antigen-binding domain"). The antigen-binding activity of an antigen-binding domain under a high ion concentration condition may be higher (stronger) or lower (weaker) than that under a low ion concentration condition. In one embodiment, ion concentration-dependent antigen-binding domains (such as pH-dependent antigen-binding domains or calcium ion concentration-dependent antigen-binding domains) can be obtained by known methods, for example, described in WO 2009/125825, WO 2012/073992, and WO 2013/046722.

[0266] In the present invention, the antigen-binding activity of an antigen-binding domain under a high calcium ion concentration condition may be higher than under a low calcium ion concentration condition. The high calcium ion concentration is not particularly limited to but may be a concentration selected between 100 micro M and 10 mM, between 200 micro M and 5 mM, between 400 micro M and 3 mM, between 200 micro M and 2 mM, between 400 micro M and 1 mM, or between 500 micro M and 2.5 mM, which is preferable to be close to the plasma (blood) concentration of calcium ion in vivo. Meanwhile, the low calcium ion concentration is not particularly limited to but may be a concentration selected between 0.1 micro M and 30 micro M, between 0.2 micro M and 20 micro M, between 0.5 micro M and 10 micro M, between 1 micro M and 5 micro M, or between 2 micro M and 4 micro M, which is preferable to be close to the concentration of calcium ion in early endosomes in vivo.

[0267] In one embodiment, the ratio between the antigen-binding activities under a low calcium ion concentration condition and a high calcium ion concentration condition is

not limited but the ratio of the dissociation constant (KD) under a low calcium ion concentration condition to the KD under a high calcium ion concentration condition, i.e., $KD(\text{low calcium ion concentration condition})/KD(\text{high calcium ion concentration condition})$, is 2 or more, 10 or more, or 40 or more. The upper limit of the ratio may be 400, 1000, or 10000, as long as such an antigen-binding domain can be produced by techniques known to those skilled in the art. Alternatively, for example, the dissociation rate constant (kd) can be used instead of the KD. In this case, the ratio of the kd under a low calcium ion concentration condition to the kd under a high calcium ion concentration condition, i.e., $kd(\text{low calcium ion concentration condition})/kd(\text{high calcium ion concentration condition})$, is 2 or more, 5 or more, 10 or more, or 30 or more. The upper limit of the ratio may be 50, 100, or 200, as long as the antigen-binding domain can be produced based on the common technical knowledge of those skilled in the art.

[0268] In the present invention, the antigen-binding activity of an antigen-binding domain under a low hydrogen ion concentration (neutral pH) may be higher than under a high hydrogen ion concentration (acidic pH). The acidic pH may be, for example, a pH selected from pH4.0 to pH6.5, selected from pH4.5 to pH6.5, selected from pH5.0 to pH6.5, or selected from pH5.5 to pH6.5, which is preferable to be close to the in vivo pH in early endosomes. The acidic pH may also be, for example, pH5.8 or pH6.0. In particular embodiments, the acidic pH is pH5.8. Meanwhile, the neutral pH may be, for example, a pH selected from pH6.7 to pH10.0, selected from pH6.7 to pH9.5, selected from pH7.0 to pH9.0, or selected from pH7.0 to pH8.0, which is preferable to be close to the in vivo pH in plasma (blood). The neutral pH may also be, for example, pH7.4 or pH7.0. In particular embodiments, the neutral pH is pH7.4.

[0269] In one embodiment, the ratio between the antigen-binding activities under an acidic pH condition and a neutral pH condition is not limited but the ratio of the dissociation constant (KD) under an acidic pH condition to the KD under a neutral pH condition, i.e., $KD(\text{acidic pH condition})/KD(\text{neutral pH condition})$, is 2 or more, 10 or more, or 40 or more. The upper limit of the ratio may be 400, 1000, or 10000, as long as such an antigen-binding domain can be produced by techniques known to those skilled in the art. Alternatively, for example, the dissociation rate constant (kd) can be used instead of the KD. In this case, the ratio of the kd under an acidic pH condition to the kd under a neutral pH condition, i.e., $kd(\text{acidic pH condition})/kd(\text{neutral pH condition})$ is 2 or more, 5 or more, 10 or more, or 30 or more. The upper limit of the ratio may be 50, 100, or 200, as long as the antigen-binding domain can be produced based on the common technical knowledge of those skilled in the art.

[0270] In one embodiment, for example, at least one amino acid residue is substituted with an amino acid residue with a side-chain pKa of 4.0-8.0, and/or at least one amino acid

with a side-chain pKa of 4.0-8.0 is inserted in the antigen-binding domain, as described in WO 2009/125825. The amino acid may be substituted and/or inserted at any site as long as the antigen-binding activity of the antigen-binding domain becomes weaker under an acidic pH condition than under a neutral pH condition as compared to before the substitution or insertion. When the antigen-binding domain has a variable region or CDR, the site may be within the variable region or CDR. The number of amino acids that are substituted or inserted can be appropriately determined by those skilled in the art; and the number may be one or more. Amino acids with a side-chain pKa of 4.0-8.0 can be used to change the antigen-binding activity of the antigen-binding domain according to the hydrogen ion concentration condition. Such amino acids include, for example, natural amino acids such as His (H) and Glu (E), and unnatural amino acids such as histidine analogs (US2009/0035836), m-NO₂-Tyr (pKa 7.45), 3,5-Br₂-Tyr (pKa 7.21), and 3,5-I₂-Tyr (pKa 7.38) (Heyl et al., *Bioorg. Med. Chem.* 11(17):3761-3768 (2003)). Amino acids with a side-chain pKa of 6.0-7.0 can also be used, which include, e.g., His (H).

[0271] In another embodiment, preferable antigen-binding domains for the variant Fc region with increased pI are described and can be obtained by methods described in Japanese patent applications JP2015-021371 and JP2015-185254.

[0272] In certain embodiments, the variant Fc region with increased pI comprises at least two amino acid alterations of at least two positions selected from the group consisting of: 285, 311, 312, 315, 318, 333, 335, 337, 341, 342, 343, 384, 385, 388, 390, 399, 400, 401, 402, 413, 420, 422, and 431, according to EU numbering.

[0273] In further embodiments, the variant Fc region with increased pI comprises at least two amino acid alterations of at least two positions selected from the group consisting of: 311, 341, 343, 384, 399, 400, 401, 402, and 413, according to EU numbering.

[0274] In another aspect, the invention provides polypeptides comprising variant Fc regions with increased pI comprising amino acid alterations of any one of the following (1)-(10): (1) positions 311 and 341; (2) positions 311 and 343; (3) positions 311, 343 and 413; (4) positions 311, 384 and 413; (5) positions 311 and 399; (6) positions 311 and 401; (7) positions 311 and 413; (8) positions 400 and 413; (9) positions 401 and 413; and (10) positions 402 and 413; according to EU numbering.

[0275] A method for increasing the pI of a protein is, for example, to reduce the number of amino acids with a negatively charged side chain (for example, aspartic acid and glutamic acid) and/or to increase the number of amino acids with a positively charged side chain (for example, arginine, lysine and histidine) at a neutral pH condition. Amino acids with a negatively charged side chain have a negative charge represented as -1 at a pH condition that is sufficiently higher than their side chain pKa, which is a theory well known to those skilled in the art. For example, the theoretical pKa for the

side chain of aspartic acid is 3.9, and the side chain has a negative charge represented as -1 at a neutral pH condition (for example, in a solution of pH7.0). Conversely, amino acids with a positively charged side chain have a positive charge represented as +1 at a pH condition that is sufficiently lower than their side chain pKa. For example, the theoretical pKa for the side chain of arginine is 12.5, and the side chain has a positive charge represented as +1 at a neutral pH condition (for example, in a solution of pH7.0). Meanwhile, amino acids whose side chain has no charge at a neutral pH condition (for example, in a solution of pH7.0) are known to include 15 types of natural amino acids, i.e., alanine, cysteine, phenylalanine, glycine, isoleucine, leucine, methionine, asparagine, proline, glutamine, serine, threonine, valine, tryptophan, and tyrosine. As a matter of course, it is understood that amino acids for increasing the pI may be unnatural amino acids.

[0276] From the above, a method for increasing the pI of a protein at a neutral pH condition (for example, in a solution of pH7.0) can confer a charge alteration of +1 to a protein of interest, for example, by substituting amino acids with non-charged side chains for aspartic acid or glutamic acid (whose side chain has a negative charge of -1) in the amino acid sequence of the protein. Furthermore, a charge alteration of +1 can be conferred to the protein, for example, by substituting arginine or lysine (whose side chain has a positive charge of +1) for amino acids whose side chain has no charge. Moreover, a charge alteration of +2 can be conferred at a time to the protein by substituting arginine or lysine (whose side chain has a positive charge of +1) for aspartic acid or glutamic acid (whose side chain has a negative charge of -1). Alternatively, to increase the pI of a protein, amino acids with a side chain having no charge and/or preferably amino acids having a positively charged side chain can be added or inserted into the amino acid sequence of the protein, or amino acids with a side chain having no charge and/or preferably amino acids with a negatively charged side chain present in the amino acid sequence of the protein can be deleted. It is understood that, for example, the N-terminal and C-terminal amino acid residues of a protein have a main chain-derived charge (NH_3^+ of the amino group at the N-terminus and COO^- of the carbonyl group at the C-terminus) in addition to their side chain-derived charges. Thus, the pI of a protein can also be increased by performing to the main chain-derived functional groups some addition, deletion, substitution, or insertion.

[0277] The substitution of an amino acid to increase the pI includes, for example, substitution of an amino acid whose side chain has no charge for an amino acid having a negatively charged side chain, substitution of an amino acid having a positively charged side chain for an amino acid whose side chain has no charge, and substitution of an amino acid having a positively charged side chain for an amino acid having a negatively charged side chain in the amino acid sequence of a parent Fc region, which

are performed alone or in appropriate combinations.

[0278] The insertion or addition of an amino acid to increase the pI includes, for example, insertion or addition of an amino acid whose side chain has no charge, and/or insertion or addition of an amino acid having a positively charged side chain in the amino acid sequence of a parent Fc region, which are performed alone or in appropriate combinations.

[0279] The deletion of an amino acid to increase the pI includes, for example, deletion of an amino acid whose side chain has no charge, and/or deletion of an amino acid having a negatively charged side chain in the amino acid sequence of a parent Fc region, which are performed alone or in appropriate combinations.

[0280] In one embodiment, natural amino acids used for increasing pI can be classified as follows: (a) an amino acid with a negatively charged side chain can be Glu (E) or Asp (D); (b) an amino acid whose side chain has no charge can be Ala (A), Asn (N), Cys (C), Gln (Q), Gly (G), His (H), Ile (I), Leu (L), Met (M), Phe (F), Pro (P), Ser (S), Thr (T), Trp (W), Tyr (Y), or Val (V); and (c) an amino acid with a positively charged side chain can be His (H), Lys (K), or Arg (R). In one embodiment, the amino acid insertion or substitution after modification is Lys (K) or Arg (R).

[0281] In another aspect, the invention provides isolated polypeptides comprising variant Fc regions with enhanced Fc gamma RIIB-binding activity and increased pI. In certain embodiments, a variant Fc region described herein comprises at least two amino acid alterations in a parent Fc region.

[0282] In one aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIB-binding activity and increased pI comprising at least three amino acid alterations comprising: (a) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 236, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering, and (b) at least two amino acid alterations of at least two positions selected from the group consisting of: 285, 311, 312, 315, 318, 333, 335, 337, 341, 342, 343, 384, 385, 388, 390, 399, 400, 401, 402, 413, 420, 422, and 431, according to EU numbering.

[0283] In one aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIB-binding activity and increased pI, and that comprise at least three amino acid alterations comprising: (a) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 235, 236, 239, 268, 295, 298, 326, 330, and 396, according to EU numbering, and (b) at least two amino acid alterations of at least two positions selected from the group consisting of: 311, 341, 343, 384, 399, 400, 401, 402, and 413, according to EU numbering.

[0284] In another aspect, the invention provides polypeptides comprising variant Fc regions

with enhanced Fc gamma RIIb-binding activity and increased pI comprising amino acid alterations of any one of the following (1)-(9): (1) positions 235, 236, 268, 295, 311, 326, 330 and 343; (2) positions 236, 268, 295, 311, 326, 330 and 343; (3) positions 236, 268, 295, 311, 330 and 413; (4) positions 236, 268, 311, 330, 396 and 399; (5) positions 236, 268, 311, 330 and 343; (6) positions 236, 268, 311, 330, 343 and 413; (7) positions 236, 268, 311, 330, 384 and 413; (8) positions 236, 268, 311, 330 and 413; and (9) positions 236, 268, 330, 396, 400 and 413; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0285] In one aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity and increased pI comprising at least three amino acid alterations comprising: (a) at least one amino acid alteration of at least one position selected from the group consisting of: 234, 238, 250, 264, 267, 307, and 330, and (b) at least two amino acid alterations of at least two positions selected from the group consisting of: 285, 311, 312, 315, 318, 333, 335, 337, 341, 342, 343, 384, 385, 388, 390, 399, 400, 401, 402, 413, 420, 422, and 431, according to EU numbering. In further embodiments, the polypeptides comprise at least two amino acid alterations of at least two positions selected from the group consisting of: 311, 341, 343, 384, 399, 400, 401, 402, and 413, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0286] In another aspect, the invention provides polypeptides comprising variant Fc regions with enhanced Fc gamma RIIb-binding activity and increased pI comprising amino acid alterations of any one of the following (1)-(16): (1) positions 234, 238, 250, 264, 307, 311, 330 and 343; (2) positions 234, 238, 250, 264, 307, 311, 330 and 413; (3) positions 234, 238, 250, 264, 267, 307, 311, 330 and 343; (4) positions 234, 238, 250, 264, 267, 307, 311, 330 and 413; (5) positions 234, 238, 250, 267, 307, 311, 330 and 343; (6) positions 234, 238, 250, 267, 307, 311, 330 and 413; (7) positions 234, 238, 250, 307, 311, 330 and 343; (8) positions 234, 238, 250, 307, 311, 330 and 413; (9) positions 238, 250, 264, 267, 307, 311, 330 and 343; (10) positions 238, 250, 264, 267, 307, 311, 330 and 413; (11) positions 238, 250, 264, 307, 311, 330 and 343; (12) positions 238, 250, 264, 307, 311, 330 and 413; (13) positions 238, 250, 267, 307, 311, 330 and 343; (14) positions 238, 250, 267, 307, 311, 330 and 413; (15) positions 238, 250, 307, 311, 330 and 343; and (16) positions 238, 250, 307, 311, 330 and 413; according to EU numbering.

- [0287] In a further embodiment, the variant Fc region comprises amino acid alterations selected from any single alteration, combination of single alterations, or combination alterations described in Tables 14-30.
- [0288] In some embodiments, a polypeptide comprises a variant Fc region of the present invention. In a further embodiment, the polypeptide is an antibody heavy chain constant region. In a further embodiment, the polypeptide is an antibody heavy chain. In a further embodiment, the polypeptide is an antibody. In a further embodiment, the polypeptide is an Fc fusion protein.
- [0289] In a further embodiment, the invention provides a polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 229-381.
- [0290] A "parent Fc region" as used herein refers to an Fc region prior to introduction of amino acid alteration(s) described herein. Preferred examples of the parent Fc region include Fc regions derived from native antibodies. Antibodies include, for example, IgA (IgA1, IgA2), IgD, IgE, IgG (IgG1, IgG2, IgG3, IgG4), and IgM, or such. Antibodies may be derived from human or monkey (e.g., cynomolgus, rhesus macaque, marmoset, chimpanzee, or baboon). Native antibodies may also include naturally-occurring mutations. A plurality of allotype sequences of IgGs due to genetic polymorphism are described in "Sequences of proteins of immunological interest", NIH Publication No. 91-3242, and any of them may be used in the present invention. In particular, for human IgG1, the amino acid sequence at positions 356 to 358 (EU numbering) may be either DEL or EEM. Preferred examples of the parent Fc region include Fc regions derived from a heavy chain constant region of human IgG1 (SEQ ID NO: 195), human IgG2 (SEQ ID NO: 196), human IgG3 (SEQ ID NO: 197), and human IgG4 (SEQ ID NO: 198). Another preferred example of the parent Fc region is an Fc region derived from a heavy chain constant region SG1 (SEQ ID NO: 9). Furthermore, the parent Fc region may be an Fc region produced by adding an amino acid alteration(s) other than the amino acid alteration(s) described herein to an Fc region derived from a native antibody.
- [0291] In addition, amino acid alterations performed for other purpose(s) can be combined in a variant Fc region described herein. For example, amino acid substitutions that improve FcRn-binding activity (Hinton et al., *J. Immunol.* 176(1):346-356 (2006); Dall'Acqua et al., *J. Biol. Chem.* 281(33):23514-23524 (2006); Petkova et al., *Intl. Immunol.* 18(12):1759-1769 (2006); Zalevsky et al., *Nat. Biotechnol.* 28(2):157-159 (2010); WO 2006/019447; WO 2006/053301; and WO 2009/086320), and amino acid substitutions for improving antibody heterogeneity or stability (WO 2009/041613) may be added. Alternatively, polypeptides with the property of promoting antigen clearance, which are described in WO 2011/122011, WO 2012/132067, WO 2013/046704 or WO 2013/180201, polypeptides with the property of specific binding

to a target tissue, which are described in WO 2013/180200, polypeptides with the property for repeated binding to a plurality of antigen molecules, which are described in WO 2009/125825, WO 2012/073992 or WO 2013/047752, can be combined with a variant Fc region described herein. Alternatively, with the objective of conferring binding ability to other antigens, the amino acid alterations disclosed in EP1752471 and EP1772465 may be combined in CH3 of a variant Fc region described herein. Alternatively, with the objective of increasing plasma retention, amino acid alterations that decrease the pI of the constant region (WO 2012/016227) may be combined in a variant Fc region described herein. Alternatively, with the objective of promoting uptake into cells, amino acid alterations that increase the pI of the constant region (WO 2014/145159) may be combined in a variant Fc region described herein. Alternatively, with the objective of promoting elimination of a target molecule from plasma, amino acid alterations that increase the pI of the constant region (Japanese patent application numbers JP2015-021371 and JP2015-185254) may be combined in a variant Fc region described herein. In one embodiment, such alteration may include, for example, substitution at at least one position selected from the group consisting of 311, 343, 384, 399, 400, and 413 according to EU numbering. In a further embodiment, such substitution may be a replacement of an amino acid with Lys or Arg at each position.

[0292] Amino acid alterations of enhancing human FcRn-binding activity under acidic pH can also be combined in a variant Fc region described herein. Specifically, such alterations may include, for example, substitution of Leu for Met at position 428 and substitution of Ser for Asn at position 434, according to EU numbering (Zalevsky et al., *Nat. Biotechnol.* 28:157-159 (2010)); substitution of Ala for Asn at position 434 (Deng et al., *Metab. Dispos.* 38(4):600-605 (2010)); substitution of Tyr for Met at position 252, substitution of Thr for Ser at position 254 and substitution of Glu for Thr at position 256 (Dall'Acqua et al., *J. Biol. Chem.* 281:23514-23524 (2006)); substitution of Gln for Thr at position 250 and substitution of Leu for Met at position 428 (Hinton et al., *J. Immunol.* 176(1):346-356 (2006)); substitution of His for Asn at position 434 (Zheng et al., *Clin. Pharmacol. Ther.* 89(2):283-290 (2011), and alterations described in WO 2010/106180, WO 2010/045193, WO 2009/058492, WO 2008/022152, WO 2006/050166, WO 2006/053301, WO 2006/031370, WO 2005/123780, WO 2005/047327, WO 2005/037867, WO 2004/035752, or WO 2002/060919. Such alterations may include, for example, at least one alteration selected from the group consisting of substitution of Leu for Met at position 428, substitution of Ala for Asn at position 434 and substitution of Thr for Tyr at position 436. Those alterations may further include substitution of Arg for Gln at position 438 and/or substitution of Glu for Ser at position 440 (Japanese patent application numbers JP2015-021371 and JP2015-185254).

- [0293] Two or more polypeptides comprising a variant Fc region described herein can be included in one molecule, wherein two polypeptides comprising variant Fc regions are associated, much like in an antibody. The type of antibody is not limited, and IgA (IgA1, IgA2), IgD, IgE, IgG (IgG1, IgG2, IgG3, IgG4), and IgM, or such can be used.
- [0294] The two associated polypeptides comprising variant Fc regions may be polypeptides comprising variant Fc regions into which the same amino acid alteration(s) have been introduced (hereinafter, referred to as homologous variant Fc regions), or polypeptides comprising variant Fc regions into which different amino acid alteration(s) have been introduced, or alternatively polypeptides comprising variant Fc regions where amino acid alteration(s) have been introduced into only one of the Fc regions (hereinafter, referred as a heterologous polypeptides comprising variant Fc regions). One of the preferable amino acid alterations is an alteration in the loop structure from positions 233 to 239 (EU numbering) in the CH2 domain of the Fc region, which is involved in binding with Fc gamma RIIb and Fc gamma RIIa. Preferably, an alteration is introduced in the loop structure of the CH2 domain of one of the Fc regions that enhances Fc gamma RIIb-binding activity and/or selectivity, and another alteration is introduced in the loop structure of the CH2 domain of the other Fc region that destabilizes it. Examples of amino acid alterations that can destabilize the loop structure of the CH2 domain may be substitution of at least one amino acid selected from amino acids at positions 235, 236, 237, 238, and 239 to another amino acid. Specifically, it can be destabilized, for example, by altering the amino acid at position 235 to Asp, Gln, Glu, or Thr, altering the amino acid at position 236 to Asn, altering the amino acid at position 237 to Phe or Trp, altering the amino acid at position 238 to Glu, Gly, or Asn, and altering the amino acid at position 239 to Asp or Glu, according to EU numbering.
- [0295] For association of heterologous polypeptides comprising variant Fc regions, a technique of suppressing unintended association of homologous polypeptides comprising variant Fc regions by introducing electrostatic repulsion into the interface of the CH2 or CH3 domain of the Fc region can be applied, as described in WO 2006/106905.
- [0296] Examples of amino acid residues in contact at the interface of the CH2 or CH3 domain of the Fc region include the residue at position 356 (EU numbering), the residue at position 439 (EU numbering), the residue at position 357 (EU numbering), the residue at position 370 (EU numbering), the residue at position 399 (EU numbering), and the residue at position 409 (EU numbering) in the CH3 domain.
- [0297] More specifically, for example, the Fc region in which one to three pairs of amino acid residues selected from (1) to (3) shown below have the same charge can be produced: (1) amino acid residues at positions 356 and 439 (EU numbering) in the

CH3 domain; (2) amino acid residues at positions 357 and 370 (EU numbering) in the CH3 domain; and (3) amino acid residues at positions 399 and 409 (EU numbering) in the CH3 domain.

- [0298] Furthermore, heterologous polypeptides comprising variant Fc regions can be produced, wherein one to three pairs of amino acid residues selected from (1) to (3) indicated above have the same charge in the CH3 domain of the first Fc region, and the pairs of amino acid residues selected in the aforementioned first Fc region also have the same charge in the CH3 domain of the second Fc region, provided that the charges in the first and second Fc regions are opposite.
- [0299] In the above-mentioned Fc regions, for example, negatively-charged amino acid residues are preferably selected from glutamic acid (E) and aspartic acid (D), and positively-charged amino acid residues are preferably selected from lysine (K), arginine (R), and histidine (H).
- [0300] Other known techniques can be used additionally for association of heterologous polypeptides comprising variant Fc regions. Specifically, such a technique is conducted by substituting an amino acid side chain present in one of the Fc regions with a larger side chain (knob; which means "bulge"), and substituting an amino acid side chain present in the Fc region with a smaller side chain (hole; which means "void"), to place the knob within the hole. This can promote efficient association between Fc-region-containing polypeptides having different amino acid sequences from each other (WO 1996/027011; Ridgway et al., *Prot. Eng.* 9:617-621 (1996); Merchant et al., *Nat. Biotech.* 16, 677-681 (1998)).
- [0301] In addition, other known techniques can also be used for heterologous association of polypeptides comprising variant Fc regions. Association of polypeptides comprising an Fc region can be induced efficiently using strand-exchange engineered domain CH3 heterodimers (Davis et al., *Prot. Eng. Des. & Sel.*, 23:195-202 (2010)). This technique can also be used to efficiently induce association between Fc region-containing polypeptides having different amino acid sequences.
- [0302] In addition, heterodimerized antibody production techniques that use association of antibody CH1 and CL, and association of VH and VL, which are described in WO 2011/028952, can also be used.
- [0303] As with the method described in WO 2008/119353 and WO 2011/131746, it is also possible to use the technique of producing heterodimerized antibodies by producing two types of homodimerized antibodies in advance, incubating the antibodies under reducing conditions to dissociate them, and allowing them to associate again.
- [0304] As with the method described in Strop (*J. Mol. Biol.* 420:204-219 (2012)), it is also possible to use the technique of producing heterodimerized antibodies by introducing charged residues such as Lys, Arg, Glu, and Asp so that electrostatic repulsion is in-

roduced into CH3 domains.

[0305] Furthermore, as with the method described in WO 2012/058768, it is also possible to use the technique of producing heterodimerized antibodies by adding alterations to the CH2 and CH3 domains.

[0306] When simultaneously expressing two polypeptides comprising a variant Fc region which have different amino acid sequences, in order to produce polypeptides comprising heterologous variant Fc regions, polypeptides comprising homologous variant Fc regions are also usually produced as impurities. In such cases, polypeptides comprising heterologous variant Fc regions can be efficiently obtained by separating and purifying them from polypeptides comprising homologous variant Fc regions using known technologies. A method has been reported to efficiently separate and purify heterodimerized antibodies from a homodimerized antibodies using ion exchange chromatography, by introducing amino acid alterations into the variable regions of the two types of antibody heavy chains to create a difference in isoelectric points between the homodimerized antibodies and the heterodimerized antibodies (WO 2007/114325). Another method has been reported to purify heterodimerized antibodies using Protein A chromatography, by constructing a heterodimerized antibody comprising two types of heavy chains derived from mouse IgG2a that binds to Protein A and rat IgG2b that does not bind to Protein A (WO 1998/050431 and WO 1995/033844).

[0307] Furthermore, a heterodimerized antibody can be efficiently purified using Protein A chromatography, by substituting amino acid residues at positions 435 and 436 (EU numbering), which are located in the Protein A binding site of an antibody heavy chain, with amino acids such as Tyr or His, to yield different Protein A binding affinities.

[0308] In the present invention, amino acid alteration means any of substitution, deletion, addition, insertion, and modification, or a combination thereof. In the present invention, amino acid alteration may be rephrased as amino acid mutation.

[0309] When substituting amino acid residues, substitution to a different amino acid residue can be carried out with the objective of altering aspects such as (a)-(c) described below: (a) polypeptide backbone structure in the sheet-structure or helical-structure region; (b) electric charge or hydrophobicity at the target site; or (c) size of the side chain.

[0310] Amino acid residues are classified into the following groups based on their general side chain properties: (a) hydrophobic: Norleucine, Met, Ala, Val, Leu, and Ile; (b) neutral hydrophilic: Cys, Ser, Thr, Asn, and Gln; (c) acidic: Asp and Glu; (d) basic: His, Lys, and Arg; (e) residues that affect the chain orientation: Gly and Pro; and (f) aromatic: Trp, Tyr, and Phe.

- [0311] Amino acid alterations are produced by various methods known to those skilled in the art. Such methods include the site-directed mutagenesis method (Hashimoto-Gotoh et al., *Gene* 152:271-275 (1995); Zoller, *Meth. Enzymol.* 100:468-500 (1983); Kramer et al., *Nucleic Acids Res.* 12: 9441-9456 (1984)); Kramer and Fritz, *Methods Enzymol.* 154: 350-367 (1987); and Kunkel, *Proc. Natl. Acad. Sci. USA* 82:488-492 (1985)), the PCR mutation method, and the cassette mutation method, but are not limited thereto.
- [0312] The number of amino acid alterations introduced into an Fc region is not limited. In certain embodiments, it can be 1, 2 or less, 3 or less, 4 or less, 5 or less, 6 or less, 8 or less, 10 or less, 12 or less, 14 or less, 16 or less, 18 or less, or 20 or less.
- [0313] Amino acid modification includes post-translational modification. A specific post-translational modification may be addition or deletion of a sugar chain. For example, the amino acid residue at position 297 (EU numbering) in the IgG1 constant region may be sugar chain-modified. The sugar chain structure for the modification is not limited. For example, sialic acid may be added to the sugar chain of an Fc region (*MAbs* 2010 Sep-Oct, 2(5): 519-527). Generally, antibodies expressed in eukaryotic cells comprise glycosylation in the constant region. For example, it is known that some type of sugar chain are normally added to antibodies expressed in cells such as naturally-occurring antibody-producing cells of mammals or eukaryotic cells transformed with an expression vector comprising a DNA encoding an antibody.
- [0314] Eukaryotic cells shown here include yeast and animal cells. For example, CHO cells and HEK293 cells are representative animal cells used in transformation with an expression vector comprising an antibody-encoding DNA. On the other hand, constant regions without glycosylation are also included in the present invention. Antibodies whose constant region is not glycosylated can be obtained by expressing an antibody-encoding gene in prokaryotic cells such as *Escherichia coli*.
- [0315] Furthermore, a polypeptide comprising a variant Fc region of the present invention may be chemically modified with various molecules such as polyethylene glycol (PEG) and cytotoxic substances. Methods for such chemical modification of a polypeptide are established in the art.
- [0316] In one aspect, the invention provides an isolated polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity. In some aspects, the polypeptide is an antibody. In some aspects, the polypeptide is an Fc fusion protein. In one aspect, the invention provides an isolated polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity. In some aspects, the polypeptide is an antibody. In certain embodiments, an antibody is a chimeric antibody, or a humanized antibody. The origin of an antibody is not particularly limited, but examples include a human antibody, a mouse antibody, a rat antibody, and

a rabbit antibody. In some aspects, the polypeptide is an Fc fusion protein.

- [0317] The variable regions of antibodies that comprise a variant Fc region provided herein and the protein binding motifs of Fc fusion proteins comprising a variant Fc region can recognize any antigen. Examples of antigens that can be bound by such antibodies and fusion proteins include, but are not limited to ligands (cytokines, chemokines, and such), receptors, cancer antigens, MHC antigens, differentiation antigens, immunoglobulins, and immune complexes partly containing immunoglobulins.
- [0318] Examples of cytokines that can be bound by an antibody or fusion protein containing a variant Fc region of the invention, and/or recombinantly fused with a polypeptide comprising a disclosed variant Fc region include but are not limited to, interleukins 1 to 18, colony stimulating factors (G-CSF, M-CSF, GM-CSF, etc.), interferons (IFN-alpha, IFN-beta, IFN-gamma, etc.), growth factors (EGF, FGF, IGF, NGF, PDGF, TGF, HGF, etc.), tumor necrosis factors (TNF-alpha and TNF-beta), lymphotoxin, erythropoietin, leptin, SCF, TPO, MCAF, and BMP.
- [0319] Examples of chemokines that can be bound by an antibody or fusion protein containing a variant Fc region of the invention, and/or recombinantly fused with a polypeptide comprising a disclosed variant Fc region include but are not limited to, CC chemokines such as CCL1 to CCL28, CXC chemokines such as CXCL1 to CXCL17, C chemokines such as XCL1 to XCL2, and CX3C chemokines such as CX3CL1.
- [0320] Examples of receptors that can be bound by an antibody or fusion protein containing a variant Fc region of the invention, and/or recombinantly fused with a polypeptide comprising a disclosed variant Fc region include but are not limited to, receptors belonging to receptor families such as the hematopoietic growth factor receptor family, cytokine receptor family, tyrosine kinase-type receptor family, serine/threonine kinase-type receptor family, TNF receptor family, G protein-coupled receptor family, GPI anchor-type receptor family, tyrosine phosphatase-type receptor family, adhesion factor family, and hormone receptor family. The receptors belonging to these receptor families and their characteristics have been described in many documents such as Cooke, ed. *New Comprehensive Biochemistry Vol.18B "Hormones and their Actions Part II"* pp.1-46 (1988) Elsevier Science Publishers BV; Patthy (*Cell* 61(1):13-14 (1990)); Ullrich (*Cell* 61(2):203-212 (1990)); Massague (*Cell* 69(6):1067-1070 (1992)); Miyajima et al. (*Annu. Rev. Immunol.* 10:295-331 (1992)); Taga et al. (*FASEB J.* 6:3387-3396 (1992)); Fantl et al. (*Annu. Rev. Biochem.* 62:453-481 (1993)); Smith et al. (*Cell* 76(6):959-962 (1994)); and Flower (*Biochim. Biophys. Acta* 1422(3): 207-234 (1999)).
- [0321] Examples of specific receptors belonging to the above-mentioned receptor families include human or mouse erythropoietin (EPO) receptors (Jones et al., *Blood* 76(1):31-35 (1990); D'Andrea et al., *Cell* 57(2):277-285 (1989)), human or mouse

granulocyte-colony stimulating factor (G-CSF) receptors (Fukunaga et al., Proc. Natl. Acad. Sci. USA 87(22):8702-8706 (1990), mG-CSFR; Fukunaga et al., Cell 61(2): 341-350 (1990)), human or mouse thrombopoietin (TPO) receptors (Vigon et al., Proc. Natl. Acad. Sci. USA. 89(12):5640-5644 (1992); Skoda et al., EMBO J. 12(7):2645-2653 (1993)), human or mouse insulin receptors (Ullrich et al., Nature 313(6005):756-761 (1985)), human or mouse Flt-3 ligand receptors (Small et al., Proc. Natl. Acad. Sci. USA. 91(2):459-463 (1994)), human or mouse platelet-derived growth factor (PDGF) receptors (Gronwald et al., Proc. Natl. Acad. Sci. USA. 85(10):3435-3439 (1988)), human or mouse interferon (IFN)-alpha and beta receptors (Uze et al., Cell 60(2): 225-234 (1990); Novick et al., Cell 77(3):391-400 (1994)), human or mouse leptin receptors, human or mouse growth hormone (GH) receptors, human or mouse interleukin (IL)-10 receptors, human or mouse insulin-like growth factor (IGF)-I receptors, human or mouse leukemia inhibitory factor (LIF) receptors, and human or mouse ciliary neurotrophic factor (CNTF) receptors.

[0322] Cancer antigens are antigens that are expressed as cells become malignant, and they are also called tumor-specific antigens. Abnormal sugar chains that appear on cell surfaces or protein molecules when cells become cancerous are also cancer antigens, and they are also called sugar-chain cancer antigens. Examples of cancer antigens that can be bound by an antibody or fusion protein containing a variant Fc region of the invention include but are not limited to, GPC3 which is a receptor belonging to the GPI anchor-type receptor family mentioned above, and is also expressed in several cancers including liver cancer (Midorikawa et al., Int. J. Cancer 103(4):455-465 (2003)), as well as EpCAM which is expressed in several cancers including lung cancer (Linnenbach et al., Proc. Natl. Acad. Sci. USA 86(1):27-31 (1989)), CA19-9, CA15-3, and sialyl SSEA-1 (SLX).

[0323] MHC antigens are roughly classified into MHC class I antigens and MHC class II antigens. MHC class I antigens include HLA-A, -B, -C, -E, -F, -G, and -H, and MHC class II antigens include HLA-DR, -DQ, and -DP.

[0324] Examples of differentiation antigens that can be bound by an antibody or fusion protein containing a variant Fc region of the invention, and/or recombinantly fused with a polypeptide comprising a disclosed variant Fc region include but are not limited to, CD1, CD2, CD4, CD5, CD6, CD7, CD8, CD10, CD11a, CD11b, CD11c, CD13, CD14, CD15s, CD16, CD18, CD19, CD20, CD21, CD23, CD25, CD28, CD29, CD30, CD32, CD33, CD34, CD35, CD38, CD40, CD41a, CD41b, CD42a, CD42b, CD43, CD44, CD45, CD45RO, CD48, CD49a, CD49b, CD49c, CD49d, CD49e, CD49f, CD51, CD54, CD55, CD56, CD57, CD58, CD61, CD62E, CD62L, CD62P, CD64, CD69, CD71, CD73, CD95, CD102, CD106, CD122, CD126, and CDw130.

[0325] Immunoglobulins include IgA, IgM, IgD, IgG, and IgE. Immune complexes include

a component of at least any of the immunoglobulins.

[0326] Other examples of antigens that can be bound by an antibody or fusion protein containing a variant Fc region of the invention, and/or recombinantly fused with a polypeptide comprising a disclosed variant Fc region include but are not limited to, 17-IA, 4-1BB, 4Dc, 6-keto-PGF1a, 8-iso-PGF2a, 8-oxo-dG, A1 adenosine receptor, A33, ACE, ACE-2, activin, activin A, activin AB, activin B, activin C, activin RIA, activin RIA ALK-2, activin RIB ALK-4, activin RIIA, activin RIIB, ADAM, ADAM10, ADAM12, ADAM15, ADAM17/TACE, ADAM8, ADAM9, ADAMTS, ADAMTS4, ADAMTS5, addressin, aFGF, ALCAM, ALK, ALK-1, ALK-7, alpha-1-antitrypsin, alpha-V/beta-1 antagonist, ANG, Ang, APAF-1, APE, APJ, APP, APRIL, AR, ARC, ART, artemin, anti-Id, ASPARTIC, atrial natriuretic peptide, av/b3 integrin, Axl, b2M, B7-1, B7-2, B7-H, B-lymphocyte stimulating factor (BlyS), BACE, BACE-1, Bad, BAFF, BAFF-R, Bag-1, BAK, Bax, BCA-1, BCAM, Bcl, BCMA, BDNF, b-ECGF, bFGF, BID, Bik, BIM, BLC, BL-CAM, BLK, BMP, BMP-2 BMP-2a, BMP-3 Osteogenin, BMP-4, BMP-2b, BMP-5, BMP-6 Vgr-1, BMP-7 (OP-1), BMP-8 (BMP-8a, OP-2), BMPR, BMPR-IA (ALK-3), BMPR-IB (ALK-6), BRK-2, RPK-1, BMPR-II (BRK-3), BMP, b-NGF, BOK, bombesin, bone-derived neurotrophic factor, BPDE, BPDE-DNA, BTC, complement factor 3 (C3), C3a, C4, C5, C5a, C10, CA125, CAD-8, calcitonin, cAMP, carcinoembryonic antigen (CEA), cancer associated antigen, cathepsin A, cathepsin B, cathepsin C/DPPI, cathepsin D, cathepsin E, cathepsin H, cathepsin L, cathepsin O, cathepsin S, cathepsin V, cathepsin X/Z/P, CBL, CCI, CCK2, CCL, CCL1, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL2, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9/10, CCR, CCR1, CCR10, CCR11, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CD1, CD2, CD3, CD3E, CD4, CD5, CD6, CD7, CD8, CD10, CD11a, CD11b, CD11c, CD13, CD14, CD15, CD16, CD18, CD19, CD20, CD21, CD22, CD23, CD25, CD27L, CD28, CD29, CD30, CD30L, CD32, CD33 (p67 protein), CD34, CD38, CD40, CD40L, CD44, CD45, CD46, CD49a, CD52, CD54, CD55, CD56, CD61, CD64, CD66e, CD74, CD80 (B7-1), CD89, CD95, CD123, CD137, CD138, CD140a, CD146, CD147, CD148, CD152, CD164, CEACAM5, CFTR, cGMP, CINC, Botulinum toxin, Clostridium perfringens toxin, CKb8-1, CLC, CMV, CMV UL, CNTF, CNTN-1, COX, C-Ret, CRG-2, CT-1, CTACK, CTGF, CTLA-4, CX3CL1, CX3CR1, CXCL, CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCR, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, cytokeratin tumor associated antigen, DAN, DCC, DcR3, DC-SIGN, complement regulatory factor (Decay accelerating factor), des(1-3)-IGF-I (brain IGF-

1), Dhh, digoxin, DNAM-1, Dnase, Dpp, DPPIV/CD26, Dtk, ECAD, EDA, EDA-A1, EDA-A2, EDAR, EGF, EGFR (ErbB-1), EMA, EMMPRIN, ENA, endothelin receptor, enkephalinase, eNOS, Eot, eotaxin 1, EpCAM, ephrin B2/EphB4, EPO, ERCC, E-selectin, ET-1, factor IIa, factor VII, factor VIIIc, factor IX, fibroblast activation protein (FAP), Fas, FcR1, FEN-1, ferritin, FGF, FGF-19, FGF-2, FGF3, FGF-8, FGFR, FGFR-3, fibrin, FL, FLIP, Flt-3, Flt-4, follicle stimulating hormone, fractalkine, FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, G250, Gas6, GCP-2, GCSF, GD2, GD3, GDF, GDF-1, GDF-3 (Vgr-2), GDF-5 (BMP-14, CDMP-1), GDF-6 (BMP-13, CDMP-2), GDF-7 (BMP-12, CDMP-3), GDF8 (myostatin), GDF-9, GDF-15 (MIC-1), GDNF, GFAP, GFRA-1, GFR-alpha1, GFR-alpha2, GFR-alpha3, GITR, glucagon, Glut4, glycoprotein IIb/IIIa (GPIIb/IIIa), GM-CSF, gp130, gp72, GRO, growth hormone releasing hormone, hapten (NP-cap or NIP-cap), HB-EGF, HCC, HCMV gB envelope glycoprotein, HCMV gH envelope glycoprotein, HCMV UL, hematopoietic growth factor (HGF), Hep B gp120, heparanase, Her2, Her2/neu (ErbB-2), Her3 (ErbB-3), Her4 (ErbB-4), herpes simplex virus (HSV) gB glycoprotein, HSV gD glycoprotein, HGFA, high molecular weight melanoma-associated antigen (HMW-MAA), HIV gp120, HIV IIIB gp 120 V3 loop, HLA, HLA-DR, HM1.24, HMFG PEM, HRG, Hrk, human cardiac myosin, human cytomegalovirus (HCMV), human growth hormone (HGH), HVEM, I-309, IAP, ICAM, ICAM-1, ICAM-3, ICE, ICOS, IFNg, Ig, IgA receptor, IgE, IGF, IGF binding protein, IGF-1R, IGFBP, IGF-I, IGF-II, IL, IL-1, IL-1R, IL-2, IL-2R, IL-4, IL-4R, IL-5, IL-5R, IL-6, IL-6R, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-18, IL-18R, IL-23, interferon (IFN)-alpha, IFN-beta, IFN-gamma, inhibin, iNOS, insulin A chain, insulin B chain, insulin-like growth factor1, integrin alpha2, integrin alpha3, integrin alpha4, integrin alpha4/beta1, integrin alpha4/beta7, integrin alpha5 (alpha V), integrin alpha5/beta1, integrin alpha5/beta3, integrin alpha6, integrin beta1, integrin beta2, interferon gamma, IP-10, I-TAC, JE, kallikrein 2, kallikrein 5, kallikrein 6, kallikrein 11, kallikrein 12, kallikrein 14, kallikrein 15, kallikrein L1, kallikrein L2, kallikrein L3, kallikrein L4, KC, KDR, keratinocyte growth factor (KGF), laminin 5, LAMP, LAP, LAP (TGF-1), latent TGF-1, latent TGF-1 bp1, LBP, LDGF, LECT2, lefty, Lewis-Y antigen, Lewis-Y associated antigen, LFA-1, LFA-3, Lfo, LIF, LIGHT, lipoprotein, LIX, LKN, Lptn, L-selectin, LT-a, LT-b, LTB4, LTBP-1, lung surface, luteinizing hormone, lymphotoxin beta receptor, Mac-1, MAdCAM, MAG, MAP2, MARC, MCAM, MCK-2, MCP, M-CSF, MDC, Mer, METALLOPROTEASES, MGDF receptor, MGMT, MHC (HLA-DR), MIF, MIG, MIP, MIP-1-alpha, MK, MMAC1, MMP, MMP-1, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-2, MMP-24, MMP-3, MMP-7, MMP-8, MMP-9, MPIF, Mpo, MSK, MSP, mucin (Muc1), MUC18, Mullerian-inhibiting substance, Mug, MuSK, NAIP, NAP, NCAD, N-Cadherin, NCA

90, NCAM, neprilysin, neurotrophin-3, -4, or -6, neurturin, nerve growth factor (NGF), NGFR, NGF-beta, nNOS, NO, NOS, Npn, NRG-3, NT, NTN, OB, OGG1, OPG, OPN, OSM, OX40L, OX40R, p150, p95, PADPr, parathyroid hormone, PARC, PARP, PBR, PBSF, PCAD, P-cadherin, PCNA, PDGF, PDK-1, PECAM, PEM, PF4, PGE, PGF, PGI2, PGJ2, PIN, PLA2, placental alkaline phosphatase (PLAP), PIGF, PLP, PP14, proinsulin, prorelaxin, protein C, PS, PSA, PSCA, prostate-specific membrane antigen (PSMA), PTEN, PTHrp, Ptk, PTN, R51, RANK, RANKL, RANTES, relaxin A chain, relaxin B chain, renin, respiratory syncytial virus (RSV) F, RSV Fgp, Ret, Rheumatoid factor, RLIP76, RPA2, RSK, S100, SCF/KL, SDF-1, SERINE, serum albumin, sFRP-3, Shh, SIGIRR, SK-1, SLAM, SLPI, SMAC, SMDF, SMOH, SOD, SPARC, Stat, STEAP, STEAP-II, TACE, TACI, TAG-72 (tumor-associated glycoprotein-72), TARC, TCA-3, T-cell receptor (for example, T-cell receptor alpha/beta), TdT, TECK, TEM1, TEM5, TEM7, TEM8, TERT, testis PLAP-like alkaline phosphatase, Tfr, TGF, TGF-alpha, TGF-beta, TGF-beta Pan Specific, TGF-betaRI (ALK-5), TGF-betaRII, TGF-betaRIIb, TGF-betaRIII, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta4, TGF-beta5, thrombin, thymus Ck-1, thyroid-stimulating hormone, Tie, TIMP, TIQ, tissue factor, TMEFF2, Tmpo, TMPRSS2, TNF, TNF-alpha, TNF-alphabeta, TNF-beta2, TNF-c, TNF-RI, TNF-RII, TNFRSF10A (TRAIL R1 Apo-2, DR4), TNFRSF10B (TRAIL R2 DR5, KILLER, TRICK-2A, TRICK-B), TNFRSF10C (TRAIL R3 DcR1, LIT, TRID), TNFRSF10D (TRAIL R4 DcR2, TRUND), TNFRSF11A (RANK ODF R, TRANCE R), TNFRSF11B (OPG OCIF, TR1), TNFRSF12 (TWEAK R FN14), TNFRSF13B (TACI), TNFRSF13C (BAFF R), TNFRSF14 (HVEM ATAR, HveA, LIGHT R, TR2), TNFRSF16 (NGFR p75NTR), TNFRSF17 (BCMA), TNFRSF18 (GITR AITR), TNFRSF19 (TROY TAJ, TRADE), TNFRSF19L (RELT), TNFRSF1A (TNF RI CD120a, p55-60), TNFRSF1B (TNF RII CD120b, p75-80), TNFRSF26 (TNFRH3), TNFRSF3 (LTbR TNF RIII, TNFC R), TNFRSF4 (OX40 ACT35, TXGP1 R), TNFRSF5 (CD40 p50), TNFRSF6 (Fas Apo-1, APT1, CD95), TNFRSF6B (DcR3 M68, TR6), TNFRSF7 (CD27), TNFRSF8 (CD30), TNFRSF9 (4-1BB CD137, ILA), TNFRSF21 (DR6), TNFRSF22 (DcTRAIL R2 TNFRH2), TNFRST23 (DcTRAIL R1 TNFRH1), TNFRSF25 (DR3 Apo-3, LARD, TR-3, TRAMP, WSL-1), TNFSF10 (TRAIL Apo-2 ligand, TL2), TNFSF11 (TRANCE/RANK ligand ODF, OPG ligand), TNFSF12 (TWEAK Apo-3 ligand, DR3 ligand), TNFSF13 (APRIL TALL2), TNFSF13B (BAFF BLYS, TALL1, THANK, TNFSF20), TNFSF14 (LIGHT HVEM ligand, LTg), TNFSF15 (TL1A/VEGI), TNFSF18 (GITR ligand AITR ligand, TL6), TNFSF1A (TNF-a Conectin, DIF, TNFSF2), TNFSF1B (TNF-b LTa, TNFSF1), TNFSF3 (LTb TNFC, p33), TNFSF4 (OX40 ligand gp34, TXGP1), TNFSF5 (CD40 ligand CD154, gp39, HIGM1, IMD3, TRAP), TNFSF6 (Fas ligand Apo-1 ligand, APT1 ligand), TNFSF7 (CD27 ligand

CD70), TNFSF8 (CD30 ligand CD153), TNFSF9 (4-1BB ligand CD137 ligand), TP-1, t-PA, Tpo, TRAIL, TRAIL R, TRAIL-R1, TRAIL-R2, TRANCE, transferrin receptor, TRF, Trk, TROP-2, TSG, TSLP, tumor associated antigen CA125, tumor associated antigen expressing Lewis-Y associated carbohydrates, TWEAK, TXB2, Ung, uPAR, uPAR-1, urokinase, VCAM, VCAM-1, VECAD, VE-Cadherin, VE-cadherin-2, VEGFR-1 (flt-1), VEGF, VEGFR, VEGFR-3 (flt-4), VEGI, VIM, virus antigen, VLA, VLA-1, VLA-4, VNR integrin, von Willebrand factor, WIF-1, WNT1, WNT2, WNT2B/13, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, WNT16, XCL1, XCL2, XCR1, XCR1, XEDAR, XIAP, XPD, HMGB1, IgA, A-beta, CD81, CD97, CD98, DDR1, DKK1, EREG, Hsp90, IL-17/IL-17R, IL-20/IL-20R, oxidized LDL, PCSK9, prekallikrein, RON, TMEM16F, SOD1, Chromogranin A, Chromogranin B, tau, VAP1, high molecular weight kininogen, IL-31, IL-31R, Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.5, Nav1.6, Nav1.7, Nav1.8, Nav1.9, EPCR, C1, C1q, C1r, C1s, C2, C2a, C2b, C3, C3a, C3b, C4, C4a, C4b, C5, C5a, C5b, C6, C7, C8, C9, factor B, factor D, factor H, properdin, sclerostin, fibrinogen, fibrin, prothrombin, thrombin, tissue factor, factor V, factor Va, factor VII, factor VIIa, factor VIII, factor VIIa, factor IX, factor IXa, factor X, factor Xa, factor XI, factor XIa, factor XII, factor XIIa, factor XIII, factor XIIIa, TFPI, antithrombin III, EPCR, thrombomodulin, TAPI, tPA, plasminogen, plasmin, PAI-1, PAI-2, GPC3, Syndecan-1, Syndecan-2, Syndecan-3, Syndecan-4, LPA, and S1P; and receptors for hormone and growth factors.

[0327] As discussed herein, one or more amino acid residue alterations are allowed in the amino acid sequences constituting the variable regions as long as their antigen-binding activities are maintained. When altering a variable region amino acid sequence, there is no particularly limitation on the site of alteration and number of amino acids altered. For example, amino acids present in CDR and/or FR can be altered appropriately. When altering amino acids in a variable region, the binding activity is preferably maintained without particular limitation; and for example, as compared to before alteration, the binding activity may be 50% or more, 80% or more, and 100% or more. Furthermore, the binding activity may be increased by amino acid alterations. For example, the binding activity may be 2-, 5-, 10-times higher or such than that before alteration. Alteration of amino acid sequence may be at least one of amino acid residue substitution, addition, deletion, and modification.

[0328] For example, the modification of the N-terminal glutamine of a variable region into pyroglutamic acid by pyroglutamylation is a modification well known to those skilled in the art. Thus, when the heavy-chain N terminus is glutamine, antibodies described herein may comprise the variable regions in which the glutamine is modified to pyroglutamic acid.

[0329] Antibody variable regions described herein may have any sequences, and they may be antibody variable regions of any origin, such as mouse antibodies, rat antibodies, rabbit antibodies, goat antibodies, camel antibodies, humanized antibodies produced by humanizing these non-human antibodies, and human antibodies. Furthermore, these antibodies may have various amino acid substitutions introduced into their variable regions to improve their antigen binding, pharmacokinetics, stability, and immunogenicity. Variable regions may be able to bind antigens repeatedly due to their pH dependency in antigen binding (WO 2009/125825).

[0330] kappa chain and lambda chain are present in antibody light-chain constant regions, and either one is acceptable. Furthermore, they may have some amino acid alterations such as substitutions, deletions, additions, and/or insertions.

[0331] Furthermore, polypeptides comprising variant Fc regions described herein may be made into Fc fusion proteins by linking to other proteins such as physiologically active peptides. Such fusion proteins may be a multimer of at least two polypeptides comprising the variant Fc regions. Examples of the other proteins include receptors, adhesion molecules, ligands, and enzymes, but are not limited thereto.

[0332] Examples of Fc fusion proteins include proteins fused with an Fc region to a receptor that binds to a target molecule, including TNFR-Fc fusion protein, IL1R-Fc fusion protein, VEGFR-Fc fusion protein, and CTLA4-Fc fusion protein (Economides et al., *Nat. Med.* 9(1):47-52 (2003); Dumont et al., *BioDrugs.* 20(3):151-60 (2006)). Furthermore, proteins to be fused may be other molecules that have a target-binding activity, for example, scFvs (WO 2005/037989), single-domain antibodies (WO 2004/058821; WO 2003/002609), antibody-like molecules (Davinder, *Curr. Op. Biotech.* 17:653-658 (2006); *Current Opinion in Biotechnology* 18:1-10 (2007); Nygren et al., *Curr. Op. Struct. Biol.* 7:463-469 (1997); and Hoss, *Protein Science* 15:14-27 (2006)) such as DARPin (WO 2002/020565), Affibody (WO 1995/001937), Avimer (WO 2004/044011; WO 2005/040229), and Adnectin (WO 2002/032925). Furthermore, antibodies and Fc fusion proteins may be multispecific and may bind to multiple types of target molecules or epitopes.

[0333] B. Recombinant Methods and Compositions

Antibodies may be produced using recombinant methods and compositions, e.g., as described in US Patent No. 4,816,567. In one embodiment, isolated nucleic acid encoding an anti-myostatin antibody described herein is provided. In another embodiment, isolated nucleic acid encoding a polypeptide comprising a variant Fc region or a parent Fc region described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic

acid are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, e.g., a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., a Y0, NS0, and Sp20 cell). In one embodiment, a method of making an anti-myostatin antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium). In another embodiment, a method of making a polypeptide comprising a variant Fc region or a parent Fc region is provided, wherein the method comprises culturing a host cell comprising the nucleic acid(s) encoding a polypeptide such as, an antibody, Fc region, or variant Fc region, as provided above, under conditions suitable for expression of the polypeptide, and optionally recovering the polypeptide from the host cell (or host cell culture medium).

[0334] For recombinant production of an anti-myostatin antibody, nucleic acids encoding an antibody, e.g., as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. For recombinant production of an Fc region, nucleic acid encoding an Fc region is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0335] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., US Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (See also, Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0336] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi

and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0337] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0338] Plant cell cultures can also be utilized as hosts. See, e.g., US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0339] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR- CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

[0340] Antibodies with pH-dependent characteristics may be obtained using screening methods and/or mutagenesis methods e.g., as described in WO 2009/125825. The screening methods may comprise any process by which an antibody having pH-dependent binding characteristics is identified within a population of antibodies specific for a particular antigen. In certain embodiments, the screening methods may comprise measuring one or more binding parameters (e.g., KD or kd) of individual antibodies within an initial population of antibodies both at acidic and neutral pH. The binding parameters of the antibodies may be measured using, e.g., surface plasmon resonance, or any other analytic method that allows for the quantitative or qualitative assessment of the binding characteristics of an antibody to a particular antigen. In

certain embodiments, the screening methods may comprise identifying an antibody that binds to an antigen with an acidic/neutral KD ratio of 2 or greater. In further embodiments, the screening methods may comprise identifying an antibody that binds to an antigen with a pH5.8/pH7.4 KD ratio of 2 or greater. Alternatively, the screening methods may comprise identifying an antibody that binds to an antigen with an acidic/neutral kd ratio of 2 or greater. In further embodiments, the screening methods may comprise identifying an antibody that binds to an antigen with a pH5.8/pH7.4 kd ratio of 2 or greater.

[0341] In another embodiment, the mutagenesis methods may comprise incorporating a deletion, substitution, or addition of an amino acid within the heavy and/or light chain of the antibody to enhance the pH-dependent binding of the antibody to an antigen. In certain embodiments, the mutagenesis may be carried out within one or more variable domains of the antibody, e.g., within one or more HVRs (e.g., CDRs). For example, the mutagenesis may comprise substituting an amino acid within one or more HVRs (e.g., CDRs) of the antibody with another amino acid. In certain embodiments, the mutagenesis may comprise substituting one or more amino acids in at least one HVR (e.g., CDR) of the antibody with a histidine. In certain embodiments, "enhanced pH-dependent binding" means that the mutated version of the antibody exhibits a greater acidic/neutral KD ratio, or a greater acidic/neutral kd ratio, than the original "parent" (i.e., the less pH-dependent) version of the antibody prior to mutagenesis. In certain embodiments, the mutated version of the antibody has an acidic/neutral KD ratio of 2 or greater. In certain embodiments, the mutated version of the antibody has a pH5.8/pH7.4 KD ratio of 2 or greater. Alternatively, the mutated version of the antibody has an acidic/neutral kd ratio of 2 or greater. In further embodiments, the mutated version of the antibody has a pH5.8/pH7.4 kd ratio of 2 or greater.

[0342] Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen 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_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

[0343] Animals (usually non-human mammals) are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 micro g or 5 micro g of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with 1/5 to 1/10 the original amount of peptide or

conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

- [0344] Monoclonal antibodies are obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translational modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies.
- [0345] For example, the monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., *Nature* 256(5517):495-497 (1975). In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro.
- [0346] The immunizing agent will typically include the antigenic protein or a fusion variant thereof. Generally either peripheral blood lymphocytes (PBLs) are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, Academic Press (1986), pp. 59-103).
- [0347] Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which are substances that prevent the growth of HGPRT-deficient cells.
- [0348] Preferred immortalized myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred are murine

myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 cells (and derivatives thereof, e.g., X63-Ag8-653) available from the American Type Culture Collection, Manassas, Virginia USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor et al. *J. Immunol.* 133(6):3001-3005 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, Marcel Dekker, Inc., New York, pp. 51-63 (1987)).

- [0349] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA). Such techniques and assays are known in the art. For example, binding affinity may be determined by the Scatchard analysis of Munson, *Anal. Biochem.* 107(1):220-239 (1980).
- [0350] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, *supra*). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown *in vivo* as tumors in a mammal.
- [0351] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxyapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.
- [0352] Antibodies may be produced by immunizing an appropriate host animal against an antigen. In one embodiment, the antigen is a polypeptide comprising a full-length myostatin. In one embodiment, the antigen is a polypeptide comprising latent myostatin. In one embodiment, the antigen is a polypeptide comprising a myostatin propeptide. In one embodiment, the antigen is a polypeptide comprising the region corresponding to the amino acids at positions 21 to 100 of myostatin propeptide (SEQ ID NO: 78). In one embodiment, the antigen is a polypeptide comprising amino acids at positions 21-80, 41-100, 21-60, 41-80, 61-100, 21-40, 41-60, 61-80, or 81-100 of myostatin propeptide (SEQ ID NO: 78). Also included in the present invention are antibodies produced by immunizing an animal against the antigen. The antibodies may incorporate any of the features, singly or in combination, as described in "Exemplary Anti-myostatin Antibodies" above.
- [0353] An Fc region may be obtained by re-eluting the fraction adsorbed onto protein A column after partially digesting IgG1, IgG2, IgG3, IgG4 monoclonal antibodies or

such using a protease such as pepsin. The protease is not particularly limited as long as it can digest a full-length antibody so that Fab and F(ab')₂ will be produced in a restrictive manner by appropriately setting the enzyme reaction conditions such as pH, and examples include pepsin and papain.

- [0354] Furthermore, the present invention provides a method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity in comparison with a polypeptide comprising a parent Fc region, which comprises introducing at least one amino acid alteration to the parent Fc region. In some aspects, the produced polypeptide is an antibody. In certain embodiments, an antibody is a chimeric antibody, or a humanized antibody. In some aspects, the produced polypeptide is an Fc fusion protein.
- [0355] In certain embodiments, the production method comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least one amino acid alteration to the parent Fc region within the polypeptide; (c) measuring the monkey Fc gamma RIIb-binding activities of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with enhanced monkey Fc gamma RIIb-binding activity in comparison with the polypeptide comprising the parent Fc region.
- [0356] In certain embodiments, the production method comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least one amino acid alteration to the parent Fc region within the polypeptide; (c) measuring the monkey Fc gamma RIIIa-binding activities of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with decreased monkey Fc gamma RIIIa-binding activity in comparison with the polypeptide comprising the parent Fc region.
- [0357] In certain embodiments, the production method comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least one amino acid alteration to the parent Fc region within the polypeptide; (c) measuring the human Fc gamma RIIb-binding activities of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with enhanced human Fc gamma RIIb-binding activity in comparison with the polypeptide comprising the parent Fc region.
- [0358] In certain embodiments, the production method comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least one amino acid alteration to the parent Fc region within the polypeptide; (c) measuring the human Fc gamma RIIIa-binding activities of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with decreased human Fc gamma RIIIa-

- binding activity in comparison with the polypeptide comprising the parent Fc region.
- [0359] In certain embodiments, the production method comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least one amino acid alteration to the parent Fc region within the polypeptide; (c) measuring the human Fc gamma RIIa (type H)-binding activities of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with decreased human Fc gamma RIIa (type H)-binding activity in comparison with the polypeptide comprising the parent Fc region.
- [0360] In certain embodiments, the production method comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least one amino acid alteration to the parent Fc region within the polypeptide; (c) measuring the human Fc gamma RIIa (type R)-binding activities of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with decreased human Fc gamma RIIa (type R)-binding activity in comparison with the polypeptide comprising the parent Fc region.
- [0361] In one aspect, at least one amino acid is altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 236, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).
- [0362] In another aspect, one amino acid is altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, at position 236.
- [0363] In another aspect, at least two amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, the alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 233, 234, 235, 237, 238, 239, 264, 266, 267, 268, 271, 295, 298, 325, 326, 327, 328, 330, 331, 332, 334, and 396, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0364] In another aspect, at least two amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, the alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 231, 232, 235, 239, 268, 295, 298, 326, 330, and 396, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0365] In another aspect, at least two amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, the alterations comprising: (a) one amino acid alteration at position 236, and (b) at least one amino acid alteration of at least one position selected from the group consisting of: 268, 295, 326, and 330, according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0366] In another aspect, amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, at positions of any one of the following (1)-(37): (1) at positions 231, 236, 239, 268 and 330; (2) at positions 231, 236, 239, 268, 295 and 330; (3) at positions 231, 236, 268 and 330; (4) at positions 231, 236, 268, 295 and 330; (5) at positions 232, 236, 239, 268, 295 and 330; (6) at positions 232, 236, 268, 295 and 330; (7) at positions 232, 236, 268 and 330; (8) at positions 235, 236, 268, 295, 326 and 330; (9) at positions 235, 236, 268, 295 and 330; (10) at positions 235, 236, 268 and 330; (11) at positions 235, 236, 268, 330 and 396; (12) at positions 235, 236, 268 and 396; (13) at positions 236, 239, 268, 295, 298 and 330; (14) at positions 236, 239, 268, 295, 326 and 330; (15) at positions 236, 239, 268, 295 and 330; (16) at positions 236, 239, 268, 298 and 330; (17) at positions 236, 239, 268, 326 and 330; (18) at positions 236, 239, 268 and 330; (19) at positions 236, 239, 268, 330 and 396; (20) at positions 236, 239, 268 and 396; (21) at positions 236 and 268; (22) at positions 236, 268 and 295; (23) at positions 236, 268, 295, 298 and 330; (24) at positions 236, 268, 295, 326 and 330; (25) at positions 236, 268, 295, 326, 330 and 396; (26) at positions 236, 268, 295 and 330; (27) at positions 236, 268, 295, 330 and 396; (28) at positions 236, 268, 298 and 330; (29) at positions 236, 268, 298 and 396; (30) at positions 236, 268, 326 and 330; (31) at positions 236, 268, 326, 330 and 396; (32) at positions 236, 268 and 330; (33) at positions 236, 268, 330 and 396; (34) at positions 236, 268 and 396; (35)

at positions 236 and 295; (36) at positions 236, 330 and 396; and (37) at positions 236 and 396; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0367] In a further aspect, an amino acid alteration in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, is selected at each position from the group consisting of: (a) Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 231; (b) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 232; (c) Asp at position 233; (d) Trp, Tyr at position 234; (e) Trp at position 235; (f) Ala, Asp, Glu, His, Ile, Leu, Met, Asn, Gln, Ser, Thr, Val at position 236; (g) Asp, Tyr at position 237; (h) Glu, Ile, Met, Gln, Tyr at position 238; (i) Ile, Leu, Asn, Pro, Val at position 239; (j) Ile at position 264; (k) Phe at position 266; (l) Ala, His, Leu at position 267; (m) Asp, Glu at position 268; (n) Asp, Glu, Gly at position 271; (o) Leu at position 295; (p) Leu at position 298; (q) Glu, Phe, Ile, Leu at position 325; (r) Thr at position 326; (s) Ile, Asn at position 327; (t) Thr at position 328; (u) Lys, Arg at position 330; (v) Glu at position 331; (w) Asp at position 332; (x) Asp, Ile, Met, Val, Tyr at position 334; and (y) Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Gln, Arg, Ser, Thr, Val, Trp, Tyr at position 396; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0368] In a further aspect, an amino acid alteration in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, is selected at each position from the group consisting of: (a) Gly, Thr at position 231; (b) Asp at position 232; (c) Trp at position 235; (d) Asn, Thr at position 236; (e) Val at position 239; (f) Asp, Glu at position 268; (g) Leu at position 295; (h) Leu at position 298; (i) Thr at position 326; (j) Lys, Arg at position 330, and (k) Lys, Met at position 396; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0369] In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asn at position 236, Glu at position 268, Lys at position 330, and Met at position 396; according to EU numbering. In a further aspect, amino

acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asn at position 236, Asp at position 268, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asn at position 236, Asp at position 268, Leu at position 295, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Thr at position 236, Asp at position 268, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asn at position 236, Asp at position 268, Leu at position 295, Thr at position 326, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Trp at position 235, Asn at position 236, Asp at position 268, Leu at position 295, Thr at position 326, and Lys at position 330; according to EU numbering.

[0370] In one aspect, at least one amino acid is altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, of at least one position selected from the group consisting of: 234, 238, 250, 264, 267, 307, and 330 according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0371] In another aspect, one amino acid is altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, at position 238.

[0372] In another aspect, at least two amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, the alterations comprising: (i) one amino acid alteration at position 238, and (ii) at least one amino acid alteration of at least one position selected from the group consisting of: 234, 250, 264, 267, 307, and 330 according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

[0373] In another aspect, amino acids are altered in the above-mentioned method for

producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, at positions of any one of the following (1)-(9): (1) at positions 234, 238, 250, 307 and 330; (2) at positions 234, 238, 250, 264, 307 and 330; (3) at positions 234, 238, 250, 264, 267, 307 and 330; (4) at positions 234, 238, 250, 267, 307 and 330; (5) at positions 238, 250, 264, 307 and 330; (6) at positions 238, 250, 264, 267, 307 and 330; (7) at positions 238, 250, 267, 307 and 330; (8) at positions 238, 250 and 307; and (9) at positions 238, 250, 307 and 330; according to EU numbering.

[0374] In a further aspect, an amino acid alteration in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, is selected at each position from the group consisting of: (a) Tyr at position 234; (b) Asp at position 238; (c) Val at position 250; (d) Ile at position 264; (e) Ala at position 267; (f) Pro at position 307; and (g) Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asp at position 238; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asp at position 238, Val at position 250, and Pro at position 307; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asp at position 238, Val at position 250, Pro at position 307, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asp at position 238, Val at position 250, Ile at position 264, Pro at position 307, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asp at position 238, Val at position 250, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Tyr at position 234, Asp at position 238, Val at position 250, Pro at position 307, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Tyr at position 234, Asp at position 238, Val at position 250, Ala at position 267, Pro at position 307, and Lys at

position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Asp at position 238, Val at position 250, Ile at position 264, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Tyr at position 234, Asp at position 238, Val at position 250, Ile at position 264, Pro at position 307, and Lys at position 330; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with enhanced Fc gamma RIIb-binding activity, are: Tyr at position 234, Asp at position 238, Val at position 250, Ile at position 264, Ala at position 267, Pro at position 307, and Lys at position 330; according to EU numbering. In certain embodiments, the Fc gamma RIIb has the sequence of cynomolgus monkey Fc gamma RIIb (SEQ ID NO:223). In certain embodiments, the Fc gamma RIIb has the sequence of human Fc gamma RIIb (e.g., SEQ ID NOS:212, 213, or 214).

- [0375] Furthermore, the present invention provides a method for producing a polypeptide comprising a variant Fc region with increased pI in comparison with a polypeptide comprising a parent Fc region, which comprises introducing at least two amino acid alterations to the parent Fc region.
- [0376] In certain embodiments, the production method for producing a polypeptide comprising a variant Fc region provided herein comprises the following steps: (a) preparing a polypeptide comprising a parent Fc region; (b) introducing at least two amino acid alterations to the parent Fc region within the polypeptide; (c) measuring the pI's of the polypeptide comprising the parent Fc region and the polypeptide comprising the Fc region in step (b); and (d) selecting a polypeptide comprising a variant Fc region with increased pI in comparison with the corresponding polypeptide comprising the parent Fc region.
- [0377] In one aspect, at least two amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, of at least two positions selected from the group consisting of: 285, 311, 312, 315, 318, 333, 335, 337, 341, 342, 343, 384, 385, 388, 390, 399, 400, 401, 402, 413, 420, 422, and 431, according to EU numbering. In a further aspect, the produced polypeptide comprises a variant Fc region with increased pI, of at least two positions selected from the group consisting of: 311, 341, 343, 384, 399, 400, 401, 402, and 413, according to EU numbering.
- [0378] In another aspect, amino acids are altered in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, at positions

of any one of the following (1)-(10): (1) at positions 311 and 341; (2) at positions 311 and 343; (3) at positions 311, 343 and 413; (4) at positions 311, 384 and 413; (5) at positions 311 and 399; (6) at positions 311 and 401; (7) at positions 311 and 413; (8) at positions 400 and 413; (9) at positions 401 and 413; and (10) at positions 402 and 413; according to EU numbering.

[0379] In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 400 and Lys at position 413; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 311 and Lys at position 413; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 311 and Arg at position 399; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 311 and Arg at position 343; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 311 and Arg at position 413; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 311, Arg at position 343, and Arg at position 413; according to EU numbering. In a further aspect, amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are: Arg at position 311, Arg at position 384, and Arg at position 413; according to EU numbering.

[0380] In a further aspect, the amino acid alterations in the above-mentioned method for producing a polypeptide comprising a variant Fc region with increased pI, are selected from Lys or Arg at each position.

[0381] In a further aspect, the amino acid alterations in the above-mentioned production methods are selected from any single alteration, combination of single alterations, or combination alterations described in Tables 14-30.

[0382] Optionally, the following additional steps can be included in the above-mentioned methods for producing a polypeptide comprising a variant Fc region, when the polypeptide further comprises an antigen-binding domain: (e) assessing pharmacokinetic of the antigen in plasma, after administration of the polypeptide comprising the parent Fc region and the polypeptide comprising the variant Fc region in animals such as mice, rats, rabbits, dogs, monkeys, and humans; and (f) selecting a polypeptide comprising a variant Fc region with enhanced ability of antigen elimination from

plasma in comparison with the polypeptide comprising the parent Fc region.

[0383] Polypeptides comprising a variant Fc region produced by any of the above-mentioned methods or other methods known in the art are included in the present invention.

[0384] C. Assays

Anti-myostatin antibodies provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

[0385] Variant Fc regions provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays described herein or otherwise known in the art.

[0386] 1. Binding assays and other assays

In one aspect, an antibody of the invention is tested for its antigen binding activity, by known methods such as ELISA, Western blot, BIACORE (registered trademark), etc. In one aspect, a polypeptide comprising an variant Fc region of the invention is tested for its Fc receptor binding activity, by known methods such as BIACORE (registered trademark), etc.

[0387] In another aspect, competition assays may be used to identify an antibody that competes for binding to myostatin with any anti-myostatin antibody described herein. In certain embodiments, when such a competing antibody is present in excess, it blocks (e.g., reduces) the binding of a reference antibody to myostatin by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more. In some instances, binding is inhibited by at least 80%, 85%, 90%, 95%, or more. In certain embodiments, such a competing antibody binds to the same epitope (e.g., a linear or a conformational epitope) that is bound by an anti-myostatin antibody described herein (e.g., an anti-myostatin antibody described in Tables 2a, 11a, or 13). In further aspects, the reference antibody has a VH and a VL pair described in Table 2a, 11a, or 13. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

[0388] In an exemplary competition assay, immobilized latent myostatin or myostatin propeptide is incubated in a solution comprising a first labeled antibody that binds to the myostatin and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to the myostatin. The second antibody may be present in a hybridoma supernatant. As a control, immobilized myostatin is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to the myostatin, excess unbound antibody is removed, and the amount

of label associated with immobilized myostatin is measured. If the amount of label associated with immobilized myostatin is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to the myostatin. See, Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

- [0389] Assays for determining the binding activity of a polypeptide containing a variant Fc region towards one or more Fc gamma R family members are described herein or otherwise known in the art. Such binding assays include but are not limited to BIACORE (registered trademark) analysis, which utilizes the surface plasmon resonance (SPR) phenomena, Amplified Luminescent Proximity Homogeneous Assay (ALPHA) screening, ELISA, and fluorescence activated cell sorting (FACS) (Lazar et al., *Proc. Natl. Acad. Sci. USA* (2006) 103(11): 4005-4010).
- [0390] In one embodiment, BIACORE (registered trademark) analysis can be used to evaluate whether the binding activity of a polypeptide comprising a variant Fc region is enhanced, or maintained or decreased with respect to a particular Fc gamma R family member. For example, by observing whether there is a decrease or an increase in the dissociation constant (KD) value obtained from sensorgram analysis, where various Fc gamma Rs are subjected to interaction as an analyte with polypeptides comprising a variant Fc region immobilized or captured onto the sensor chip using known methods and reagents such as Protein A, Protein L, Protein A/G, Protein G, anti-lambda chain antibodies, anti-kappa chain antibodies, antigenic peptides, antigenic proteins). Alterations in binding activity can also be determined by comparing changes in the resonance unit (RU) value on the sensorgram before and after the one or more types of Fc gamma Rs are subjected to interaction as analytes with the captured polypeptides comprising the variant Fc region. Alternatively, Fc gamma R can be immobilized or captured onto the sensor chips, and the polypeptides comprising the variant Fc region are used as an analyte.
- [0391] In BIACORE (registered trademark) analysis, one of the substances (the ligand) in observation of an interaction is immobilized onto a gold thin film on a sensor chip, and by shining light from the reverse side of the sensor chip so that total reflection takes place at the interface between the gold thin film and glass, a portion of reduced reflection intensity is formed in part of the reflected light (SPR signal). When the other one of the substances (the analyte) in observation of an interaction is made to flow on the sensor chip surface and the ligand binds to the analyte, the mass of the immobilized ligand molecule increases and the refractive index of the solvent on the sensor chip surface changes. The position of the SPR signal shifts as a result of this change in refractive index (on the other hand, the signal position returns when this binding dis-

sociates). The BIACORE (registered trademark) system indicates the amount of shift mentioned above, or more specifically the time variable of mass by plotting the change in mass on the sensor chip surface on the ordinate as the measurement data (sensorgram). The amount of analyte bound to the ligand trapped on the sensor chip surface is determined from the sensorgram. Kinetic parameters such as association rate constants (k_a) and dissociation rate constants (k_d) are determined from the curves of the sensorgram, and the dissociation constants (K_D) are determined from the ratio of these constants. In the BIACORE (registered trademark) method, a method for measuring inhibition is preferably used. An example of the method for measuring inhibition is described in Lazar et al., Proc. Natl. Acad. Sci. USA 103(11):4005-4010 (2006).

[0392] ALPHA screening is performed by ALPHA technology which uses two beads, a donor and an acceptor, based on the following principles. Luminescent signals are detected only when molecules bound to donor beads physically interact with molecules bound to the acceptor beads, and the two beads are in close proximity to each other. Laser-excited photosensitizer in the donor beads converts ambient oxygen to excited-state singlet oxygen. Singlet oxygen is dispersed around the donor beads, and when it reaches the adjacent acceptor beads, chemiluminescent reaction is induced in the beads, and light is ultimately emitted. When the molecules bound to the donor beads do not interact with the molecules bound to the acceptor beads, the chemiluminescent reaction does not take place because singlet oxygen produced by the donor beads does not reach the acceptor beads.

[0393] For example, a biotinylated polypeptide complex is bound to the donor beads, and Fc gamma receptor tagged with glutathione S transferase (GST) is linked to the acceptor beads. In the absence of a competing polypeptide complex comprising a variant Fc region, the polypeptide complex comprising a parent Fc region interacts with the Fc gamma receptor and produces 520-620 nm signals. The polypeptide complex comprising an untagged variant Fc region competes with the polypeptide complex comprising a parent Fc region for interaction with the Fc gamma receptor. Relative binding activities can be determined by quantifying the decrease in fluorescence observed as a result of the competition. Biotinylation of polypeptide complexes such as antibodies using Sulfo-NHS-biotin and such is well known. The method of expressing the Fc gamma receptor and GST in a cell carrying a fusion gene produced by fusing a polynucleotide encoding the Fc gamma receptor in frame with a polynucleotide encoding GST in an expressible vector, and performing purification using a glutathione column is appropriately adopted as a method for tagging an Fc gamma receptor with GST. The obtained signals are preferably analyzed, for example, by fitting them to a one-site competition model which uses a non-linear regression analysis using software

such as GRAPHPAD PRISM (GraphPad, San Diego).

- [0394] A variant Fc region with decreased Fc gamma R-binding activity refers to an Fc region which binds to Fc gamma R with essentially weaker binding activity than a parent Fc region when assays are performed using substantially the same amount of a corresponding parent Fc region and a variant Fc region. Furthermore, a variant Fc region with enhanced Fc gamma R-binding activity refers to an Fc region which binds to Fc gamma R with essentially stronger binding activity than a corresponding parent Fc region when assays are performed using substantially the same amount of a parent Fc region and a variant Fc region. A variant Fc region with maintained Fc gamma R-binding activity refers to an Fc region that binds to Fc gamma R with binding activity equivalent to or essentially not different from that of a parent Fc region when assays are performed using substantially the same amount of the corresponding parent Fc region and the polypeptide containing the variant Fc region.
- [0395] Whether or not the binding activities of an Fc region towards various Fc gamma Rs were enhanced or decreased can be determined from the increase or decrease in the amount of binding of the various Fc gamma Rs to the Fc region, which were determined according to the above-mentioned measurement method. Here, the amount of binding of the various Fc gamma Rs to the Fc region can be evaluated as a value obtained by dividing the difference in the RU values of sensorgrams that changed before and after interaction of various Fc gamma Rs as the analyte with the Fc region, by the difference in the RU values of sensorgrams that changed before and after capturing the Fc regions to the sensor chips.
- [0396] In the present invention, enhanced Fc gamma RIIb-binding activity preferably means, for example, that the ratio of [KD value of a parent Fc region for Fc gamma RIIb]/[KD value of a variant Fc region for Fc gamma RIIb] in the KD values measured by the above-mentioned measurement method preferably becomes 2.0 or greater, 3.0 or greater, 4.0 or greater, 5.0 or greater, 6.0 or greater, 7.0 or greater, 8.0 or greater, 9.0 or greater, 10 or greater, 15 or greater, 20 or greater, 25 or greater, 30 or greater, 35 or greater, 40 or greater, 45 or greater, or even 50 or greater, 55 or greater, 60 or greater, 65 or greater, 70 or greater, 75 or greater, 80 or greater, 85 or greater, 90 or greater, 95 or greater, or 100 or greater.
- [0397] The KD value (mol/L) of a variant Fc region described herein for Fc gamma RIIb is preferably less than that of a parent Fc region for Fc gamma RIIb, and may be, for example, 2.0×10^{-6} M or smaller, 1.0×10^{-6} M or smaller, 9.0×10^{-7} M or smaller, 8.0×10^{-7} M or smaller, 7.0×10^{-7} M or smaller, 6.0×10^{-7} M or smaller, 5.0×10^{-7} M or smaller, 4.0×10^{-7} M or smaller, 3.0×10^{-7} M or smaller, 2.0×10^{-7} M or smaller, 1.0×10^{-7} M or smaller, 9.0×10^{-8} M or smaller, 8.0×10^{-8} M or smaller, 7.0×10^{-8} M or smaller, 6.0×10^{-8} M or smaller, 5.0×10^{-8} M or smaller.

[0398] Furthermore, a variant Fc region with enhanced binding selectivity to Fc gamma RIIb compared to Fc gamma RIIa refers to an Fc region where: (a) Fc gamma RIIb-binding activity is enhanced, and Fc gamma RIIa-binding activity is maintained or decreased; (b) Fc gamma RIIb-binding activity is enhanced and Fc gamma RIIa-binding activity is also enhanced, but the degree of enhancement of Fc gamma RIIa-binding activity is lower than the degree of enhancement of Fc gamma RIIb-binding activity; or (c) Fc gamma RIIb-binding activity is decreased and Fc gamma RIIa-binding activity is also decreased, but the degree of decrease of Fc gamma RIIb-binding activity is less than the degree of decrease of Fc gamma RIIa-binding activity. Whether or not a variant Fc region has improved binding selectivity for Fc gamma RIIb rather than for Fc gamma RIIa can be determined, for example, by comparing the ratio of the KD value for Fc gamma RIIa to the KD value for Fc gamma RIIb of the variant Fc region (the ratio of [KD value of the variant Fc region for Fc gamma RIIa]/[KD value of the variant Fc region for Fc gamma RIIb]), with the ratio of the KD value for Fc gamma RIIa to the KD value for Fc gamma RIIb of the parent Fc region (the ratio of [KD value of the parent Fc region for Fc gamma RIIa]/[KD value of the parent Fc region for Fc gamma RIIb]), which were determined according to the above-mentioned examples. Specifically, when the KD ratio for the variant Fc region is greater than that of the parent Fc region, the variant Fc region can be determined to have an improved binding selectivity for Fc gamma RIIb rather than for Fc gamma RIIa in comparison with the parent Fc region. Especially in human, the Fc gamma RIIb-binding activity is likely to correlate with binding activity to Fc gamma RIIa (type R) than to Fc gamma RIIa (type H) since the amino acid sequence of Fc gamma RIIb shares higher identity with Fc gamma RIIa (type R) than Fc gamma RIIa (type H). Therefore, finding amino acid alteration(s) that can enhance binding selectivity to human Fc gamma RIIb compared to human Fc gamma RIIa (type R) is important for enhancing binding selectivity to Fc gamma RIIb compared to Fc gamma RIIa in humans.

[0399] When a variant Fc region of the present invention has higher binding activity against Fc gamma RIIb and lower binding activity against Fc gamma RIII (such as Fc gamma RIIIa or Fc gamma RIIIb) compared to those of a parent Fc region, the variant Fc region can be said to be Fc gamma RIIb-specific.

[0400] 2. Activity assays

In one aspect, assays are provided for identifying anti-myostatin antibodies having biological activity. Biological activity may include, e.g., inhibiting the activation of myostatin, blocking the release of mature myostatin from latent myostatin, inhibiting the proteolytic cleavage of latent myostatin, blocking the access of a protease to latent myostatin, etc. Antibodies having such biological activity in vivo and/or in vitro are

also provided. In certain embodiments, an antibody of the invention is tested for such biological activity.

[0401] In certain embodiments, whether a test antibody inhibits the cleavage of latent myostatin is determined by detecting the cleavage product of latent myostatin (myostatin) using a method known in the art such as electrophoresis, chromatography, immunoblot analysis, an enzyme-linked immunosorbent assay (ELISA), or mass spectrometry, after a protease that can cleave latent myostatin is contacted with the latent myostatin in the presence or absence of the test antibody (see, for example, Thies et al., *Growth Factors* 18(4):251-259 (2001)). Where a decreased amount of the cleavage product of latent myostatin (e.g., human myostatin propeptide) is detected in the presence of (or following contact with) the test antibody, the test antibody is identified as an antibody that can inhibit the cleavage of latent myostatin. In certain embodiments, whether a test antibody blocks access of a protease to latent myostatin is determined by methods for the detection of protein interactions between the protease and latent myostatin, e.g., ELISAs or BIACORE (registered trademark). Where a decreased interaction between the protease and latent myostatin is detected in the presence of (or following contact with) the test antibody, the test antibody is identified as an antibody that can block access of the protease to latent myostatin.

[0402] In certain embodiments, whether a test antibody blocks the release of mature myostatin from latent myostatin is determined by detecting mature myostatin activity, for example, the activity of binding to a myostatin receptor, or the activity of mediating signal transduction in a cell expressing a myostatin receptor (e.g., ActRIIb). Cells useful for such an assay can be those that express an endogenous myostatin receptor, for example, L6 myocytes, or can be those that are genetically modified, transiently or stably, to express a transgene encoding a myostatin receptor, for example, an activin receptor such as an activin type II receptor (Thies et al, *Supra*). Binding of myostatin to a myostatin receptor can be detected using a receptor binding assay. Myostatin mediated signal transduction can be detected at any level in the signal transduction pathway, for example, by examining phosphorylation of a Smad polypeptide, examining expression of a myostatin regulated gene including a reporter gene, or measuring proliferation of a myostatin-dependent cell. Where a decreased mature myostatin activity is detected in the presence of (or following contact with) the test antibody, the test antibody is identified as an antibody that can block the release of mature myostatin from latent myostatin.

[0403] Inhibition of myostatin activation can also be detected and/or measured using the methods set forth and exemplified in the working examples. Using assays of these or other suitable types, test antibodies can be screened for those capable of inhibiting the activation of myostatin. In certain embodiments, inhibition of myostatin activation

includes at least a 5%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% or greater decrease in myostatin activation in the assay as compared to a negative control under similar conditions. In some embodiments, it refers to the inhibition of myostatin activation of at least 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% or greater.

[0404] In another aspect, assays for identifying anti-myostatin antibodies that form an immune complex (i.e., an antigen-antibody complex) with myostatin are provided. Antibodies having such biological activity in vivo and/or in vitro are also provided.

[0405] In certain embodiments, an antibody of the invention is tested for such biological activity.

[0406] In certain embodiments, the formation of an immune complex is evaluated by a method such as size exclusion (gel filtration) chromatography, ultracentrifugation, light scattering, electron microscope, or mass spectrometry (Mol. Immunol. 39:77-84 (2002), Mol. Immunol. 47:357-364 (2009)). These methods make use of the property that an immune complex is a larger molecule than an antibody alone, or an antigen alone. Where a large complex containing two or more antibodies and two or more antigens (e.g., myostatin molecules) is detected in the presence of a test antibody and an antigen, the test antibody is identified as an antibody that can form an immune complex containing two or more antibodies and two or more molecules of myostatin. In another embodiment, formation of an immune complex is evaluated by a method such as, ELISA, FACS, or SPR (surface plasmon resonance assay; for example, using BIACORE (registered trademark)) (Shields et al., J. Biol. Chem. 276(9):6591-6604 (2001); Singh et al., J. Immunol. Methods 50:109-114 (1982); Suzuki et al., J. Immunol. 184(4):1968-1976 (2010); Luo et al., mAbs 1(5):491-504 (2009)). These methods make use of the property that an immune complex containing two or more antibodies and two or more antigens can bind more strongly to an Fc receptor or a complement component than an antibody or antigen alone can. Where an increased binding to an Fc receptor or a complement component is detected in the presence of both a test antibody and an antigen compared to in the presence of an antibody alone, the test antibody is identified as an antibody that can form an immune complex containing two or more antibodies and two or more molecules of myostatin. In another embodiment, formation of an immune complex is evaluated by administering a test antibody to an animal (e.g., a mouse) and measuring the clearance of antigen from plasma. As described above, an antibody which forms an immune complex containing two or more antibodies with two or more antigens is expected to accelerate the elimination of antigens from plasma. Therefore, where an accelerated elimination of myostatin from plasma is observed in a test antibody-administered mouse compared to in a reference antibody-administered mouse, the test antibody is identified as an antibody that can form an immune complex containing two or more antibodies and two

or more molecules of myostatin more efficiently than the reference antibody.

[0407] D. Immunoconjugates

In some embodiments, the invention provides immunoconjugates comprising an anti-myostatin antibody herein conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (e.g., protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[0408] In some embodiments, the invention provides immunoconjugates comprising a polypeptide comprising a variant Fc region herein conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (e.g., protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[0409] In one embodiment, an immunoconjugate is an antibody-drug conjugate (ADC) in which an antibody is conjugated to one or more drugs, including but not limited to a maytansinoid (see US Patent Nos. 5,208,020, 5,416,064 and EP Patent EP 0 425 235 B1); an auristatin such as monomethylauristatin drug moieties DE and DF (MMAE and MMAF) (see US Patent Nos. 5,635,483 and 5,780,588, and 7,498,298); a dolastatin; a calicheamicin or derivative thereof (see US Patent Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, and 5,877,296; Hinman et al., *Cancer Res.* 53:3336-3342 (1993); and Lode et al., *Cancer Res.* 58:2925-2928 (1998)); an anthracycline such as daunomycin or doxorubicin (see Kratz et al., *Current Med. Chem.* 13:477-523 (2006); Jeffrey et al., *Bioorganic & Med. Chem. Letters* 16:358-362 (2006); Torgov et al., *Bioconj. Chem.* 16:717-721 (2005); Nagy et al., *Proc. Natl. Acad. Sci. USA* 97:829-834 (2000); Dubowchik et al., *Bioorg. & Med. Chem. Letters* 12:1529-1532 (2002); King et al., *J. Med. Chem.* 45:4336-4343 (2002); and US Patent No. 6,630,579); methotrexate; vindesine; a taxane such as docetaxel, paclitaxel, larotaxel, tesetaxel, and ortataxel; a trichothecene; and CC1065.

[0410] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, croton, *sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and a tricothecene.

[0411] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples

include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese and iron.

[0412] Conjugates of an antibody and cytotoxic agent may be made using a variety of bi-functional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO 1994/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., Cancer Res. 52:127-131 (1992); US Patent No. 5,208,020) may be used.

[0413] The immunoconjugates or ADCs herein expressly contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (e.g., from Pierce Biotechnology, Inc., Rockford, IL., U.S.A).

[0414] E. Methods and Compositions for Diagnostics and Detection

In certain embodiments, any of the anti-myostatin antibodies provided herein is useful for detecting the presence of myostatin in a biological sample. The term "detecting" as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue, such as serum, whole blood, plasma, biopsy sample, tissue sample, cell suspension, saliva, sputum, oral fluid, cerebrospinal fluid, amniotic fluid, ascites fluid, milk, colostrum, mammary gland secretion, lymph, urine, sweat, lacrimal fluid, gastric fluid, synovial fluid, peritoneal fluid, ocular lens fluid or mucus.

[0415] In one embodiment, an anti-myostatin antibody for use in a method of diagnosis or detection is provided. In a further aspect, a method of detecting the presence of latent myostatin or myostatin propeptide in a biological sample is provided. In certain embodiments, the method comprises contacting the biological sample with an anti-myostatin antibody as described herein under conditions permissive for binding of the anti-myostatin antibody to myostatin, and detecting whether a complex is formed between the anti-myostatin antibody and myostatin. Such method may be an in vitro or in vivo method. In one embodiment, an anti-myostatin antibody is used to select subjects eligible for therapy with an anti-myostatin antibody, e.g., where myostatin is a biomarker for selection of patients.

[0416] In certain embodiments, labeled anti-myostatin antibodies are provided. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, e.g., through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P , ^{14}C , ^{125}I , ^3H , and ^{131}I , fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luciferases, e.g., firefly luciferase and bacterial luciferase (US Patent No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, beta-galactosidase, glucoamylase, lysozyme, saccharide oxidases, e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

[0417] F. Pharmaceutical Formulations

Pharmaceutical formulations of an anti-myostatin antibody as described herein are prepared by mixing such antibody having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions.

[0418] Pharmaceutical formulations of a polypeptide comprising a variant Fc region as described herein are prepared by mixing such polypeptide having the desired degree of purity with one or more optional pharmaceutically acceptable carriers in the form of lyophilized formulations or aqueous solutions.

[0419] Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: 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 counterions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX (registered trademark), Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Publ. Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

- [0420] Exemplary lyophilized antibody formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO 2006/044908, the latter formulations including a histidine-acetate buffer.
- [0421] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.
- [0422] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).
- [0423] Sustained-release preparations may be prepared. 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.

- [0424] The formulations to be used for in vivo administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.
- [0425] G. Therapeutic Methods and Compositions
Any of the anti-myostatin antibodies provided herein may be used in therapeutic methods. Likewise, any of the polypeptides comprising an variant Fc region provided herein may be used in therapeutic methods.
- [0426] In one aspect, an anti-myostatin antibody for use as a medicament is provided. In further aspects, an anti-myostatin antibody for use in treating a disease is provided. In certain embodiments, an anti-myostatin antibody for use in a method of treatment is provided. In certain embodiments, the invention provides an anti-myostatin antibody for use in a method of treating an individual having a disease comprising administering to the individual an effective amount of the anti-myostatin antibody. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent. An "individual" according to any of the above embodiments is preferably a human.
- [0427] An anti-myostatin antibody of the present invention may exhibit pH-dependent binding characteristics. In further embodiments, the invention provides an anti-myostatin antibody for use in enhancing the clearance of myostatin from plasma. In certain embodiments, the invention provides an anti-myostatin antibody for use in a method of enhancing the clearance of myostatin from plasma in an individual comprising administering to the individual an effective amount of the anti-myostatin antibody to enhance the clearance of myostatin from plasma. In one embodiment, an anti-myostatin antibody with pH-dependent binding characteristics enhances the clearance of myostatin from plasma, compared to a conventional anti-myostatin antibody which does not have pH-dependent binding characteristics. In a further embodiment, an anti-myostatin antibody with a pH-dependent binding characteristic between binding at pH5.8 and pH7.4 enhances the clearance of myostatin from plasma, compared to a conventional anti-myostatin antibody which does not have pH-dependent binding characteristics. An "individual" according to any of the above embodiments is preferably a human.
- [0428] In a further aspect, the invention provides the use of an anti-myostatin antibody in the manufacture or preparation of a medicament. In one embodiment, the medicament is for treatment of a disease. In a further embodiment, the medicament is for use in a method of treating a disease comprising administering to an individual having a disease an effective amount of the medicament. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent. An "individual" according to any of the above embodiments may be a human.

- [0429] An anti-myostatin antibody of the present invention may exhibit pH-dependent binding characteristics. In a further embodiment, the medicament is for enhancing the clearance of myostatin from plasma. In a further embodiment, the medicament is for use in a method of enhancing the clearance of myostatin from plasma in an individual comprising administering to the individual an effective amount of the medicament to enhance the clearance of myostatin from plasma. In one embodiment, an anti-myostatin antibody with pH-dependent binding characteristics enhances the clearance of myostatin from plasma, compared to a conventional anti-myostatin antibody which does not have pH-dependent binding characteristics. In a further embodiment, the anti-myostatin antibody exhibits different pH-dependent binding characteristics between pH5.8 and pH7.4. An "individual" according to any of the above embodiments is preferably a human.
- [0430] In another aspect, the invention provides a method for treating a disease. In one embodiment, the method comprises administering to an individual having such a disease an effective amount of an anti-myostatin antibody provided herein. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent. The "individual" according to any of the above embodiments may be a human.
- [0431] An anti-myostatin antibody of the present invention may exhibit pH-dependent binding characteristics. In a further embodiment, the invention provides a method for enhancing the clearance of myostatin from plasma in an individual. In one embodiment, the method comprises administering to the individual an effective amount of an anti-myostatin antibody provided herein to enhance the clearance of myostatin from plasma. In one embodiment, an anti-myostatin antibody with pH-dependent binding characteristics enhances the clearance of myostatin from plasma, compared to a conventional anti-myostatin antibody which does not have pH-dependent binding characteristics. In a further embodiment, the anti-myostatin antibody exhibits different pH-dependent binding characteristics between pH5.8 and pH7.4. In one embodiment, an "individual" is a human.
- [0432] In a further aspect, the invention provides pharmaceutical formulations comprising any of the anti-myostatin antibodies provided herein, e.g., for use in any of the above therapeutic methods. In one embodiment, a pharmaceutical formulation comprises any of the anti-myostatin antibodies provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises any of the anti-myostatin antibodies provided herein and at least one additional therapeutic agent.
- [0433] In a further aspect, the pharmaceutical formulation is for treatment of a disease. An anti-myostatin antibody of the present invention may exhibit pH-dependent binding characteristics. In a further embodiment, the pharmaceutical formulation is for

enhancing the clearance of myostatin from plasma. In one embodiment, the pharmaceutical formulation is administered to an individual having a disease. An "individual" according to any of the above embodiments is preferably a human.

- [0434] In a further aspect, the invention provides methods for preparing a medicament or a pharmaceutical formulation, comprising mixing any of the anti-myostatin antibodies provided herein with a pharmaceutically acceptable carrier, e.g., for use in any of the above therapeutic methods. In one embodiment, the methods for preparing a medicament or a pharmaceutical formulation further comprise adding at least one additional therapeutic agent to the medicament or pharmaceutical formulation.
- [0435] Any of the polypeptide comprising a variant Fc region provided herein may be used in therapeutic methods. In a further aspect, the invention provides pharmaceutical formulations comprising a polypeptide comprising any of the polypeptides comprising variant Fc regions provided herein, e.g., for use in therapeutic methods. In one embodiment, a pharmaceutical formulation comprises a polypeptide comprising any of the polypeptides comprising variant Fc regions provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises a polypeptide comprising any of the variant Fc regions provided herein and at least one additional therapeutic agent.
- [0436] In one aspect, a polypeptide comprising a variant Fc region for use as a medicament is provided. In further aspects, a polypeptide comprising a variant Fc region for use in treating a disorder is provided. In certain embodiments, a polypeptide comprising a variant Fc region for use in a method of treatment is provided. In certain embodiments, the invention provides a polypeptide comprising a variant Fc region for use in a method of treating an individual having a disorder comprising administering to the individual an effective amount of the polypeptide comprising a variant Fc region provided herein. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent. In one embodiment, the "individual" is a human.
- [0437] In a further aspect, the invention provides the use of a polypeptide comprising a variant Fc region in the manufacture or preparation of a medicament. In one embodiment, the medicament is for treatment of a disorder. In some aspects, the polypeptide is an antibody. In some aspects, the polypeptide is an Fc fusion protein. In a further embodiment, the medicament is for use in a method of treating a disorder comprising administering to an individual having the disorder to be treated an effective amount of the medicament. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent. In one embodiment, the "individual" is a human.
- [0438] In a further aspect, the invention provides a method for treating a disorder. In one

embodiment, the method comprises administering to an individual having such a disorder an effective amount of a polypeptide comprising a variant Fc region. In one embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent. In one embodiment, the "individual" is a human.

[0439] In a further aspect, the invention provides pharmaceutical formulations comprising a polypeptide comprising a variant Fc region provided herein, for use in a therapeutic method such as any of the therapeutic methods described herein. In one embodiment, a pharmaceutical formulation comprises a polypeptide comprising a variant Fc region provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises a polypeptide comprising a variant Fc region provided herein and at least one additional therapeutic agent.

[0440] In a further aspect, the pharmaceutical formulation is for treatment of a disorder. In one embodiment, the pharmaceutical formulation is administered to an individual having a disorder. In one embodiment, the "individual" is a human.

[0441] Antibodies which have been modified to have enhanced binding activity to Fc gamma Rs including Fc gamma RIIb by modification of at least one amino acid residue can promote antigen elimination from the plasma, as described or suggested in, for example, WO 2013/047752, WO 2013/125667, WO 2014/030728, or WO 2014/163101.

[0442] Without being bound by a particular theory, an antibody having an increased Fc gamma R-binding activity under a neutral pH condition is rapidly taken up into cells together with its antigen complexed with the antibody, and as a result, antigen elimination from plasma can be promoted when the antibody is administered in vivo.

[0443] Antibodies which have been modified to have an increased pI by modification of at least one amino acid residue that can be exposed on the antibody surface can be incorporated more rapidly into cells or can promote antigen elimination from the plasma, as described or suggested in, for example, WO 2007/114319, WO 2009/041643, WO 2014/145159, or WO 2012/016227.

[0444] Without being bound by a particular theory, it is believed that the pH of biological fluids (for example, plasma) is in a neutral pH range. In biological fluids, the net positive charge of a pI-increased antibody is increased due to the increased pI, and as a result the antibody is more strongly attracted by physicochemical Coulomb interaction to the endothelial cell surface that has a net negative charge compared to an antibody not having an increased pI. That means, via such non-specific binding, uptake into cells of the antibody complexed with its antigen is enhanced, which results in enhancement of antigen elimination from plasma. These phenomena are expected to occur commonly in vivo, regardless of cell type, tissue type, organ type, etc.

- [0445] Herein, enhancement of antigen elimination from plasma means, for example, that the rate of antigen elimination from plasma is increased as compared to that when a polypeptide comprising a corresponding Fc region that has not been so modified has been administered. The increase of antigen elimination from plasma can be assessed, for example, by measuring the concentration of the antigen in plasma. Various methods for measuring antigen concentration in plasma are known in the art.
- [0446] In further embodiments, the invention provides a polypeptide comprising a variant Fc region for use in promoting elimination of an antigen from plasma. In certain embodiments, the invention provides a polypeptide comprising a variant Fc region for use in a method of promoting elimination of an antigen from plasma in an individual comprising administering to the individual an effective amount of the polypeptide comprising a variant Fc region to promote elimination of an antigen from plasma. In those embodiments, it is preferable that the polypeptide further comprises an antigen-binding domain. An "individual" according to any of the above embodiments is preferably a human.
- [0447] In a further aspect, the invention provides the use of a polypeptide comprising a variant Fc region in the manufacture or preparation of a medicament. In some aspects, the polypeptide is an antibody. In some aspects, the polypeptide is an Fc fusion protein. In a further embodiment, the medicament is for promoting elimination of an antigen from plasma. In a further embodiment, the medicament is for use in a method of promoting elimination of an antigen from plasma in an individual comprising administering to the individual an effective amount of the medicament to promote elimination of an antigen from plasma. In those embodiments, it is preferable that the polypeptide further comprises an antigen-binding domain. An "individual" according to any of the above embodiments may be a human.
- [0448] In a further embodiment, the invention provides a method for promoting elimination of an antigen from plasma in an individual. In one embodiment, the method comprises administering to the individual an effective amount of a polypeptide comprising a variant Fc region to promote elimination of an antigen from plasma. In those embodiments, it is preferable that the polypeptide further comprises an antigen-binding domain. In one embodiment, an "individual" is a human.
- [0449] In a further aspect, the invention provides pharmaceutical formulations comprising any of the polypeptides comprising a variant Fc region provided herein. In a further embodiment, the pharmaceutical formulation is for promoting elimination of an antigen from plasma. In that embodiment, it is preferable that the polypeptide further comprises an antigen-binding domain.
- [0450] In one embodiment, when compared to before amino acid modification, an antibody having a variant Fc region of the present invention enhances antigen elimination from

plasma, for example, by at least 1.1-fold, 1.25-fold, 1.5-fold, 1.75-fold, 2.0-fold, 2.25-fold, 2.5-fold, 2.75-fold, 3.0-fold, 3.25-fold, 3.5-fold, 3.75-fold, 4.0-fold, 4.25-fold, 4.5-fold, 4.75-fold, 5.0-fold, 5.5-fold, 6.0-fold, 6.5-fold, 7.0-fold, 7.5-fold, 8.0-fold, 8.5-fold, 9.0-fold, 9.5-fold, or 10.0-fold or more, when the antibody is administered in vivo.

- [0451] In a further aspect, the invention provides methods for preparing a medicament or a pharmaceutical formulation, comprising mixing any of the polypeptides comprising a variant Fc region provided herein with a pharmaceutically acceptable carrier, e.g., for use in any of the above therapeutic methods. In one embodiment, the methods for preparing a medicament or a pharmaceutical formulation further comprise adding at least one additional therapeutic agent to the medicament or pharmaceutical formulation.
- [0452] Antibodies of the invention can be used either alone or in combination with other agents in a therapy. For instance, an antibody of the invention may be co-administered with at least one additional therapeutic agent.
- [0453] Likewise, polypeptides comprising a variant Fc region of the invention can be used either alone or in combination with other agents in a therapy. For instance, a polypeptide comprising a variant Fc region of the invention may be co-administered with at least one additional therapeutic agent.
- [0454] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the antibody or polypeptide comprising a variant Fc region of the invention can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents. In one embodiment, the administration of the anti-myostatin antibody and the administration of an additional therapeutic agent occur within about one month, or within about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other.
- [0455] In another embodiment, the administration of the polypeptide comprising the variant Fc region and the administration of an additional therapeutic agent occur within about one month, or within about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other.
- [0456] An antibody or a polypeptide comprising a variant Fc region of the invention (and optionally any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g., by injections, such as intravenous or subcutaneous in-

jections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[0457] Antibodies or polypeptides comprising a variant Fc region of the invention can be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The antibody need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0458] For the prevention or treatment of disease, the appropriate dosage of an antibody of the invention (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the type of antibody, the type of polypeptide comprising a variant Fc region, the severity and course of the disease, whether the antibody or polypeptide comprising the variant Fc region, is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody or polypeptide comprising the variant Fc region, and the discretion of the attending physician. The antibody or polypeptide comprising a variant Fc region of the invention is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 micro g/kg to 15 mg/kg (e.g., 0.1mg/kg-10mg/kg) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 micro g/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 would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the antibody or polypeptide comprising the variant Fc region would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g., every week or every three weeks (e.g., such that the patient receives from about two to about twenty, or e.g.,

about six doses of the antibody or polypeptide comprising the variant Fc region). An initial higher loading dose, followed by one or more lower doses may be administered. The progress of this therapy is easily monitored by conventional techniques and assays.

[0459] It is understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to an anti-myostatin antibody.

[0460] It is likewise understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to a polypeptide comprising a variant Fc region provided herein.

[0461] H. Articles of Manufacture

In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and 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). At least one active agent in the composition is an antibody of the invention. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antibody of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0462] It is understood that any of the above articles of manufacture may include an immunoconjugate of the invention in place of or in addition to an anti-myostatin antibody.

Examples

[0463] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.

Example 1

[0464] Expression and purification of human, cynomolgus monkey, and mouse myostatin latent and mature form

Human latent myostatin (also described herein as human myostatin latent form) (SEQ ID NO: 1) was expressed transiently using FreeStyle293-F cells (FS293-F cells) (Thermo Fisher, Carlsbad, CA, USA). Conditioned media containing expressed human myostatin latent form was acidified to pH6.8 and diluted with 1/2 vol of milliQ water, followed by application to a Q-sepharose FF anion exchange column (GE healthcare, Uppsala, Sweden). The flow-through fraction was adjusted to pH5.0 and applied to a SP-sepharose HP cation exchange column (GE healthcare, Uppsala, Sweden), and then eluted with a NaCl gradient. Fractions containing the human myostatin latent form were collected and subsequently subjected to a Superdex 200 gel filtration column (GE healthcare, Uppsala, Sweden) equilibrated with 1x PBS. Fractions containing the human myostatin latent form were then pooled and stored at -80 degrees C.

[0465] Human mature myostatin (also described herein as human myostatin mature form) (SEQ ID NO: 2) was purified from the purified human myostatin latent form. The human myostatin latent form was acidified by addition of 0.1% trifluoroacetic acid (TFA) and applied to a Vydac 214TP C4 reverse phase column (Grace, Deerfield, IL, USA) and eluted with a TFA/CH₃CN gradient. Fractions containing human mature myostatin were pooled, dried and stored at -80 degrees C. To reconstitute, human mature myostatin was dissolved in 4mM HCl.

[0466] Expression and purification of myostatin latent and mature form from cynomolgus monkey (cynomolgus or cyno) (SEQ ID NOs: 3 and 4, respectively) and mouse (SEQ ID NOs: 5 and 6, respectively) were all performed exactly the same way as the human counterpart. The sequence homology of mature form among human, cyno, and mouse are 100% identical, therefore, any of mature myostatin regardless of species were used as mature myostatin in all the necessary experiments.

Example 2

[0467] Identification of anti-latent myostatin antibody

Anti-latent myostatin antibodies were prepared, selected, and assayed as follows.

[0468] Twelve to sixteen week old NZW rabbits were immunized intradermally with mouse latent myostatin and/or human latent myostatin (50-100 micro g/dose/rabbit). This dose was repeated 3-4 times over a one month period. One week after the final immu-

nization, the spleen and blood from the immunized rabbit were collected. Antigen-specific B-cells were stained with labelled antigen, sorted with FCM cell sorter (FACS aria III, BD), and plated in 96-well plates at a one cell/well density together with 25,000 cells/well of EL4 cells (European Collection of Cell Cultures) and with rabbit T-cell conditioned medium diluted 20 times, and were cultured for 7-12 days. EL4 cells were treated with mitomycin C (Sigma) for 2 hours and washed 3 times in advance. The rabbit T-cell conditioned medium was prepared by culturing rabbit thymocytes in RPMI-1640 containing Phytohemagglutinin-M (Roche), phorbol 12-myristate 13-acetate (Sigma) and 2% FBS. After cultivation, B-cell culture supernatants were collected for further analysis and pellets were cryopreserved.

[0469] An ELISA assay was used to test the specificity of antibodies in a B-cell culture supernatant. Streptavidin (GeneScript) was coated onto a 384-well MAXISorp (Nunc) at 50nM in PBS for 1 hour at room temperature. Plates were then blocked with Blocking One (Nacalai Tesque) diluted 5 times. Human or mouse latent myostatin was labelled with NHS-PEG4-Biotin (PIERCE) and was added to the blocked ELISA plates, incubated for 1 hour, and washed with Tris-buffered saline with 0.05% Tween-20 (TBS-T). B-cell culture supernatants were added to the ELISA plates, incubated for 1 hour, and washed with TBS-T. Binding was detected by goat anti-rabbit IgG-horseradish peroxidase (BETHYL) followed by the addition of ABTS (KPL).

[0470] A total of 17,818 B-cell lines were screened for binding specificity to mouse and/or human latent myostatin and 299 lines were selected and designated MST0255-287, 630-632, 677-759, 910, 932-1048, 1050-1055, 1057-1066, 1068, 1070-1073, 1075-1110, 1113-1119. RNA was purified from corresponding cell pellets using ZR-96 Quick-RNA kits (ZYMO RESEARCH).

[0471] DNA encoding the variable regions of the heavy and light chain of each selected cell line was amplified by reverse transcription PCR and cloned into expression vectors with the heavy chain constant region G1m sequence (SEQ ID NO: 50 (the amino acid sequence is shown in SEQ ID NO: 7)) and with the light chain constant region k0MTC or k0MC sequence (SEQ ID NO: 53 or 194 (the amino acid sequence (both are the same) is shown in SEQ ID NO: 8)), respectively. Recombinant antibodies were expressed transiently using the FreeStyle FS293-F cells and 293fectin (Life technologies), according to the manufacturer's instructions. Culture supernatant or recombinant antibodies were used for screening. Recombinant antibodies were purified with protein A (GE Healthcare) and eluted in D-PBS or His buffer (20mM Histidine, 150mM NaCl, pH6.0). Size exclusion chromatography was further conducted to remove high molecular weight and/or low molecular weight component, if necessary.

Example 3

- [0472] Characterization of anti-latent myostatin antibody
(HEK Blue Assay (BMP1 activation))

A reporter gene assay was used to assess the biological activity of active myostatin in vitro. HEK-Blue™ TGF-beta cells (Invivogen) which express a Smad3/4-binding elements (SBE)-inducible SEAP reporter genes, allow the detection of bioactive myostatin by monitoring the activation of the activin type 1 and type 2 receptors. Active myostatin stimulates the production of SEAP which is secreted into the cell supernatant. The quantity of SEAP secreted is then assessed using QUANTIBLue™ (Invivogen).

- [0473] HEK-Blue™ TGF-beta cells were maintained in DMEM medium (Gibco) supplemented with 10% fetal bovine serum, 50 micro g/mL streptomycin, 50 U/mL penicillin, 100 micro g/mL Normocin™, 30micro g/mL of Blasticidin, 200 micro g/mL of HygroGold™ and 100 micro g/mL of Zeocin™. During the functional assay, cells were changed to assay medium (DMEM with 0.1% bovine serum albumin, streptomycin, penicillin and Normocin™) and seeded to a 96-well plate. Human, cynomolgus, or mouse latent myostatin was incubated with recombinant human BMP1 (R&D Systems) and anti-latent antibody at 37 degrees C overnight. The sample mixtures were transferred to cells. After 24-hour incubation, the cell supernatants were mixed with QUANTIBLue™ and the optical density at 620 nm was measured in a colorimetric plate reader. As shown as Figure 1, mAb MST1032-G1m (see Table 2a for amino acid and nucleotide sequences) prevented protease-mediated activation of human, cynomolgus, and mouse latent myostatin, as reflected by lowered concentrations of secreted SEAP. MST1032-G1m showed almost comparable inhibition activity against human, cynomolgus, and mouse latent myostatin.

- [0474]

[Table 2a]

Anti-latent myostatin antibodies and their DNA and amino acid sequences (shown as SEQ ID NOs)

Antibody name	Abbreviation	Variable region						Constant region					
		Heavy			Light			Heavy			Light		
		DNA	PROTEIN	DNA	PROTEIN	DNA	PROTEIN	DNA	PROTEIN	DNA	PROTEIN	DNA	PROTEIN
MS_MST1032Ha-G1m/MST1032La-k0MC	MST1032-G1m	039	012	041	014	050	007	194	008				
MS_MST1032Ha-F760/MST1032La-k0MC	MST1032-F760	039	012	041	014	051	011	194	008				
MS_M103205H000-SG1/M103202L000-SK1	MS1032L000-SG1 or Ab001	040	013	042	015	052	009	054	010				
MS_M103205H000-F760/M103202L000-SK1	MS1032L000-F760	040	013	042	015	051	011	054	010				
MS_M103205H714-SG1/M103202L861-SK1	MS1032L001-SG1	043	032	046	035	052	009	054	010				
MS_M103205H781-SG1/M103202L719-SK1	MS1032L002-SG1	044	033	047	036	052	009	054	010				
MS_M103205H781-SG1/M103202L813-SK1	MS1032L003-SG1	044	033	048	037	052	009	054	010				
MS_M103205H707-SG1/M103202L802-SK1	MS1032L004-SG1	045	034	049	038	052	009	054	010				
MS_M103205H714-F760/M103202L861-SK1	MS1032L001-F760	043	032	046	035	051	011	054	010				
MS_M103205H781-F760/M103202L719-SK1	MS1032L002-F760	044	033	047	036	051	011	054	010				
MS_M103205H781-F760/M103202L813-SK1	MS1032L003-F760	044	033	048	037	051	011	054	010				
MS_M103205H707-F760/M103202L802-SK1	MS1032L004-F760	045	034	049	038	051	011	054	010				

[0475] [Table 2b]

HVR amino acid sequences of anti-latent myostatin antibodies (shown as SEQ ID NOs)

Antibody name	Abbreviation	Hyper Variable region (HVR)						
		H1	H2	H3	L1	L2	L3	
MS_MST1032Ha-G1m/MST1032La-KOMC	MST1032-G1m	055	058	061	065	070	073	
MS_MST1032Ha-F760/MST1032La-KOMC	MST1032-F760	055	058	061	065	070	073	
MS_M103205H000-SG1/M103202L000-SK1	MS1032L000-SG1 or Ab001	055	058	061	065	070	073	
MS_M103205H000-F760/M103202L000-SK1	MS1032L000-F760	055	058	061	065	070	073	
MS_M103205H714-SG1/M103202L861-SK1	MS1032L001-SG1	057	058	063	067	071	074	
MS_M103205H781-SG1/M103202L719-SK1	MS1032L002-SG1	057	060	063	066	072	073	
MS_M103205H781-SG1/M103202L813-SK1	MS1032L003-SG1	057	060	063	068	070	074	
MS_M103205H707-SG1/M103202L802-SK1	MS1032L004-SG1	056	058	063	069	071	073	
MS_M103205H714-F760/M103202L861-SK1	MS1032L001-F760	057	058	063	067	071	074	
MS_M103205H781-F760/M103202L719-SK1	MS1032L002-F760	057	060	063	066	072	073	
MS_M103205H781-F760/M103202L813-SK1	MS1032L003-F760	057	060	063	068	070	074	
MS_M103205H707-F760/M103202L802-SK1	MS1032L004-F760	056	058	063	069	071	073	

Example 4

- [0476] Characterization of anti-latent myostatin antibody
(HEK Blue Assay (Spontaneous activation))

Human, cynomolgus, or mouse latent myostatin was incubated with the anti-latent myostatin antibody at 37 degrees C overnight and the sample mixtures were transferred to HEK-Blue™ TGF-beta cells. After 24-hour incubation, cell supernatant was mixed with QUANTIBLUE™ and the optical density at 620 nm was measured in a colorimetric plate reader. As shown as Figure 2, the liberation of active myostatin from its latent form was detected after incubation at 37 degrees C. The presence of mAb MST1032-G1m, myostatin activation was inhibited and thus a lower SEAP level was detected in the cell supernatant. MST1032-G1m inhibited spontaneous activation of latent myostatin, and showed almost comparable inhibition activity against human, cynomolgus, and mouse latent myostatin.

Example 5

- [0477] Characterization of anti-latent myostatin antibody (ELISA)

Uncoated ELISA plates (NUNC-IMMUNO plate MAXISORP surface, Nalge Nunc International) were coated with 20 micro L of 50nM streptavidin (GenScript) for 1 hour at room temperature. Plates were then washed with PBST three times and blocked with 50 micro L 20% Blocking One (Nacalai Tesque) overnight. On the next day, each well of each plate was incubated with biotinylated mature myostatin, human or mouse biotinylated latent myostatin, or biotinylated recombinant mouse myostatin propeptide-Fc chimera protein (R&D Systems) at 4nM/well/20 micro L for 2 hours. After washing, 20 micro L of antibody sample was added to the wells and the plates were left for 1 hour. The plates were washed and 20 micro L of anti-human IgG-horseradish peroxidase (HRP) (Abcam) diluted in HEPES-buffered saline was added, and the plates were left for another hour. The plates were then washed again, and then 50 micro L ABTS (KPL) was added to each well, and the plates were incubated for 1 hour. The signal was detected at 405 nm in a colorimetric plate reader. The results of the binding experiment are shown in Figure 3. MST1032-G1m bound to latent myostatin (i.e., the non-covalent complex of mature myostatin and propeptides) and propeptide, but did not bind to mature myostatin. These results show that MST1032-G1m specifically binds to the myostatin propeptide (e.g., the propeptide portion), but not to active myostatin (e.g., mature region).

Example 6

- [0478] Characterization of anti-latent myostatin antibody (Western Blot)

Mouse latent myostatin was incubated with recombinant human BMP1 (R&D Systems), with or without MST1032-G1m at 37 degrees C overnight. The samples

were then mixed with 4x reducing SDS-PAGE sample buffer (Wako) and heated at 95 degrees C for 5 minutes and then loaded for SDS gel electrophoresis. Proteins were transferred to membrane by Trans-Blot (registered trademark) Turbo™ Transfer System (Bio-rad). Myostatin propeptide was detected using a sheep anti-mouse GDF8 propeptide antibody (R&D Systems), which was then detected by anti-sheep IgG-HRP (Santa Cruz). The membrane was incubated with ECL substrate, and imaged using an ImageQuant LAS 4000 (GE Healthcare). As shown in Figure 4, propeptide cleavage by BMP1 was inhibited by MST1032-G1m.

Example 7

[0479] Characterization of anti-latent myostatin antibody (BIACORE (registered trademark))

The kinetic parameters of anti-latent myostatin antibodies against human, cynomolgus monkey (cyno), and mouse latent myostatin were assessed at 37 degrees C at pH7.4 using a BIACORE (registered trademark) T200 instrument (GE Healthcare). ProA/G (Pierce) was immobilized onto all flow cells of a CM4 chip using amine coupling kit (GE Healthcare). Anti-latent myostatin antibody and analytes were prepared in ACES pH7.4 (20 mM ACES, 150 mM NaCl, 1.2 mM CaCl₂, 0.05% Tween 20, 0.005% NaN₃). Antibody was captured onto the sensor surface by ProA/G. Antibody capture levels were typically 150 to 220 resonance units (RU). Then human, cyno, or mouse latent myostatin was injected at 3.125 to 50 nM prepared by two-fold serial dilution, followed by dissociation. The sensor surface was regenerated with 25 mM NaOH. Kinetic parameters were determined by processing and fitting the data to a 1:1 binding model using BIACORE (registered trademark) T200 Evaluation software, version 2.0 (GE Healthcare). The sensorgrams are shown in Figure 5. Association rate (ka), dissociation rate (kd), and binding affinity (KD) are listed in Table 3. The kinetic parameters of MST1032-G1m toward human, cyno, and mouse latent myostatin were comparable.

[0480] [Table 3]

ka, kd, and KD of anti-latent myostatin antibody MST1032-G1m

	<i>ka</i> (M ⁻¹ s ⁻¹)	<i>kd</i> (s ⁻¹)	<i>KD</i> (M)
Human latent myostatin	1.13E+06	8.65E-05	7.66E-11
Mouse latent myostatin	1.41E+06	8.16E-05	5.79E-11
Cyno latent myostatin	1.09E+06	7.79E-05	7.17E-11

Example 8

[0481] Humanization of anti-latent myostatin antibody

Amino acid residues of an antibody variable region are numbered according to Kabat

(Kabat et al., Sequence of proteins of immunological interest, 5th Ed., Public Health Service, National Institutes of Health, Bethesda, MD (1991)).

[0482] Variable regions of the heavy and light chains for humanized MST1032 antibodies were designed. Some of the humanized MST1032 antibodies contain back mutation in framework region. The polynucleotides of the designed heavy and light chain variable regions were synthesised by GenScript Inc., and were cloned into expression vectors containing the heavy chain constant region SG1 sequence (SEQ ID NO: 52 (the amino acid sequence is shown in SEQ ID NO: 9)) and the light chain constant region SK1 sequence (SEQ ID NO: 54 (the amino acid sequence is shown in SEQ ID NO: 10)), respectively. Humanized antibodies were transiently expressed in FS293-F cells, and HEK Blue Assay and BIACORE (registered trademark) analysis were carried out as described above. As shown in Figure 6 and Table 4, and compared to Figures 1 and 2, humanized antibody (MS1032LO00-SG1) showed comparable inhibition activity and affinity to chimeric antibody (MST1032-G1m).

[0483] [Table 4]

Kinetic parameters of humanized anti-latent myostatin antibody

	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	KD (M)
MST1032-G1m	1.13E+06	8.65E-05	7.66E-11
MS1032LO00-SG1	1.27E+06	9.52E-05	7.50E-11

Example 9

[0484] Generation of pH-dependent anti-latent myostatin antibody

To generate pH-dependent anti-latent myostatin antibodies, histidine scanning mutagenesis was conducted for all CDRs of mAb MS1032LO00-SG1. Each amino acid in the CDRs was individually mutated to histidine using In-Fusion HD Cloning Kit (Clontech Inc. or Takara Bio company) according to the manufacturer's instructions. After confirming through sequencing that each variant was mutated correctly, variants were transiently expressed and purified by the method described above. All histidine-substituted variants were evaluated by a modified BIACORE (registered trademark) assay as compared to that described above. Briefly, an additional dissociation phase at pH5.8 was integrated into the BIACORE (registered trademark) assay immediately after the dissociation phase at pH7.4. This is to assess the pH-dependent dissociation between antibody (Ab) and antigen (Ag) from the complexes formed at pH7.4 as opposed to the corresponding dissociation at pH5.8. The dissociation rate at pH5.8 buffer was determined by processing and fitting data using the Scrubber 2.0 (BioLogic Software) curve fitting software.

[0485] As shown in Figure 7, the parental antibody (Ab001) showed no reduction in binding response at pH5.8 compared to the pH7.4 dissociation phase. Several of the single-

histidine substitutions resulted in a moderate to strong reduction in binding response at pH5.8 compared to the pH7.4 dissociation phase. The dissociation rate at pH5.8 for each of the single-histidine substitution variants are shown in Table 5. As shown in Table 5, Ab002 showed the fastest Ab/Ag complex dissociation rate at pH5.8, more than 200 fold faster than parental antibody (Ab001). Antibodies with a combination of these mutations in the CDRs were then generated. The CDR sequences of the antibodies containing these various mutations are shown in Table 6.

[0486] [Table 5]

pH5.8 dissociation rate for single histidine substituted anti-latent myostatin antibodies

Name of variable region		Abbreviation	kd (1/s)
Heavy chain	Light chain		
M103205H000	M103202L000	Ab001	2.92E-05
M103205H001	M103202L000	Ab002	6.09E-03
M103205H009	M103202L000	Ab003	8.80E-04
M103205H026	M103202L000	Ab004	1.86E-04
M103205H028	M103202L000	Ab005	7.63E-05
M103205H000	M103202L008	Ab006	8.58E-05
M103205H028	M103202L008	Ab007	4.15E-04

[0487]

[Table 6]

CDR sequences and their SEQ ID NOs of histidine substituted anti-latent myostatin antibodies

Heavy chain	Variable region				Kabat No.																														
	H1	H2	H3	HVR1	31	32	33	34	35	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	95	96	97	98	99	100	100a	100b	100c	101
M103205H020	055	058	061	013	S	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	T	G	G	D	L
M103205H001	056	058	061	016	H	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	T	G	G	D	L
M103205H009	065	059	061	017	S	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	T	G	G	D	L
M103205H028	055	058	062	018	S	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	T	G	G	D	L
M103205H028	055	058	063	019	S	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	H	G	G	D	L
M103205H033	056	059	061	020	H	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	T	G	G	D	L
M103205H034	055	059	062	021	S	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	T	G	G	D	L
M103205H035	056	058	062	022	H	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	T	G	G	D	L
M103205H036	056	059	062	023	H	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	T	G	G	D	L
M103205H707	056	058	063	024	H	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	H	G	G	D	L
M103205H708	055	059	063	025	S	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	H	G	G	D	L
M103205H709	055	058	064	026	S	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	H	G	G	D	L
M103205H710	056	059	063	027	H	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	Y	S	H	G	G	D	L
M103205H711	065	059	064	028	S	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	H	G	G	D	L
M103205H712	056	058	064	029	H	Y	D	I	S	I	S	Y	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	H	G	G	D	L
M103205H713	056	059	064	030	H	Y	D	I	S	I	S	H	A	G	S	T	Y	Y	A	S	W	A	K	G	G	V	P	A	H	S	H	G	G	D	L

Light chain	Variable region				Kabat No.																												
	L1	L2	L3	HVR1	24	25	26	27	27a	27b	28	29	30	31	32	33	34	50	51	52	53	54	55	56	89	90	91	92	93	94	95	95a	96
M103202L000	065	070	073	015	Q	S	S	Q	S	V	V	D	N	N	W	L	S	W	A	S	T	L	A	S	A	G	G	Y	G	G	L	Y	A
M103202L008	066	070	073	031	Q	S	S	Q	S	V	Y	H	N	N	W	L	S	W	A	S	T	L	A	S	A	G	G	Y	G	G	L	Y	A

Example 10

[0488] Affinity improvement of pH-dependent anti-latent myostatin antibody

To identify mutations which improve affinity at pH7.4 and/or in vitro inhibition activity, more than 500 variants were generated for heavy and light chain respectively, using at least one variant generated in Example 9 as a template. These variants had each amino acid in the CDRs substituted with 18 other amino acids, excluding the original amino acid and Cysteine. The binding ability of variants to human latent myostatin was assessed at 37 degrees C under pH7.4 using BIACORE (registered trademark) 4000 instrument (GE Healthcare). Culture supernatant containing variants in FS293-F cells was prepared with ACES pH7.4 buffer containing 10mg/ml BSA and 0.1mg/ml carboxymethyl dextran (CMD). Each antibody was captured onto the flow cells until the capture level reached around 200 RU. Then 25 nM human latent myostatin was injected over the flow cells. An additional dissociation phase at pH5.8 was integrated into the BIACORE (registered trademark) assay immediately after the dissociation phase at pH7.4. This additional dissociation phase assesses the pH-dependent dissociation between antibody (Ab) and antigen (Ag) from the complexes formed at pH7.4. The flow cell surface was regenerated with 25 mM NaOH. Kinetic parameters were determined using BIACORE (registered trademark) 4000 Evaluation software, version 2.0 (GE Healthcare). Analysis of additional dissociation at pH5.8 was performed using Scrubber2 (BioLogic Software).

[0489] Variants with improved affinity at pH7.4 and/or in vitro inhibition activity were selected, and combined with mutations improving pH dependency identified in Example 9. After combination of these mutations, four variants (MS1032LO01, 02, 03, and 04) were selected, and transiently expressed in SG1 or F760 (SEQ ID NO: 11 and 51) for BIACORE (registered trademark) binding kinetic analysis, in vitro and/or in vivo assays. Both SG1 and F760 are human heavy chain constant regions. The binding affinities of SG1 against human Fc gamma Rs are comparable to that for the natural IgG1 constant region, but that of F760 is abolished by Fc modification (also described herein as silent Fc). Amino acid and nucleotide sequences of the four anti-myostatin variants are shown in Table 2a.

Example 11

[0490] Characterization of pH-dependent MS1032 variants
(HEK Blue Assay (BMP1 and Spontaneous activation))

All experimental settings were the same in Examples 3 and 4. As shown in Figure 8, all variants showed comparable inhibition activity against human latent myostatin to MS1032LO00-SG1.

Example 12

[0491] Characterization of pH-dependent MS1032 variants (BIAcore (registered trademark))

All experimental settings were the same as in Example 7, except that measurements were also performed in ACES pH5.8 buffer in addition to ACES pH7.4 condition. Some antibodies were only measured against human latent myostatin. Antibody capture level was aimed at 185 RU and 18.5 RU, for avidity and affinity assay, respectively. Kinetic parameters were determined using 1:1 Binding fitting using BIAcore (registered trademark) T200 Evaluation software, version 2.0 (GE Healthcare). The sensorgrams of all antibodies against human latent myostatin with avidity condition are shown in Figure 9, and k_a , k_d , and K_D calculated from different conditions are listed in Tables 7-10. Under the avidity condition, all antibodies except MS1032LO00-SG1 showed a faster dissociation rate under acidic pH than neutral pH. Under the affinity condition, all antibodies except MS1032LO00-SG1 showed a weak interaction with latent myostatin under acidic pH and therefore, kinetic parameters were not determined.

[0492] [Table 7]

***k_a*, *k_d*, and *K_D* of avidity condition assay under neutral pH**

	Human latent myostatin			Mouse latent myostatin			Cyno latent myostatin		
	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)
MS1032LO00-SG1	1.27E+06	9.52E-05	7.50E-11	1.52E+06	7.18E-05	4.71E-11	1.21E+06	8.08E-05	6.66E-11
MS1032LO01-SG1	1.27E+06	2.16E-04	1.70E-10	1.45E+06	2.17E-04	1.49E-10	1.19E+06	1.97E-04	1.65E-10
MS1032LO02-SG1	8.36E+05	2.49E-04	2.98E-10	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO03-SG1	9.81E+05	1.92E-04	1.96E-10	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO04-SG1	1.33E+06	2.17E-04	1.63E-10	N/T	N/T	N/T	N/T	N/T	N/T

N/T: not tested

[0493] [Table 8]

***k_a*, *k_d*, and *K_D* of avidity condition assay under acidic pH**

	Human latent myostatin			Mouse latent myostatin			Cyno latent myostatin		
	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)
MS1032LO00-SG1	1.60E+06	1.28E-04	7.97E-11	2.32E+06	2.02E-05	8.70E-12	1.79E+06	1.58E-05	8.83E-12
MS1032LO01-SG1	1.22E+06	2.42E-02	1.99E-08	1.02E+06	6.25E-03	6.15E-09	7.64E+05	6.80E-03	8.90E-09
MS1032LO02-SG1	1.70E+06	4.14E-02	2.43E-08	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO03-SG1	5.43E+05	5.24E-03	9.66E-09	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO04-SG1	7.81E+05	7.13E-03	9.13E-09	N/T	N/T	N/T	N/T	N/T	N/T

N/T: not tested

[0494] [Table 9]

***k_a*, *k_d*, and *K_D* of affinity condition assay under neutral pH**

	Human latent myostatin			Mouse latent myostatin			Cyno latent myostatin		
	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)	<i>k_a</i> (M ⁻¹ s ⁻¹)	<i>k_d</i> (s ⁻¹)	<i>K_D</i> (M)
MS1032LO00-SG1	1.07E+06	2.45E-04	2.30E-10	1.31E+06	1.60E-04	1.22E-10	1.02E+06	2.13E-04	2.09E-10
MS1032LO01-SG1	1.64E+06	1.29E-03	7.88E-10	1.50E+06	1.07E-03	7.13E-10	1.15E+06	1.10E-03	9.54E-10
MS1032LO02-SG1	1.09E+06	1.79E-03	1.64E-09	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO03-SG1	1.08E+06	1.17E-03	1.08E-09	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO04-SG1	1.54E+06	1.25E-03	8.12E-10	N/T	N/T	N/T	N/T	N/T	N/T

N/T: not tested

[0495] [Table 10]

ka, kd, and KD of affinity condition assay under acidic pH

	Human latent myostatin			Mouse latent myostatin			Cyno latent myostatin		
	ka (M ⁻¹ s ⁻¹)	kd (s ⁻¹)	KD (M)	ka (M ⁻¹ s ⁻¹)	kd (s ⁻¹)	KD (M)	ka (M ⁻¹ s ⁻¹)	kd (s ⁻¹)	KD (M)
MS1032LO00-SG1	1.09E+06	2.35E-04	2.15E-10	1.62E+06	7.08E-05	4.38E-11	1.41E+06	1.96E-04	1.39E-10
MS1032LO01-SG1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
MS1032LO02-SG1	n.d.	n.d.	n.d.	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO03-SG1	n.d.	n.d.	n.d.	N/T	N/T	N/T	N/T	N/T	N/T
MS1032LO04-SG1	n.d.	n.d.	n.d.	N/T	N/T	N/T	N/T	N/T	N/T

n.d.: not determined, N/T: not tested

Example 13

[0496] Comparison of plasma total myostatin concentration between antibodies with Fc gamma R binding and an abolished Fc gamma R binding in mice
In vivo test using C.B-17 SCID mice

The accumulation of endogenous myostatin was assessed in vivo upon administration of anti-latent myostatin antibody in C.B-17 SCID mice (In Vivos, Singapore). An anti-latent myostatin antibody (3mg/ml) was administered at a single dose of 10 ml/kg into the caudal vein. Blood was collected 5 minutes, 7 hours, 1 day, 2 days, 3 days, 7 days, 14 days, 21 days, and 28 days after administration. The collected blood was centrifuged immediately at 14,000 rpm in 4 degrees C for 10 minutes to separate the plasma. The separated plasma was stored at or below -80 degrees C until measurement. The anti-latent myostatin antibodies used were MS1032LO00-SG1 and MS1032LO00-F760.

[0497] Measurement of total myostatin concentration in plasma by electrochemiluminescence (ECL)

The concentration of total myostatin in mouse plasma was measured by ECL. Anti-mature myostatin-immobilized plates were prepared by dispensing anti-mature myostatin antibody RK35 (as described in WO 2009/058346) onto a MULTI-ARRAY 96-well plate (Meso Scale Discovery) and incubated overnight at 4 degrees C. Mature myostatin calibration curve samples and mouse plasma samples diluted 40-fold or more were prepared. The samples were mixed in an acidic solution (0.2 M Glycine-HCl, pH2.5) to dissociate mature myostatin from its binding protein (such as propeptide). Subsequently, the samples were added onto an anti-mature myostatin-immobilized plate, and allowed to bind for 1 hour at room temperature before washing. Next, SULFO TAG labelled anti-mature myostatin antibody RK22 (as described in WO 2009/058346) was added and the plate was incubated for 1 hour at room temperature before washing. Read Buffer T (x4) (Meso Scale Discovery) was immediately added to the plate and signal was detected by SECTOR Imager 2400 (Meso Scale Discovery). The mature myostatin concentration was calculated based on the response of the calibration curve using the analytical software SOFTmax PRO (Molecular

Devices). The time course of total myostatin concentration in plasma after intravenous administration of anti-latent myostatin antibody measured by this method is shown in Figure 10.

[0498] Effect of Fc gamma R binding on myostatin accumulation in vivo

After administration of antibody MS1032LO00-F760, the plasma total myostatin concentration at day 28 accumulated 248 fold compared to plasma total myostatin concentration at 5 minutes. In contrast, after administration of MS1032LO00-SG1, plasma total myostatin concentration at day 28 accumulated 37 fold compared to plasma total myostatin concentration at 5 minutes. An approximately 7 fold difference of plasma total myostatin concentration at day28 was observed between MS1032LO00-F760 (silent Fc) and MS1032LO00-SG1 due to Fc gamma R binding. In human soluble IL-6R (hsIL-6R), no significant difference in plasma hsIL-6R concentration was observed between anti-hsIL-6R antibody-F760 (silent Fc) and -SG1 as described in WO 2013/125667. Since hsIL-6R is a monomeric antigen, antibody-hsIL-6R complex contains only 1 Fc. Therefore, the result in WO 2013/125667 suggested that an antibody-antigen complex with 1 Fc has no significant binding to Fc gamma R in vivo to accelerate the uptake of immune complex by cells. On the other hand, a multimeric antigen (such as myostatin), antibody can make a large immune complex and the antibody-antigen complex contains more than 2 Fc. Therefore, a significant difference in plasma antigen concentration can be observed between F760 and SG1 due to strong avidity binding against Fc gamma R. The result suggests that MST1032 can form a large immune complex which contains more than 2 antibodies with myostatin.

Example 14

[0499] Comparison of plasma total myostatin concentration between non-pH dependent anti-latent myostatin antibody and pH-dependent anti-latent myostatin antibody in mice
In vivo test using C.B-17 SCID mice

The in vivo accumulation of endogenous mouse myostatin was assessed after administering anti-latent myostatin antibody in C.B-17 SCID mice (In Vivos, Singapore) as described in Example 13. The anti-latent myostatin antibodies used were MS1032LO01-SG1 and MS1032LO01-F760.

[0500] Measurement of total myostatin concentration in plasma by ECL

The concentration of total myostatin in mouse plasma was measured by ECL as described in Example 13. The time course of plasma total myostatin concentration after intravenous administration of anti-latent myostatin antibody as measured by this method is shown in Figure 11.

[0501] Effect of pH-dependent myostatin binding on myostatin accumulation in vivo

The pH-dependent anti-latent myostatin antibodies (MS1032LO01-SG1 and MS1032LO01-F760) were tested in vivo and comparison of plasma total myostatin concentration was made. The total myostatin concentration measurement results after administration of MS1032LO00-SG1 and MS1032LO00-F760 described in Example 13 are also shown in Figure 11. MS1032LO00 is non pH-dependent antibody and MS1032LO01 is pH-dependent antibody. As shown in Figure 11, total myostatin concentration after administration of MS1032LO01-F760 was reduced compared to MS1032LO00-F760 due to pH-dependent binding. Moreover, total myostatin concentration after administration of MS1032LO01-SG1 was dramatically reduced compared to that of MS1032LO00-SG1 due to pH-dependent binding and increased cellular uptake by Fc gamma R binding. It is expected that MS1032LO01-SG1 has a superior property of enhancing myostatin clearance from plasma as a "sweeping antibody".

Example 15

[0502] Expression and purification of human and mouse latent GDF11

Human GDF11 with Flag-tag on N-terminus (also described herein as Flag-hGDF11, human latent GDF11, hGDF11, or human GDF11, SEQ ID NO: 85) were expressed transiently using FreeStyle293-F cells (Thermo Fisher). Conditioned media expressing Flag-hGDF11 was applied to a column packed with anti-Flag M2 affinity resin (Sigma) and eluted with Flag peptide (Sigma). Fractions containing Flag-hGDF11 were collected and subsequently subjected to a Superdex 200 gel filtration column (GE healthcare) equilibrated with 1x PBS. Fractions containing the Flag-hGDF11 were then pooled and stored at -80 degrees C.

Example 16

[0503] Characterization of anti-latent myostatin antibody (ELISA)

Uncoated ELISA plates (NUNC-IMMUNO plate MAXISORP surface, Nalge Nunc International) were coated with 20 micro L of 50nM streptavidin (GenScript) for 2 hour at room temperature. Plates were then washed with PBST three times and blocked with 50 micro L 20% Blocking One (Nacalai Tesque) for overnight. On the next day, each well of the plates was incubated with biotinylated human latent myostatin at 2nM/well/20 micro L or biotinylated human latent GDF11 at 20nM/well/20 micro L for 2 hours. After washing, 20 micro L of antibody sample was added to the wells and the plates were left for 1 hour. The plates were washed and 20 micro L of anti-human IgG-horseradish peroxidase (HRP) (Abcam) diluted in HEPES-buffered saline was added, and the plates were left for another hour. The wells were washed again, and then 50 micro L ABTS (KPL) was added to each well, and the plates were incubated for 1 hour. The signal was detected at 405 nm in a colorimetric plate reader. The

results of the binding experiment are shown in Figure 12. MST1032-G1m bound to latent myostatin (i.e., non-covalent complex of mature myostatin and propeptides), but didn't bind to hGDF11. These results show that MST1032-G1m specifically binds to myostatin, not to hGDF11.

Example 17

[0504] Characterization of anti-latent myostatin antibody
(HEK Blue Assay (BMP1 and spontaneous activation))

A reporter gene assay was used to assess the biological activity of active GDF11 in vitro. HEK-Blue™ TGF-beta cells (Invivogen) that express a Smad3/4-binding element (SBE)-inducible SEAP reporter gene, allow the detection of bioactive GDF11 by monitoring the activation of the activin type 1 and type 2 receptors. Active GDF11 stimulates the production and secretion of SEAP into the cell supernatant. The quantity of SEAP secreted is then assessed using QUANTIBLue™ (Invivogen).

[0505] HEK-Blue™ TGF-beta cells were maintained in DMEM medium (Gibco) supplemented with 10% fetal bovine serum, 50 micro g/mL streptomycin, 50 U/mL penicillin, 100 micro g/mL Normocin™, 30 micro g/mL of Blastocidin, 200 micro g/mL of HygroGold™ and 100 micro g/mL of Zeocin™. During the functional assay, cells were changed to assay medium (DMEM with 0.1% bovine serum albumin, streptomycin, penicillin and Normocin™) and seeded to a 96-well plate. Human GDF11 was incubated with or without recombinant human BMP1 (Calbiochem) and anti-latent antibody (MST1032-G1m) at 37 degrees C overnight. The sample mixtures were transferred to cells. After 24-hour incubation, the cell supernatant was mixed with QUANTIBLue™ and the optical density at 620 nm was measured in a colorimetric plate reader. As shown as Figure 13, MST1032-G1m did not prevent protease-mediated or spontaneous activation of human GDF11 and thus failed to inhibit the secretion of SEAP.

Example 18

[0506] Further optimization of MS1032 variants to enhance the sweeping effect

As the pH dependent antibody, MS1032LO01-SG1, showed superior efficacy in mouse, further optimization was conducted to increase pH dependency, to enhance uptake into cells, to increase stability, and so on by introducing mutations into the antibody CDRs or by changing framework regions. More than a thousand variants were assessed in a BIACORE (registered trademark) and/or HEK Blue Assay as described above, and MS1032LO06-SG1, MS1032LO07-SG1, MS1032LO10-SG1, MS1032LO11-SG1, MS1032LO12-SG1, MS1032LO18-SG1, MS1032LO19-SG1, MS1032LO21-SG1, MS1032LO23-SG1, MS1032LO24-SG1, MS1032LO25-SG1, and MS1032LO26-SG1 were generated. Their amino acid and nucleotide sequences of

these generate antibodies are shown in Table 11.

[0507]

[Table 11a]

MS1032 variants and their DNA and amino acid sequences (shown as SEQ ID NOs)

Antibody name	Abbreviation	Variable region				Constant region			
		Heavy		Light		Heavy		Light	
		DNA	PROTEIN	DNA	PROTEIN	DNA	PROTEIN	DNA	PROTEIN
MS_M103205H795-SG1/M103202L889-SK1	MS1032LO06-SG1	100	86	110	96	052	009	054	010
MS_M103205H1004-SG1/M103202L889-SK1	MS1032LO07-SG1	101	87	110	96	052	009	054	010
MS_M103205H1046-SG1/M103202L889-SK1	MS1032LO10-SG1	102	88	110	96	052	009	054	010
MS_M103205H1047-SG1/M103202L889-SK1	MS1032LO11-SG1	103	89	110	96	052	009	054	010
MS_M103205H1057-SG1/M103202L889-SK1	MS1032LO12-SG1	104	90	110	96	052	009	054	010
MS_M103205H1186-SG1/M103202L889-SK1	MS1032LO18-SG1	105	91	110	96	052	009	054	010
MS_M103240H795-SG1/M103202L1045-SK1	MS1032LO19-SG1	106	92	111	97	052	009	054	010
MS_M103245H795-SG1/M103202L1045-SK1	MS1032LO21-SG1	107	93	111	97	052	009	054	010
MS_M103245H1233-SG1/M103202L1045-SK1	MS1032LO23-SG1	108	94	111	97	052	009	054	010
MS_M103205H795-SG1/M103202L1060-SK1	MS1032LO24-SG1	100	86	112	98	052	009	054	010
MS_M103240H1246-SG1/M103202L1045-SK1	MS1032LO25-SG1	109	95	111	97	052	009	054	010
MS_M103240H795-SG1/M103209L1045-SK1	MS1032LO26-SG1	106	92	113	99	052	009	054	010

[0508] [Table 11b]

HVR amino acid sequences of MS1032 variants (shown as SEQ ID NOs)

Antibody name	Abbreviation	Hyper Variable region (HVR)						
		H1	H2	H3	L1	L2	L3	
MS_M103205H795-SG1/M103202L889-SK1	MS1032LO06-SG1	114	58	63	122	71	74	
MS_M103205H1004-SG1/M103202L889-SK1	MS1032LO07-SG1	114	116	121	122	71	74	
MS_M103205H1046-SG1/M103202L889-SK1	MS1032LO10-SG1	57	117	63	122	71	74	
MS_M103205H1047-SG1/M103202L889-SK1	MS1032LO11-SG1	57	118	63	122	71	74	
MS_M103205H1057-SG1/M103202L889-SK1	MS1032LO12-SG1	57	119	63	122	71	74	
MS_M103205H1186-SG1/M103202L889-SK1	MS1032LO18-SG1	114	118	63	122	71	74	
MS_M103240H795-SG1/M103202L1045-SK1	MS1032LO19-SG1	114	58	63	123	71	74	
MS_M103245H795-SG1/M103202L1045-SK1	MS1032LO21-SG1	114	58	63	123	71	74	
MS_M103245H1233-SG1/M103202L1045-SK1	MS1032LO23-SG1	115	58	63	123	71	74	
MS_M103205H795-SG1/M103202L1060-SK1	MS1032LO24-SG1	114	58	63	124	125	74	
MS_M103240H1246-SG1/M103202L1045-SK1	MS1032LO25-SG1	115	120	63	123	71	74	
MS_M103240H795-SG1/M103209L1045-SK1	MS1032LO26-SG1	114	58	63	123	71	74	

- [0509] The affinity of MS1032 variant binding to human, cynomolgus monkey (cyno), or mouse latent myostatin at pH7.4 and pH5.8 was determined at 37 degrees C using BIACORE (registered trademark) T200 instrument (GE Healthcare) to assess the effect of pH on antigen binding. ProA/G (Pierce) was immobilized onto all flow cells of a CM4 chip using an amine coupling kit (GE Healthcare). All antibodies and analytes were prepared in ACES pH7.4 or pH5.8 buffer containing 20 mM ACES, 150 mM NaCl, 1.2 mM CaCl₂, 0.05% Tween 20, 0.005% NaN₃. Each antibody was captured onto the sensor surface by proA/G. Antibody capture levels were typically 130 to 240 resonance units (RU). Human, cyno, and mouse latent myostatin was injected at 3.125 to 50 nM prepared by two-fold serial dilution, followed by dissociation. The sensor surface was regenerated each cycle with 10 mM Glycine HCl pH1.5. Binding affinity was determined by processing and fitting the data to a 1:1 binding model using BIACORE (registered trademark) T200 Evaluation software, version 2.0 (GE Healthcare).
- [0510] The affinity (KD) of MS1032 variants binding to human, cynomolgus monkey (cyno), and mouse latent myostatin at pH7.4 and pH5.8 are shown in Table 12. All variants showed a KD ratio ((KD at pH5.8)/(KD at pH7.4)) of over 5, indicating pH dependent binding to latent myostatin.
- [0511]

[Table 12]

Kinetic parameters of MS1032 variants

Ab name	Name of variable region		Human latent myostatin			Cyno latent myostatin			Mouse latent myostatin		
	Heavy chain	Light chain	KD pH 7.4 (M)	KD pH 5.8 (M)	ratio of KD at pH 5.8/pH 7.4	KD pH 7.4 (M)	KD pH 5.8 (M)	ratio of KD at pH 5.8/pH 7.4	KD pH 7.4 (M)	KD pH 5.8 (M)	ratio of KD at pH 5.8/pH 7.4
MS1032LO06-SG1	M103205H795	M103202L889	2.85E-10	3.40E-08	119	3.43E-10	2.59E-08	76	2.99E-10	2.26E-08	76
MS1032LO07-SG1	M103205H1004	M103202L889	2.75E-10	4.62E-08	168	3.39E-10	3.47E-08	102	3.19E-10	3.08E-08	97
MS1032LO10-SG1	M103205H1046	M103202L889	3.51E-10	4.38E-08	125	4.19E-10	1.61E-08	38	3.14E-10	1.09E-08	35
MS1032LO11-SG1	M103205H1047	M103202L889	4.19E-10	1.43E-07	341	5.02E-10	4.35E-08	87	3.62E-10	2.92E-08	81
MS1032LO12-SG1	M103205H1057	M103202L889	4.07E-10	8.49E-08	209	4.92E-10	3.58E-08	73	4.13E-10	2.48E-08	60
MS1032LO18-SG1	M103205H1186	M103202L889	3.29E-10	n.d.	n.d.	3.54E-10	8.09E-08	229	2.72E-10	n.d.	n.d.
MS1032LO19-SG1	M103240H795	M103202L1045	2.73E-10	4.58E-08	168	3.26E-10	3.56E-08	109	2.71E-10	2.87E-08	106
MS1032LO21-SG1	M103245H795	M103202L1045	2.57E-10	5.23E-08	204	3.09E-10	3.10E-08	100	2.61E-10	2.94E-08	113
MS1032LO23-SG1	M103245H1233	M103202L1045	2.60E-10	1.61E-08	62	2.99E-10	7.71E-09	26	2.66E-10	6.40E-09	24
MS1032LO24-SG1	M103205H795	M103202L1060	1.64E-10	1.52E-09	9	1.89E-10	9.29E-10	5	1.76E-10	1.02E-09	6
MS1032LO25-SG1	M103240H1246	M103202L1045	2.76E-10	2.55E-08	92	3.40E-10	1.41E-08	41	2.59E-10	9.88E-09	38

n.d.: not determined

Example 19

[0512] Evaluation of the neutralization activity of further optimized variants in HEK Blue Assay

We evaluated the neutralization activity of MS1032LO06-SG1, MS1032LO07-SG1, MS1032LO10-SG1, MS1032LO11-SG1, MS1032LO12-SG1, MS1032LO18-SG1, MS1032LO19-SG1, MS1032LO21-SG1, MS1032LO23-SG1 and MS1032LO25-SG1 against human latent myostatin as described in Example 3. As shown in Fig. 14, all variants showed comparable activity to MS1032LO01-SG1.

Example 20

[0513] Comparison of plasma total myostatin concentration between non-pH dependent anti-latent myostatin antibody and different pH-dependent anti-latent myostatin antibodies in mice

In vivo test using C.B-17 SCID mice

The accumulation of endogenous myostatin was assessed in vivo upon administration of anti-latent myostatin antibody in C.B-17 SCID mice (In Vivos, Singapore). An anti-latent myostatin antibody (3mg/ml) was administered at a single dose of 10 ml/kg into the caudal vein. Blood was collected 5 minutes, 7 hours, 1 day, 2 days, 3 days, 7 days, 14 days, 21 days, and 28 days after administration. The collected blood was centrifuged immediately at 14,000 rpm in 4 degrees C for 10 minutes to separate the plasma. The separated plasma was stored at or below -80 degrees C until measurement. The anti-latent myostatin antibodies tested were MS1032LO00-SG1, MS1032LO01-SG1, MS1032LO06-SG1, MS1032LO11-SG1, MS1032LO18-SG1, MS1032LO19-SG1, MS1032LO21-SG1 and MS1032LO25-SG1.

[0514] Measurement of total myostatin concentration in plasma by electrochemiluminescence (ECL)

The concentration of total myostatin in mouse plasma was measured by ECL. Anti-mature myostatin-immobilized plates were prepared by dispensing biotinylated anti-mature myostatin antibody RK35 (as described in WO 2009/058346) onto a MULTI-ARRAY 96-well streptavidin plate (Meso Scale Discovery) and incubated in blocking buffer for 2 hours at room temperature. Mature myostatin calibration curve samples and mouse plasma samples diluted 40-fold or more were prepared. The samples were mixed in an acidic solution (0.2 M Glycine-HCl, pH2.5) to dissociate mature myostatin from its binding protein (such as propeptide). Subsequently, the samples were added onto an anti-mature myostatin-immobilized plate, and allowed to bind for 1 hour at room temperature before washing. Next, SULFO TAG labelled anti-mature myostatin antibody RK22 (as described in WO 2009/058346) was added and the plate was incubated for 1 hour at room temperature before washing. Read Buffer T (x4) (Meso

Scale Discovery) was immediately added to the plate and signal was detected by SECTOR Imager 2400 (Meso Scale Discovery). The mature myostatin concentration was calculated based on the response of the calibration curve using the analytical software SOFTmax PRO (Molecular Devices). The time course of total myostatin concentration in plasma after intravenous administration of anti-latent myostatin antibody measured by this method is shown in Figure 15.

[0515] Effect of pH-dependent myostatin binding on myostatin accumulation in mice in vivo study

The effect of pH-dependency on myostatin accumulation in mice was compared using non pH-dependent anti-latent myostatin antibody (MS1032LO00-SG1) and different pH-dependent anti-latent myostatin antibodies (MS1032LO01-SG1, MS1032LO06-SG1, MS1032LO11-SG1, MS1032LO18-SG1, MS1032LO19-SG1, MS1032LO21-SG1 and MS1032LO25-SG1). Introduction of pH-dependency significantly accelerates myostatin clearance from SCID mouse plasma. As shown in Figure 15, pH-dependent anti-latent myostatin antibodies (MS1032LO01-SG1, MS1032LO06-SG1, MS1032LO11-SG1, MS1032LO18-SG1, MS1032LO19-SG1, MS1032LO21-SG1 and MS1032LO25-SG1) could reduce myostatin accumulation compared to non pH-dependent anti-latent myostatin antibody (MS1032LO00-SG1) at day 28.

Example 21

[0516] Comparison of plasma total myostatin concentration between non-pH dependent anti-latent myostatin antibody and anti-latent myostatin antibodies with both pH- and Fc engineering in cynomolgus monkey

In vivo test using cynomolgus monkey

The accumulation of endogenous myostatin was assessed in vivo upon administration of anti-latent myostatin antibody in 2-4 year old *Macaca fascicularis* (cynomolgus monkey) from Cambodia (Shin Nippon Biomedical Laboratories Ltd., Japan). A dose level of 30 mg/kg was injected into the cephalic vein of the forearm using a disposable syringe, extension tube, indwelling needle, and infusion pump. The dosing speed was 30 minutes per body. Blood was collected before the start of dosing and either 5 minutes, 7 hours and 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 and 56 days after the end of dosing, or 5 minutes and 2, 4, and 7 hours and 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 and 56 days after the end of dosing. Blood was drawn from the femoral vein with a syringe containing heparin sodium. The blood was immediately cooled on ice, and plasma was obtained by centrifugation at 4 degrees C, 1700xg for 10 minutes. The plasma samples were stored in a deep freezer (acceptable range: -70 degrees C or below) until measurement. The anti-latent myostatin antibodies used were MS1032LO00-SG1,

MS1032LO06-SG1012, MS1032LO06-SG1016, MS1032LO06-SG1029, MS1032LO06-SG1031, MS1032LO06-SG1033, and MS1032LO06-SG1034 (herein, SG1012, SG1016, SG1029, SG1031, SG1033, and SG1034 are the heavy chain constant regions constructed based on SG1 as described below).

[0517] A dose level of 2mg/kg was administered into the cephalic vein of the forearm or saphenous vein using a disposable syringe, and indwelling needle for the anti-latent myostatin antibodies MS1032LO19-SG1079, MS1032LO19-SG1071, MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081, and MS1032LO19-SG1077 (herein, SG1079, SG1071, SG1080, SG1074, SG1081, and SG1077 are the heavy chain constant regions constructed based on SG1 as described below). Blood was collected before the start of dosing and 5 minutes and 2, 4, and 7 hours and 1, 2, 3, 7, 14 days after the end of dosing. The blood was processed as described above. Plasma samples were stored in a deep freezer (acceptable range: -70 degrees C or below) until measurement.

[0518] Measurement of total myostatin concentration in plasma by electrochemiluminescence (ECL)

The concentration of total myostatin in monkey plasma was measured by ECL as described in Example 20. The time course of plasma total myostatin concentration after intravenous administration of anti-latent myostatin antibody as measured by this method is shown in Figure 16.

[0519] Measurement of ADA in monkey plasma using electrochemiluminescence (ECL)

Biotinylated drug was coated onto a MULTI-ARRAY 96-well streptavidin plate (Meso Scale Discovery) and incubated in low cross buffer (Candor) for 2 hours at room temperature. Monkey plasma samples were diluted 20 fold in low cross buffer before addition to the plate. Samples were incubated overnight at 4°C. On the next day, the plate was washed three times with wash buffer before addition of SULFO TAG labelled anti monkey IgG secondary antibody (Thermo Fisher Scientific). After incubating for an hour at room temperature, the plate was washed three times with wash buffer. Read Buffer T (x4) (Meso Scale Discovery) was immediately added to the plate and signal was detected using a SECTOR Imager 2400 (Meso Scale Discovery).

[0520] Effect of pH-dependent and Fc engineering on myostatin accumulation in monkey in vivo

In cynomolgus monkey, administration of non pH-dependent antibody (MS1032LO00-SG1) resulted in at least 60 fold increase in myostatin concentration from baseline at day 28. At day 28, pH-dependent anti-latent myostatin antibodies MS1032LO06-SG1012 and MS1032LO06-SG1033 resulted in 3 fold and 8 fold increase from baseline respectively. The strong sweeping was mainly contributed by the increase in affinity to cynomolgus monkey Fc gamma RIIb. At day 28, pH-

dependent anti-latent myostatin antibodies MS1032LO06-SG1029, MS1032LO06-SG1031 and MS1032LO06-SG1034 could sweep antigen to below baseline. The reason for strong sweeping of MS1032LO06-SG1029, MS1032LO06-SG1031 and MS1032LO06-SG1034 are an increase in non-specific uptake in the cell due to increase in positive charge cluster of the antibody and an increase in Fc gamma R-mediated cellular uptake due to enhanced binding to Fc gamma R.

[0521] Administration of pH-dependent anti-latent myostatin antibodies MS1032LO19-SG1079, MS1032LO19-SG1071, MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081 and MS1032LO19-SG1077 reduced myostatin concentration to below the detection limit ($<0.25\text{ng/mL}$) from day 1 in cynomolgus monkey. On day 14, the concentration of myostatin increased above the detection limit for MS1032LO19-SG1079 and MS1032LO19-SG1071 while the concentration of myostatin remained below the detection limit for MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081 and MS1032LO19-SG1077. The weaker suppression of MS1032LO19-SG1079 and MS1032LO19-SG1071 could be due to difference in pI mutations.

[0522] The data suggests that strong sweeping of myostatin from the plasma could be achieved by mutations that increase binding to Fc gamma RIIb or combining mutations that increase positive charge of the antibody and increase binding to Fc gamma RIIb. It is expected that strong sweeping of myostatin could be achieved in human by combining mutations that increase positive charge of the antibody and increase binding to Fc gamma R.

Example 22

[0523] Epitope mapping of anti-latent myostatin antibodies

Additional anti-human latent myostatin antibodies were generated for mapping of their corresponding binding epitopes. Two NZW rabbits were immunized and harvested as described in Example 2. 1760 antibody producing B-cell lines identified were further screened for their ability to block BMP1 mediated activation of human latent myostatin. Briefly, B-cell supernatant containing secreted antibodies were incubated with human latent myostatin in the presence of recombinant human BMP1 (R&D Systems) at 37 degrees C overnight. 50 micro L of the reaction mix were then transferred to Meso Scale Discovery MULTI-ARRAY 96-well plate coated with anti-mature myostatin antibody RK35 (as described in WO 2009/058346). After 1 hour incubation at room temperature with shaking, the plates were incubated with biotinylated anti-mature myostatin antibody RK22 (as described in WO 2009/058346) followed by SULFO-tagged streptavidin. Read Buffer T (x4) (Meso Scale Discovery) was then

added to the plate and ECL signal was detected by SECTOR Imager 2400 (Meso Scale Discovery). 94 lines showing different levels of neutralizing activities were selected for downstream analysis (MST1495-MST1588). The variable regions of these selected lines were cloned as described in Example 2, except an expression vector with the heavy chain constant region F1332m sequence (SEQ ID NO: 193) was used.

[0524] The inhibitory activity on human latent myostatin activation was further evaluated for a panel of 7 anti-latent myostatin antibodies (MST1032, MST1504, MST1538, MST1551, MST1558, MST1572, and MST1573; the sequence identifiers for amino acid sequences of these antibodies are shown in Table 13). As shown in Figure 17, all of the antibodies were able to inhibit the BMP1 mediated activation of human latent myostatin in a dose-dependent manner.

[0525] [Table 13]

Amino acid sequences of anti-latent myostatin antibodies

Antibody	SEQ ID NO:							
	VH	VL	HVR-H1	HVR-H2	HVR-H3	HVR-L1	HVR-L2	HVR-L3
MST1032	12	14	55	58	61	65	70	73
MST1504	145	151	157	163	169	175	181	187
MST1538	146	152	158	164	170	176	182	188
MST1551	147	153	159	165	171	177	183	189
MST1558	148	154	160	166	172	178	184	190
MST1572	149	155	161	167	173	179	185	191
MST1573	150	156	162	168	174	180	186	192

[0526] 4 antibodies that worked well in Western blotting were selected for epitope mapping. Fragments of the N-terminal propeptide coding region of human latent myostatin were cloned into a pGEX4.1 vector so as to produce GST tagged propeptide fragments of 100 amino acid each, with 80 amino acid overlap (Figure 18A). Protein expression was induced in transformed BL21 competent cells with Overnight Express Autoinduction System (Merck Millipore) and protein was extracted using the BugBuster protein extraction reagent (Novagen). Expression of the desired protein fragments at about 37kDa were verified by Western blotting analysis as described in Example 6 (anti-GST antibody (Abcam)) (Figure 18B). When tested with anti-human latent myostatin antibodies, as shown in Figure 18C, although all 4 antibodies could inhibit latent myostatin activation, they recognized different epitopes on human latent myostatin. MST1032 antibody could detect the first five fragments, no bands were detected after the removal of amino acid 81-100 (SEQ ID NO:78). Both MST1538 and MST1572 antibodies bind to the first three fragments only, no bands were detected in the absence of amino acid 41-60 of SEQ ID NO:78. Antibody MST1573 only bound strongly to the first two fragments, suggesting that its epitope lies within amino acid 21-40 of SEQ ID NO:78 (Figure 18D).

Example 23

[0527] Development of novel Fc gamma RIIb-enhanced Fc variants

In this example, Fc engineering to enhance myostatin clearance is illustrated.

[0528] It has been demonstrated in WO 2013/125667 that clearance of a soluble antigen can be enhanced by its administration of antigen-binding molecules comprising an Fc domain displaying an increased affinity for Fc gamma RIIb. Furthermore, Fc variants that can show enhanced binding to human Fc gamma RIIb have been illustrated in WO 2012/115241 and WO 2014/030728. It has been also illustrated that these Fc variants can show selectively enhanced binding to human Fc gamma RIIb and decreased binding to other active Fc gamma Rs. This selective enhancement of Fc gamma RIIb binding can be favorable not only for clearance of soluble antigen but also for decreasing the risk of undesired effector functions and immune response.

[0529] For development of an antibody drug, efficacy, pharmacokinetics, and safety should be evaluated in non-human animals in which the drug is pharmacologically active. If it is active only in human, alternative approaches such as the use of a surrogate antibody must be considered (Int. J. Tox. 28: 230-253 (2009)). However it would not be easy to precisely predict the effects of the interaction between the Fc region and Fc gamma Rs in human using a surrogate antibody, because the expression patterns and/or functions of Fc gamma Rs in non-human animals are not always the same as in human. It would be preferable that the Fc regions of antibody drugs should have cross-reactivity to non-human animals, especially to cynomolgus monkey which has close expression patterns and functions of Fc gamma Rs to human, so that the results obtained in non-human animals could be extrapolated into human.

[0530] Therefore Fc variants that display cross-reactivity to human and cynoFc gamma Rs were developed in this study.

[0531] Affinity measurement of an existing Fc gamma RIIb-enhanced Fc variant against human and monkey Fc gamma Rs

The heavy chain gene of the human Fc gamma RIIb enhanced variant (herein, "Fc gamma RIIb enhanced" means "with enhanced Fc gamma RIIb-binding activity") disclosed in WO 2012/115241 was generated by substituting Pro at position 238 in EU numbering with Asp in the heavy chain of MS1032LO06-SG1 which is named M103205H795-SG1 (VH, SEQ ID NO: 86; CH, SEQ ID NO: 9). The resultant heavy chain is referred to as M103205H795-MY009 (VH, SEQ ID NO: 86; CH, SEQ ID NO: 252). As the antibody light chain, M103202L889-SK1 (VL, SEQ ID NO: 96; CL, SEQ ID NO: 10) was used. The recombinant antibody was expressed according to the method shown in Example 30.

[0532] The extracellular domains of Fc gamma Rs were prepared in the following manner. The synthesis of the genes for the extracellular domain of human Fc gamma Rs were carried out in methods known to those skilled in the art based on the information

registered in the NCBI. Specifically, Fc gamma RIIa was based on the sequence of NCBI accession # NM_001136219.1, Fc gamma RIIb was on NM_004001.3, Fc gamma RIIIa was on NM_001127593.1, respectively. Allotypes of Fc gamma RIIa and Fc gamma RIIIa were prepared according to the reports about polymorphism for Fc gamma RIIa (J. Exp. Med. 172:19-25 (1990)) and for Fc gamma RIIIa (J. Clin. Invest. 100(5):1059-1070 (1997)), respectively. The synthesis of the gene for the extracellular domain of cynomolgus monkey Fc gamma Rs were constructed by cloning cDNA of each Fc gamma Rs from cynomolgus monkeys using the methods known to those skilled in the art. The amino acid sequences of the constructed extracellular domains of Fc gamma Rs were shown in the sequence list: (SEQ ID NO 210 for human Fc gamma RIIaR, SEQ ID NO 211 for human Fc gamma RIIaH, SEQ ID NO 214 for human Fc gamma RIIb, SEQ ID NO 217 for human Fc gamma RIIIaF, SEQ ID NO 218 for human Fc gamma RIIIaV, SEQ ID NO 220 for cyno Fc gamma RIIa1, SEQ ID NO 221 for cyno Fc gamma RIIa2, SEQ ID NO 222 for cyno Fc gamma RIIa3, SEQ ID NO 223 for cyno Fc gamma RIIb, SEQ ID NO 224 for cyno Fc gamma RIIIaS). Then His-tag was added to their C-terminus and the obtained each gene was inserted into expression vector designed for mammalian cell expression. The expression vector was introduced into the human embryonic kidney cell-derived FreeStyle293 cells (Invitrogen) to express the target protein. After culturing, the resulting culture supernatant was filtered and purified by the following four steps in principle. The cation exchange chromatography using SP Sepharose FF was performed as the first step, an affinity chromatography against the His-tag (HisTrap HP) as the second step, a gel filtration column chromatography (Superdex200) as the third step, and sterile filtration as the fourth step. The absorbance at 280 nm of the purified proteins were measured using a spectrophotometer and the concentration of the purified protein was determined using an extinction coefficient calculated by the method of PACE (Protein Science 4:2411-2423 (1995)).

[0533] The kinetic analysis of interactions between these antibodies and Fc gamma R was carried out using BIACORE (registered trademark) T200 or BIACORE (registered trademark) 4000 (GE Healthcare). HBS-EP+ (GE Healthcare) was used as the running buffer, and the measurement temperature was set to 25 degrees C. A chip produced by immobilizing Protein A, Protein A/G or mouse anti-human IgG kappa light chain (BD Biosciences) onto a Series S Sensor Chip CM4 or CM5 (GE Healthcare) by the amine-coupling method was used. An antibody of interest was captured onto this chip to interact with each Fc gamma R that had been diluted with the running buffer, and binding to the antibody was measured. After the measurement, the antibody captured on the chip was washed off by allowing reaction with 10 mM glycine-HCl, pH1.5 and 25 mM NaOH so that the chip was regenerated and used repeatedly. The sensorgrams

obtained as measurement results were analyzed by the 1:1 Langmuir binding model using the BIACORE (registered trademark) Evaluation Software to calculate the binding rate constant k_a (L/mol/s) and dissociation rate constant k_d (1/s), and the dissociation constant K_D (mol/L) was calculated from these values. Since the binding of MS1032LO06-MY009 to human Fc gamma RIIaH, human Fc gamma RIIIaV, and cynoFc gamma RIIIaS was weak, kinetic parameters such as K_D could not be calculated from the above-mentioned analytical method. Regarding such interactions, K_D values were calculated using the following 1:1 binding model described in BIACORE (registered trademark) T100 Software Handbook BR1006-48 Edition AE.

[0534] The behavior of interacting molecules according to the 1:1 binding model on BIACORE (registered trademark) can be described by Equation 1: $R_{eq} = C \times R_{max} / (K_D + C) + RI$, wherein, R_{eq} is a plot of steady-state binding levels to analyte concentration, C is concentration, RI is bulk refractive index contribution in the sample, and R_{max} is analyte binding capacity of the surface. When this equation is rearranged, K_D can be expressed as Equation 2: $K_D = C \times R_{max} / (R_{eq} - RI) - C$. K_D can be calculated by substituting the values of R_{max} , RI , and C into Equation 1 or Equation 2. From the current measurement conditions, $RI=0$, $C=2$ micro mol/L can be used. Furthermore, the R_{max} value obtained when globally fitting the sensorgram obtained as a result of analyzing the interaction of each Fc gamma R with IgG1 using the 1:1 Langmuir binding model was divided by the amount of SG1 captured, this was multiplied by the amount of MY009 captured, and the resulting value was used as R_{max} . This calculation is based on the hypothesis that the limit quantity of each Fc gamma R that can be bound by SG1 remains unchanged for all variants produced by introducing mutations into SG1, and the R_{max} at the time of measurement is proportional to the amount of antibody bound on the chip at the time of measurement. R_{eq} was defined as the amount of binding of each Fc gamma R to each variant on the sensor chip observed at the time of measurement.

[0535] Table 14 shows the result of kinetic analysis of SG1 and MY009 against human and cynoFc gamma Rs. The K_D values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis. Values of K_D fold were calculated by dividing the K_D value of SG1 by the K_D value of the variant for each Fc gamma R.

[0536] As shown in Table 14, human Fc gamma RIIb-enhanced variant MY009 does not show enhanced binding to cynoFc gamma RIIb but shows enhanced binding to human Fc gamma RIIb. Its affinity to cynoFc gamma RIIb was rather decreased by 0.4-fold compared to SG1, indicating that human Fc gamma RIIb-enhanced variant MY009 does not have cross-reactivity to cynoFc gamma Rs.

[0537] Development of novel Fc variant that shows enhanced binding to both human and

cynoFc gamma RIIb

Ideally, novel Fc variant should have enhanced binding to both human and cynoFc gamma RIIb selectively and a decreased binding to other active Fc gamma Rs. However, because the putative Fc binding residues in cynoFc gamma RIIb are completely the same as either allotype of cynoFc gamma RIIa (Figure 19), it is theoretically impossible to achieve selective enhancement of cynoFc gamma RIIb binding over cynoFc gamma RIIa. Therefore a novel Fc variant should have selectively enhanced binding to human Fc gamma RIIb, cynoFc gamma RIIb and cynoFc gamma RIIa.

[0538] In order to obtain a novel Fc variant that shows selectively enhanced binding to both human and cyno Fc gamma RIIb, the results of comprehensive mutagenesis study performed in WO 2012/115241 were used. In the comprehensive mutagenesis study, comprehensive mutations were introduced into all the positions in Fc gamma R binding regions in IgG1 antibodies and binding to each Fc gamma R was analyzed comprehensively as shown in the following procedures.

[0539]

[0540] The variable region of a glypican 3 antibody comprising the CDR of GpH7 which is an anti-glypican 3 antibody with improved plasma kinetics disclosed in WO 2009/041062 was used as the antibody heavy chain variable region (GpH7: SEQ ID NO: 225). Similarly, for the antibody light chain, GpL16-k0 (SEQ ID NO: 226) of the glypican 3 antibody with improved plasma kinetics disclosed in WO 2009/041062 was used. Furthermore, B3 (SEQ ID NO: 228) in which a K439E mutation has been introduced into G1d (SEQ ID NO: 227) produced by removing the C terminal Gly and Lys of IgG1 was used as the antibody H chain constant region. This heavy chain, which has been made by fusing GpH7 and B3, is referred to as GpH7-B3 (VH, SEQ ID NO: 225; CH, SEQ ID NO: 228).

[0541] With respect to GpH7-B3, the amino acid residues that are considered to be involved in Fc gamma R binding and the surrounding amino acid residues (positions 234 to 239, 265 to 271, 295, 296, 298, 300, and 324 to 337, according to EU numbering) were substituted respectively with 18 amino acid residues excluding the original amino acid residue and Cys. These Fc variants are referred to as B3 variants. B3 variants were expressed and the binding of protein-A purified antibodies to each Fc gamma R (Fc gamma RIIa type H, Fc gamma RIIa type R, Fc gamma RIIb, and Fc gamma RIIIaF) was comprehensively evaluated as follows. Analysis of interaction between each altered antibody and the Fc gamma receptor prepared as mentioned above was carried out using BIACORE (registered trademark) T100 (GE Healthcare), BIACORE (registered trademark) T200 (GE Healthcare), BIACORE (registered trademark) A100, or BIACORE (registered trademark) 4000. HBS-EP+ (GE Healthcare) was used as the running buffer, and the measurement temperature was set to 25 degrees C. Chips produced by immobilizing Protein A (Thermo Scientific), Protein A/G (Thermo Scientific), or Protein L (ACTIGEN or BioVision) by the amine coupling method to a Series S sensor Chip CM5 or CM4 (GE Healthcare) were used. After capturing of antibodies of interest onto these sensor chips, an Fc gamma receptor diluted with the running buffer was allowed to interact, the amount bound to an antibody was measured. However, since the amount of Fc gamma receptor bound depends on the amount of the captured antibodies, the amount of Fc gamma receptor bound was divided by the amount of each antibody captured to obtain corrected values, and these values were compared. Furthermore, antibodies captured onto the chips were washed by 10 mM glycine-HCl, pH1.5, and the chips were regenerated and used repeatedly. The value of the amount of Fc gamma R binding of each B3 variant was divided by the value of the amount of Fc gamma R binding of the parental B3 antibody (an antibody having the sequence of a naturally-occurring human IgG1 at positions 234 to 239, 265 to 271, 295, 296, 298, 300, and 324 to 337, according to EU numbering). The value obtained by multiplying this value by 100 was used as an indicator of the relative Fc

gamma R-binding activity of each variant.

[0542] Table 15 shows the binding profile of promising substitutions selected based on the following criteria (more than 40% to human Fc gamma RIIb, lower than 100% to human Fc gamma RIIaR and Fc gamma RIIaH, less than 10 % to human Fc gamma RIIIaF, compared to those of parental B3 antibody).

[0543] [Table 15]

Binding profile of selected substitutions against human Fc gamma Rs

Mutation	Binding to human FcγRs (parent B3 =100)			
	FcγRIIaH	FcγRIIaR	FcγRIIb	FcγRIIIaV
G236N	54	81	75	8
G237Y	77	4	85	0
G237D	74	0	95	0
P238E	21	2	97	1
P238Y	93	9	114	3
P238M	86	9	97	2
P238Q	19	4	43	-1
S239P	49	4	61	-1
V266F	91	8	88	2
S267H	27	3	42	1
S267L	63	3	112	2
N325L	93	13	116	0
N325E	49	13	40	4
N325I	76	8	97	1
N325F	65	6	72	-1
A327I	37	12	46	8

[0544] In the next step, cross-reactivity of these substitutions to cynoFc gamma Rs was evaluated. These 16 mutations were introduced into M103205H795-SG1. The variants were expressed using M103202L889-SK1 as light chain and their affinity to cynoFc gamma RIIa1, IIa2, IIa3, IIb, IIIaS were analyzed.

[0545] Table 16 shows the binding profile of these 16 variants to cynoFc gamma Rs. The value of the amount of Fc gamma R binding was obtained by dividing the amount of Fc gamma R bound by the amount of each antibody captured. This value was further normalized using the value for SG1 as 100.

[0546]

[Table 16]

Binding profile of selected substitutions to cynoFc gamma Rs

CH Name	Substitution	Binding to cynoFcγRs (SG1 = 100)				
		FcγRIIa1	FcγRIIa2	FcγRIIa3	FcγRIIb	FcγRIIIaS
SG1		100	100	100	100	100
MY001	G236N	83	86	62	85	15
SG165	G237Y	18	17	30	30	7
SG166	G237D	10	10	17	8	5
SG167	P238Y	18	14	38	22	14
SG168	P238E	21	16	30	28	13
SG169	P238M	17	16	32	22	22
SG170	P238Q	16	15	21	18	12
SG171	S239P	17	20	18	20	8
SG172	V266F	14	17	27	16	31
SG173	S267L	13	14	21	12	24
SG174	S267H	13	16	20	11	15
SG175	N325F	13	13	17	14	8
SG176	N325I	14	15	19	16	20
SG177	N325L	15	15	25	18	21
SG178	N325E	22	21	29	26	36
SG179	A327I	19	17	28	19	48

[0547] Among selected 16 Fc variants, only MY001 maintained binding to cynoFc gamma RIIb by 85% compared to SG1. Additionally MY001 showed reduced binding to cynoFc gamma RIIIaS and its binding to cynoFc gamma RIIa1, IIA2, and IIA3 is maintained. As a result, G236N mutation is the unique substitution which shows similar binding profile to both human and cynoFc gamma Rs.

[0548] Although G236N substitution shows cross-reactivity to both human and cyno Fc gamma Rs, its affinity to Fc gamma RIIb is lower than SG1 (75% for human Fc gamma RIIb and 85% for cynoFc gamma RIIb, respectively). In order to increase its affinity to Fc gamma RIIb, additional substitutions were evaluated. Specifically, substitutions that showed increased binding to human Fc gamma RIIb, reduced binding to human Fc gamma RIIIa and increased selectivity to human Fc gamma RIIb over human Fc gamma RIIa were selected based on the result of comprehensive mutagenesis study (Table 17).

[0549]

[Table 17]

Binding profile of additionally selected substitutions to human Fc gamma Rs

Mutation	Binding to human FcγRs (parent B3 =100)			
	FcγRIIaH	FcγRIIaR	FcγRIIb	FcγRIIIaV
L234W	64	63	90	36
L234Y	38	50	55	63
L235W	136	128	130	40
G236D	109	91	212	25
G236A	165	168	94	65
G236E	142	131	117	33
G236S	147	161	87	33
S239N	99	80	124	111
S239I	82	75	108	47
S239V	79	71	107	48
S267A	176	125	283	145
H268D	173	142	307	220
H268E	169	132	283	205
P271G	152	130	252	93
P271D	94	55	110	85
P271E	90	51	105	87
Q295L	128	148	156	135
S298L	99	71	114	51
K326T	138	127	195	164
A327N	95	48	123	32
L328T	156	135	179	53
A330R	116	123	92	73
A330K	121	127	96	86
P331E	96	67	100	46
I332D	129	139	198	235
K334I	169	137	174	187
K334V	172	132	184	176
K334Y	157	131	160	188
K334M	151	127	148	183
K334D	97	72	108	155

[0550] Among these substitutions, L234W and L234Y were selected for increasing selectivity to human Fc gamma RIIb over human Fc gamma RIIa. And G236A, G236S, A330R, A330K and P331E were selected for decreasing binding to human Fc gamma RIIIa. All other substitutions were selected for increasing binding to human Fc gamma RIIb. The cross-reactivity of the selected substitutions to cynoFc gamma Rs were evaluated. In addition, three substitutions, P396M, V264I, and E233D were also evaluated. The substitutions were introduced into M103205H795-SG1 and the variants were expressed using M103202L889-SK1 as light chain.

[0551] Table 18 shows kinetic analysis of selected substitutions including G236N against both human and cynoFc gamma Rs. Specifically, substitutions were introduced into M103205H795-SG1. The variants were expressed using M103202L889-SK1 as light

chain and their affinity to cynoFc gamma RIIa1, IIa2, IIa3, IIB, IIIaS were analyzed.

- [0552] The KD values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis. Values of KD fold were calculated by dividing the KD value of SG1 by the KD value of the variant for each Fc gamma R.
- [0553] G236N showed comparable binding affinity to cynoFc gamma RIIa1, cynoFc gamma RIIa2, cynoFc gamma RIIa3, and cynoFc gamma RIIb to SG1. Although the affinity to human Fc gamma RIIb is reduced to 0.6-fold, affinities to human Fc gamma RIIaH and human Fc gamma RIIaR are reduced to 0.2-fold and 0.1-fold, respectively, indicating that this substitution has high selectivity to human Fc gamma RIIb over human Fc gamma RIIa. Furthermore, its affinities to cynoFc gamma RIIIaS and human Fc gamma RIIIaV are 0.03-fold and 0.04-fold, respectively, which is favorable for eliminating ADCC activity. Based on this result, G236N showed almost ideal cross-reactivity to human and cynoFc gamma Rs although its affinity to both human and cynoFc gamma RIIb should be enhanced.
- [0554] Among additional substitutions evaluated, S298L, G236A, P331E, E233D, K334Y, K334M, L235W, S239V, K334I, L234W, K328T, Q295L, K334V, K326T, P396M, I332D, H268E, P271G, S267A and H268D showed increased binding to both human and cynoFc gamma RIIb. Specifically, H268D showed the largest effect (7-fold for human Fc gamma RIIb and 5.3-fold for cynoFc gamma RIIb). With respect to the effect of reduction in Fc gamma RIIIa binding, G236S, A330K, and G236D showed less than 0.5-fold affinity compared to SG1.
- [0555] In order to enhance the affinity to both human and cynoFc gamma RIIb of MY001, combinations of substitutions listed in Table 18 were evaluated. Specifically, substitutions were introduced into M103205H795-SG1. The variants were expressed using M103202L889-SK1 as the light chain and their affinity was analyzed. Table 19 shows the result of kinetic analysis against human and cynoFc gamma Rs. The KD values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis. Values of KD fold were calculated by dividing the KD value of SG1 by the KD value of the variant for each Fc gamma R.
- [0556]

[Table 18]

Kinetic analysis of variants against human and cynoFc gamma Rs

Heavy chain name	KD (M) for cynoFcγs			KD (M) for humanFcγs			KD fold for cynoFcγs (SG1 = 1)			KD fold for humanFcγs (SG1 = 1)		
	FcγRIIIa2	FcγRIIIa3	FcγRIIIb	FcγRIIIa3	FcγRIIIa2	FcγRIIIa1	FcγRIIIa3	FcγRIIIa2	FcγRIIIa1	FcγRIIIa3	FcγRIIIa2	FcγRIIIa1
M103205H795-SG1	3.2E-06	5.1E-06	1.7E-05	1.8E-06	3.6E-07	6.9E-07	1.1E-06	8.1E-07	1.0E-06	1.0E-06	1.0E-06	1.0E-06
M103205H795-MY016	2.9E-06	3.4E-06	3.2E-06	1.7E-06	2.3E-07	8.5E-07	9.4E-07	2.9E-06	1.1E-06	1.5E-06	0.8E-06	1.2E-06
M103205H795-MY006	2.0E-06	1.9E-06	3.6E-06	9.2E-07	3.2E-07	1.8E-06	1.8E-06	7.3E-07	4.7E-06	2.0E-06	1.1E-06	2.0E-06
M103205H795-MY013	4.5E-06	4.7E-06	5.2E-06	2.0E-06	3.3E-07	2.6E-06	5.1E-06	4.1E-07	0.7E-06	1.1E-06	1.0E-06	1.2E-06
M103205H795-MY070	2.3E-06	2.8E-06	4.7E-06	1.2E-06	4.9E-07	5.0E-07	7.4E-07	2.6E-06	1.4E-06	1.8E-06	1.5E-06	1.8E-06
M103205H795-MY001	2.9E-06	3.6E-06	1.5E-05	1.8E-05	1.2E-05	3.2E-05	8.2E-06	7.7E-06	1.1E-06	1.0E-06	0.0E-06	0.6E-06
M103205H795-MY061	6.5E-06	6.8E-06	1.8E-05	4.2E-06	3.4E-06	1.4E-06	1.3E-06	2.5E-06	0.5E-06	0.8E-06	0.1E-06	0.8E-06
M103205H795-MY071	5.0E-06	3.7E-06	2.5E-06	2.5E-06	2.8E-07	4.0E-07	4.5E-07	5.1E-07	0.6E-06	1.4E-06	1.7E-06	2.4E-06
M103205H795-MY074	2.0E-06	2.3E-06	1.1E-06	1.1E-06	2.7E-07	9.2E-08	2.1E-07	3.6E-06	1.6E-06	2.2E-06	1.3E-06	7.5E-06
M103205H795-MY124	2.6E-06	3.1E-06	1.2E-05	2.2E-06	1.3E-06	1.4E-07	5.2E-07	9.2E-06	1.2E-06	1.4E-06	0.8E-06	4.9E-06
M103205H795-MY008	4.2E-06	3.7E-06	2.4E-05	1.7E-06	3.7E-07	1.6E-06	1.8E-06	2.6E-06	0.8E-06	1.4E-06	1.1E-06	0.9E-06
M103205H795-MY037	3.8E-06	4.5E-06	9.6E-06	2.4E-06	2.0E-07	1.1E-06	9.1E-07	2.6E-06	0.8E-06	1.1E-06	1.8E-06	0.6E-06
M103205H795-MY038	3.9E-06	4.5E-06	1.1E-05	1.9E-06	3.1E-07	1.2E-06	1.5E-06	2.8E-06	0.8E-06	1.1E-06	1.5E-06	0.7E-06
M103205H795-MY011	3.5E-06	5.0E-06	1.6E-05	2.0E-06	2.2E-07	1.2E-06	1.8E-06	5.1E-06	0.9E-06	1.0E-06	1.6E-06	0.6E-06
M103205H795-MY011	2.3E-06	2.8E-06	9.9E-06	1.0E-06	1.5E-07	4.9E-07	1.7E-07	6.6E-07	1.4E-06	1.8E-06	2.4E-06	7.0E-06
M103205H795-MY017	2.7E-06	2.9E-06	5.3E-06	6.8E-07	9.8E-08	4.3E-07	2.8E-07	9.4E-07	1.2E-06	1.8E-06	3.6E-07	1.5E-06
M103205H795-MY063	1.4E-06	1.5E-06	2.0E-06	3.4E-07	6.7E-08	2.7E-07	2.1E-07	6.6E-07	2.3E-06	3.4E-06	5.3E-06	7.0E-06
M103205H795-MY012	2.1E-06	2.3E-06	7.9E-06	1.1E-06	2.0E-07	4.4E-07	2.3E-07	9.0E-07	1.5E-06	2.2E-06	1.6E-06	4.8E-06
M103205H795-MY040	5.5E-06	1.1E-05	4.4E-06	3.5E-06	3.7E-07	1.8E-06	1.2E-06	3.0E-06	0.6E-06	0.5E-06	0.9E-06	1.5E-06
M103205H795-MY073	1.2E-06	1.3E-06	5.1E-06	6.7E-07	1.7E-07	2.4E-07	5.0E-07	2.0E-06	2.7E-06	3.3E-06	2.2E-06	2.3E-06
M103205H795-MY042	5.1E-07	3.1E-06	8.0E-06	1.6E-06	4.4E-07	1.0E-06	9.8E-07	4.0E-06	6.3E-06	1.1E-06	0.8E-06	0.7E-06
M103205H795-MY069	1.6E-06	1.6E-06	6.5E-06	7.3E-07	8.6E-08	4.4E-07	3.9E-07	1.6E-06	2.0E-06	2.6E-06	2.5E-06	4.1E-06
M103205H795-MY068	5.8E-06	6.1E-05	1.8E-05	4.4E-06	8.4E-07	2.9E-06	1.5E-06	3.0E-06	0.6E-06	0.1E-06	0.9E-06	0.4E-06
M103205H795-MY014	2.1E-06	2.7E-06	5.7E-06	1.0E-06	5.8E-07	3.7E-07	5.2E-07	2.1E-06	1.5E-06	1.9E-06	1.8E-06	2.1E-06
M103205H795-MY196	2.5E-06	2.5E-06	1.2E-05	1.5E-06	4.0E-07	5.2E-07	9.6E-07	4.8E-06	1.3E-06	2.0E-06	1.4E-06	1.1E-06
M103205H795-MY044	3.2E-06	3.5E-06	5.2E-05	1.6E-06	4.7E-07	1.2E-06	9.2E-07	6.2E-06	1.3E-06	1.7E-06	0.8E-06	0.7E-06
M103205H795-MY072	1.0E-06	1.2E-06	2.6E-06	4.8E-07	5.3E-08	2.5E-07	4.8E-07	1.5E-06	3.2E-06	4.3E-06	3.8E-06	2.8E-06
M103205H795-MY045	5.7E-06	4.0E-06	6.8E-06	2.2E-06	1.4E-07	1.6E-06	1.6E-06	2.9E-06	0.6E-06	1.3E-06	0.8E-06	0.7E-06
M103205H795-MY064	2.4E-06	2.6E-06	6.9E-06	1.1E-06	1.2E-07	5.0E-07	6.8E-07	2.2E-06	1.3E-06	2.0E-06	1.6E-06	1.9E-06
M103205H795-MY065	2.9E-06	2.6E-06	4.2E-06	1.1E-06	1.1E-07	5.2E-07	5.1E-07	1.9E-06	1.4E-06	1.8E-06	2.2E-06	2.4E-06
M103205H795-MY066	2.1E-06	2.8E-06	6.7E-06	1.4E-06	1.6E-07	6.4E-07	9.7E-07	2.8E-06	1.5E-06	2.0E-06	1.1E-06	1.6E-06
M103205H795-MY067	2.1E-06	2.3E-06	6.7E-06	1.1E-06	1.0E-07	5.9E-07	7.6E-07	2.8E-06	1.5E-06	2.2E-06	1.3E-06	1.4E-06
M103205H795-MY015	1.9E-06	1.5E-06	4.7E-06	6.0E-07	1.0E-07	3.9E-07	3.2E-07	1.6E-06	2.5E-06	3.4E-06	2.1E-06	2.9E-06

[0557] [Table 19]

Kinetic analysis of variants which are composed of G236N and additional substitutions

Table with columns: Heavy chain name, Substitutions, KD (M) for cytoFcRs, KD (M) for humanFcRs, KD fold for cytoFcRs (SG1 = 1), KD fold for humanFcRs (SG1 = 1). The table lists 50 variants and their kinetic parameters.

- [0558] All the variants suppressed affinities to human Fc gamma RIIIaV by less than 0.26-fold and to cynoFc gamma RIIIaS by less than 0.42-fold compared to SG1. Furthermore, all the variants except for MY047, MY051, and MY141 successfully showed enhanced binding to both human and cynoFc gamma RIIb compared to MY001 and their human Fc gamma RIIa binding were maintained to less than 2-fold compared to SG1. Among them, MY201, MY210, MY206, MY144, MY103, MY212, MY105, MY205, MY109, MY107, MY209, MY101, MY518, MY198 and MY197 showed enhanced binding both to human and cynoFc gamma RIIb by more than 4-fold compared to SG1. Above all, MY205, MY209, MY198, and MY197 showed enhanced binding to both human and cynoFc gamma RIIb binding by more than 7-fold.
- [0559] It was illustrated in WO2014030728 that substitutions at position 396 in CH3 domain enhanced affinity to human Fc gamma RIIb. Comprehensive mutagenesis was introduced into position 396 of M103205H795-MY052, which contains G236N/H268E/P396M substitutions. The resultant variants were expressed using M103202L889-SK1 as light chain and their affinity to human and cynoFc gamma Rs were evaluated (Table 20). Values of KD fold were calculated by dividing the KD value of SG1 by the KD value of the variant for each Fc gamma R.
- [0560] Among substitutions tested, P396I, P396K, and P396L maintained human Fc gamma RIIb binding by more than 5-fold compared to SG1 and only P396L substitution enhanced affinity to human Fc gamma RIIb compared to MY052. With respect to the binding to cynoFc gamma RIIb, parent MY052 showed the highest affinity which is a 3.9-fold increase from SG1.
- [0561] Since G236N showed ideal cross-reactivity to human and cynoFc gamma Rs, other substitutions on position 236 which were not evaluated in the preceding examples were tested. Specifically, Asn in M103205H795-MY201 were substituted with Met, His, Val, Gln, Leu, Thr, and Ile. The resultant variants were expressed using M103202L889-SK1 as light chain and their affinity to human and cynoFc gamma Rs were evaluated (Table 21). The KD values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis. Values of KD fold were calculated by dividing the KD value of SG1 by the KD value of the variant for each Fc gamma R.
- [0562]

[Table 20]

Kinetic analysis of P396 variants derived from MY052

Heavy chain name	KD (M) for cynoFcγRs												KD (M) for humanFcγRs											
	FcγRIIA1	FcγRIIA2	FcγRIIA3	FcγRIIB	FcγRIIAs	FcγRIIAH	FcγRIIAR	FcγRIIBb	FcγRIIIV	FcγRIIA1	FcγRIIA2	FcγRIIA3	FcγRIIB	FcγRIIAs	FcγRIIAH	FcγRIIAR	FcγRIIBb	FcγRIIIV						
M103205H795-SG1	3.2E-06	5.1E-06	1.7E-05	1.8E-06	3.6E-07	6.9E-07	1.1E-06	4.6E-06	8.1E-07	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0					
S236N/H268E/P396M	1.4E-06	1.5E-06	3.9E-06	4.6E-07	1.5E-06	8.3E-07	1.4E-06	7.2E-07	1.5E-06	2.3	3.4	4.4	3.9	0.24	0.8	0.8	0.8	6.4	0.54					
M103205H795-MY168	2.2E-06	2.5E-06	1.0E-05	1.2E-06	4.5E-06	1.6E-06	2.8E-06	1.7E-06	8.1E-06	1.5	2.0	1.7	1.5	0.98	0.4	0.4	0.4	2.7	0.10					
M103205H795-MY169	2.3E-06	2.3E-06	9.8E-06	1.0E-06	3.5E-06	1.2E-06	2.5E-06	1.3E-06	6.2E-06	1.4	2.2	1.7	1.8	0.10	0.6	0.4	0.4	3.5	0.13					
M103205H795-MY170	2.3E-06	2.4E-06	1.2E-05	1.2E-06	2.9E-06	1.7E-06	2.3E-06	1.6E-06	6.3E-06	1.4	2.1	1.4	1.5	0.12	0.4	0.4	0.4	2.9	0.13					
M103205H795-MY171	2.3E-06	2.3E-06	9.2E-06	9.8E-07	3.3E-06	1.2E-06	2.1E-06	1.2E-06	5.9E-06	1.4	2.2	1.8	1.8	0.11	0.6	0.5	0.5	3.8	0.14					
M103205H795-MY172	2.7E-06	2.8E-06	1.1E-05	1.2E-06	3.3E-06	1.7E-06	3.1E-06	1.8E-06	6.5E-06	1.2	1.8	1.5	1.5	0.11	0.4	0.4	0.4	2.6	0.12					
M103205H795-MY173	1.7E-06	1.8E-06	8.0E-06	7.8E-07	3.1E-06	1.0E-06	1.9E-06	1.0E-06	7.0E-06	1.9	2.8	2.1	2.3	0.12	0.7	0.6	0.6	4.6	0.12					
M103205H795-MY174	1.5E-06	1.6E-06	6.4E-06	6.5E-07	2.5E-06	8.1E-07	1.4E-06	8.5E-07	6.8E-06	2.1	3.2	2.7	2.8	0.14	0.9	0.8	0.8	5.4	0.12					
M103205H795-MY175	1.4E-06	1.5E-06	7.5E-06	7.1E-07	2.6E-06	8.6E-07	1.5E-06	8.3E-07	7.6E-06	2.2	3.4	2.3	2.5	0.14	0.8	0.7	0.7	5.5	0.11					
M103205H795-MY176	1.3E-06	1.4E-06	6.0E-06	6.1E-07	2.2E-06	7.0E-07	1.3E-06	7.0E-07	6.2E-06	2.5	3.6	2.8	3.0	0.16	1.0	0.8	0.8	6.6	0.13					
M103205H795-MY177	1.9E-06	1.8E-06	8.1E-06	8.3E-07	2.9E-06	1.0E-06	2.0E-06	1.1E-06	6.2E-06	1.7	2.8	2.1	2.2	0.12	0.7	0.6	0.6	4.2	0.13					
M103205H795-MY178	2.0E-06	2.1E-06	8.7E-06	9.5E-07	3.0E-06	1.2E-06	2.3E-06	1.3E-06	4.5E-06	1.6	2.4	2.0	1.9	0.12	0.6	0.5	0.5	3.5	0.18					
M103205H795-MY179	1.9E-06	2.0E-06	7.9E-06	9.8E-07	2.7E-06	1.1E-06	2.1E-06	1.2E-06	5.9E-06	1.7	2.6	2.2	2.2	0.13	0.6	0.5	0.5	3.8	0.14					
M103205H795-MY180	2.6E-06	2.7E-06	1.2E-05	1.3E-06	3.1E-06	1.7E-06	3.0E-06	1.9E-06	5.9E-06	1.2	1.9	1.4	1.4	0.12	0.4	0.4	0.4	2.4	0.14					
M103205H795-MY181	2.3E-06	2.3E-06	9.2E-06	1.0E-06	4.1E-06	1.3E-06	2.5E-06	1.4E-06	7.3E-06	1.4	2.2	1.8	1.8	0.09	0.5	0.4	0.4	3.3	0.11					
M103205H795-MY182	2.1E-06	2.2E-06	7.8E-06	9.6E-07	3.6E-06	1.3E-06	2.1E-06	1.2E-06	7.0E-06	1.5	2.3	2.2	1.9	0.10	0.5	0.5	0.5	3.8	0.12					
M103205H795-MY183	2.1E-06	2.0E-06	8.4E-06	9.7E-07	3.5E-06	1.2E-06	2.1E-06	1.1E-06	7.2E-06	1.5	2.6	2.0	1.9	0.10	0.6	0.5	0.5	4.2	0.11					
M103205H795-MY184	1.9E-06	2.0E-06	8.4E-06	9.0E-07	3.3E-06	1.1E-06	2.0E-06	1.1E-06	6.8E-06	1.7	2.6	2.0	2.0	0.11	0.5	0.6	0.6	4.2	0.12					

- [0565] Although all the variants showed decreased affinity to both human and cynoFc gamma RIIb compared to the parent MY201, MY265, which is produced by substituting Asn with Thr at position 236 of MY201, maintained enhanced binding by 2.1-fold for human Fc gamma RIIb and 3.1-fold for cynoFc gamma RIIb, respectively compared to SG1. MY265 also maintained reduced binding to both human and cynoFc gamma RIIIa. Although affinity to human Fc gamma RIIaH and Fc gamma RIIaR was enhanced by more than 2.5-fold compared to SG1, G236T is the second favorable substitution at position 236.
- [0566] In order to improve the selectivity and affinity of MY265 to human Fc gamma RIIb, comprehensive mutagenesis study into position 231 and 232 was performed. Specifically position 231 and 232 of M103205H795-MY265 were substituted with 18 amino acid residues excluding the original amino acid and Cys. The resultant variants were expressed using M103202L889-SK1 as light chain and their affinity to human and cynoFc gamma Rs were evaluated (Table 22). Values of KD fold were calculated by dividing the KD value of SG1 by the KD value of the variant for each Fc gamma R.
- [0567] With respect to affinity to Fc gamma RIIb, the addition of A231T, A231M, A231V, A231G, A231F, A231I, A231L, A231, A231W, P232V, P232Y, P232F, P232M, P232I, P232W, P232L increased binding to both human and cynoFc gamma RIIb compared to parent MY265. Above all, addition of A231T and A231G reduced human Fc gamma RIIaR binding compared to MY265.
- [0568] The combination of the substitutions which was not evaluated in the preceding examples were evaluated. The substitutions tested and revealed to be promising were introduced into M103205H795-SG1 in combination. The resultant variants were expressed using M103202L889-SK1 as light chain and their affinity to human and cynoFc gamma Rs were evaluated. Table 23 shows the result and the KD values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis. Values of KD fold were calculated by dividing the KD value of SG1 by the KD value of the variant for each Fc gamma R. The values for MY209 which was selected as a promising variants in Table 19 were shown again for comparison.
- [0569] Among the variants tested, only MY213 showed higher binding affinity to both human and cynoFc gamma RIIb compared to MY209. However, the affinities of MY213 to human Fc gamma RIIaH and human Fc gamma RIIaR are higher than those of MY209.
- [0570]

[Table 23A]

Kinetic analysis of other combinations

Table with 4 main sections: Heavy chain name, Substitutions, KD (M) for cyneFcγR2, KD (M) for humanFcγR2, KD fold for cyneFcγR2 (SG1=1), and KD fold for humanFcγR2 (SG1=1). Each section contains multiple columns of data for various heavy chain names and substitutions, with values in scientific notation and some decimal values.

[0571] [Table 23B]

Kinetic analysis of other combinations

Table with 3 main columns: Heavy chain name, Substitutions, and KD (M) for human FcγR3 (SG1 = 1). The KD values are presented in a grid format for various combinations of heavy chain name and substitution.

[0572] [Table 24]

Binding profile of the variants tested in all human Fc gamma R transgenic mice

Heavy chain name	CH	SEQ ID NO	Substitutions	KD (M) for cynoFcγR3			KD (M) for humanFcγR3			KD fold for cynoFcγR3 (SG1 = 1)			KD fold for humanFcγR3 (SG1 = 1)					
				FcγRIIa1	FcγRIIa2	FcγRIIa3	FcγRIIa1	FcγRIIa2	FcγRIIa3	FcγRIIa1	FcγRIIa2	FcγRIIa3	FcγRIIa1	FcγRIIa2	FcγRIIa3			
M103205H795-SG1	SG1	9		3.2E-06	5.1E-06	1.7E-05	1.8E-06	3.6E-07	6.9E-07	1.1E-06	4.9E-06	1.0	1.0	1.0	1.0	1.0	1.0	
M103205H795-MY101	MY101	229	G236N/H268E/A330K/P396M	1.1E-06	1.2E-06	3.3E-06	3.5E-07	3.2E-06	4.9E-07	8.7E-07	4.9E-07	2.9	4.3	4.7	5.1	0.111	1.4	
M103205H795-PK2	PK2	230	G236N/H268E/A330K/P396M/S400R/D413K	1.3E-06	1.3E-06	3.8E-06	3.8E-07	3.9E-06	5.7E-07	1.1E-06	5.9E-07	2.5	3.9	4.5	4.7	0.05	1.2	1.0
M103205H795-MY201	MY201	231	G236N/H268D/A330K	1.4E-06	1.4E-06	3.9E-06	4.3E-07	5.7E-06	9.1E-07	1.9E-06	1.1E-06	2.3	3.6	4.4	4.2	0.06	0.8	0.6
M103205H795-MY351	MY351	232	G236N/H268D/Q311R/A330K/D413K	9.2E-07	7.8E-07	1.9E-06	3.5E-07	5.2E-06	1.0E-06	1.6E-06	1.2E-06	3.5	6.7	8.9	5.1	0.07	0.7	0.7
M103205H795-MY205	MY205	233	G236N/H268D/Q295L/A330K	9.0E-07	1.1E-06	3.0E-06	2.5E-07	6.0E-06	4.7E-07	1.3E-06	5.8E-07	3.6	4.6	5.7	7.2	0.06	1.5	0.8
M103205H795-MY244	MY244	234	G236N/H268D/Q295L/Q311R/A330K/D413K	8.9E-07	1.1E-06	2.2E-06	3.1E-07	4.9E-06	6.7E-07	1.3E-06	7.3E-07	3.6	4.6	7.7	5.3	0.07	1.0	0.9
M103205H795-MY335	MY335	235	G236Y/H268D/Q311R/A330K/D413K	2.0E-06	1.7E-06	2.7E-06	6.5E-07	1.5E-06	2.9E-07	2.9E-07	2.3E-06	1.6	3.0	6.3	2.3	0.24	2.4	3.8

Example 24

[0573] Evaluation of clearance of myostatin using Fc gamma RIIb-enhanced Fc variants in all human Fc gamma R transgenic mice

The effect of clearance of myostatin by Fc gamma RIIb-enhanced Fc variant constructed in Example 23 was evaluated in a mouse in which all murine Fc gamma Rs have been deleted and human Fc gamma Rs, encoded as transgenes, have been inserted into the mouse genome (Proc. Natl. Acad. Sci., 2012, 109, 6181). In this mice all mouse Fc gamma Rs are substituted with human ones so that the effect of affinity enhancement to human Fc gamma RIIb on clearance of soluble antigen can be evaluated in mouse. Furthermore, pI-increasing substitutions were evaluated in combination with Fc gamma RIIb-enhanced Fc variants constructed in Example 23.

[0574] Preparation and profile of tested variants

The tested 8 antibodies and their binding profiles are summarized in Table 24. The heavy chain, MS103205H795-PK2, was prepared by introducing pI-increasing substitutions (S400R/D413K) into MS103205H795-MY101. MS103205H795-MY351, MS103205H795-MY344, MS103205H795-MY335 were prepared by introducing another pI-increasing substitutions (Q311R/D413K) into MS103205H795-MY201, MS103205H795-MY205, MS103205H795-MY265, respectively. All the MS1032LO06 variants were expressed with M103202L889-SK1 as light chain according to the method shown in Example 23 and their affinities to human and cynoFc gamma Rs were evaluated using the method in Example 23.

[0575] Based on the SPR analysis summarized in Table 24, it was confirmed that the pI-increasing substitutions do not affect the Fc gamma R binding of Fc gamma RIIb-enhanced Fc variants. MY101 and PK2, which was prepared by introducing S400R/D413K into MY101, show 9-fold and 8-fold enhanced human Fc gamma RIIb binding, respectively. The affinities of MY101 and PK2 to human Fc gamma RIIa are remained comparable to SG1. With respect to other human and cynoFc gamma Rs, they show almost the same binding profile. Similarly, MY351 showed similar binding profile with that of parent MY201, MY344 with that of parent MY205, and MY335 with that of parent MY265 (Table 21), respectively. These results indicate that either pair of pI-increasing substitutions, S400R/D413K or Q311R/D413K, does not affect the affinities to human and cynoFc gamma Rs.

[0576] PK study in all human Fc gamma R transgenic mice

In vivo test using all human Fc gamma R transgenic mice

The elimination of myostatin and anti-latent myostatin antibody were assessed in vivo upon co-administration of anti-latent myostatin antibody and human latent myostatin in all human Fc gamma R transgenic mice (Figures 20 and 21). An anti-

latent myostatin antibody (0.3 mg/ml) and latent myostatin (0.05 mg/ml) were administered at a single dose of 10 ml/kg into the caudal vein. Anti-CD4 antibody (1 mg/ml) was administered three times (every 10 days) at a dose of 10 ml/kg into the caudal vein to suppress anti-drug antibody. Blood was collected at 5 minutes, 15 minutes, 1 hour, 4 hours, 7 hours, 1 day, 2 days, 7 days, 14 days, 21 days, and 28 days after administration. The collected blood was centrifuged immediately at 15,000 rpm in 4 degrees C for 5 minutes to separate the plasma. The separated plasma was stored at or below -20 degrees C until measurement. The anti-latent myostatin antibodies used were MS1032LO06-SG1, MS1032LO06-MY101, MS1032LO06-PK2, MS1032LO06-MY201, MS1032LO06-MY351, MS1032LO06-MY205, MS1032LO06-MY344 and MS1032LO06-MY335.

[0577] Measurement of total myostatin concentration in plasma by electrochemiluminescence (ECL)

The concentration of total myostatin in mouse plasma was measured by ECL. Anti-mature myostatin antibody-immobilized plates were prepared by dispensing anti-mature myostatin antibody RK35 (WO 2009058346) onto a MULTI-ARRAY 96-well plate (Meso Scale Discovery) and incubated overnight at 4 degrees C. Mature myostatin calibration curve samples and mouse plasma samples diluted 4-fold or more were prepared. The samples were mixed in an acidic solution (0.2 M Glycine-HCl, pH2.5) to dissociate mature myostatin from its binding protein (such as propeptide). Subsequently, the samples were added onto an anti-mature myostatin antibody-immobilized plate, and allowed to bind for 1 hour at room temperature before washing. Next, BIOTIN TAG labelled anti-mature myostatin antibody RK22 (WO 2009/058346) was added and the plate was incubated for 1 hour at room temperature before washing. Next, SULFO TAG labelled streptavidin (Meso Scale Discovery) was added and the plate was incubated for 1 hour at room temperature before washing. Read Buffer T (x4) (Meso Scale Discovery) was immediately added to the plate and signal was detected by SECTOR Imager 2400 (Meso Scale Discovery). The mature myostatin concentration was calculated based on the response of the calibration curve using the analytical software SOFTmax PRO (Molecular Devices). The time course of total myostatin concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figure 20.

[0578] Measurement of anti-latent myostatin antibody concentration in plasma by high-performance liquid chromatography-electrospray tandem mass spectrometry (LC/ESI-MS/MS)

Anti-latent myostatin antibody concentration in mouse plasma was measured by LC/ESI-MS/MS. The concentrations of calibration standards were 1.56 25, 3.125, 6.25,

12.5, 25, 50, 100, and 200 micro g/mL in mice plasma. Three micro L of the calibration standards and plasma samples were added to 50 micro L of Ab-Capture Mag (ProteNova), and allowed to incubate for 2 hours at room temperature. Afterward, the magnetic beads were recovered from samples and washed twice with 0.2 mL of 10 mmol/L PBS with 0.05% Tween 20. Subsequently, the magnetic beads were washed with 10 mmol/L PBS to ensure the removal of Tween 20. After washing, the magnetic beads were suspended in 25 micro L of 7.5 mol/L Urea, 8 mmol/L dithiothreitol and 1 micro g/mL lysozyme (chicken egg white) in 50 mmol/L ammonium bicarbonate and the suspended samples were incubated for 45 minutes at 56 degrees C. Then, 2 micro L of 500 mmol/L iodoacetoamide was added and the samples were incubated for 30 minutes at 37 degrees C in the dark. Next, Lysyl Endopeptidase digestion was carried out by adding 150 micro L of 0.67 micro g/mL Lysyl Endopeptidase for Biochemistry (Wako) in 50 mmol/L ammonium bicarbonate and the samples were incubated for 3 hr at 37 degrees C. Subsequently, tryptic digestion was carried out by adding 10 micro L of 10 micro g/mL sequencing grade modified trypsin (Promega) in 50 mmol/L ammonium bicarbonate. Samples were allowed to digest under mixing overnight at 37 degrees C, and quenched by adding 5 micro L of 10% trifluoroacetic acid. Fifty micro L of digestion samples were subjected to analysis by LC/ESI-MS/MS. LC/ESI-MS/MS was performed using Xevo TQ-S triple quadrupole instrument (Waters) equipped with 2D I-class UPLC (Waters). Anti-latent myostatin antibody specific peptide YAFGQGTK and Lysozyme specific peptide GTDVQAWIR as an internal standard were monitored by the selected reaction monitoring (SRM). SRM transition was $[M+2H]^{2+}$ (m/z 436.2) to y8 ion (m/z 637.3) for anti-latent myostatin antibody, and $[M+2H]^{2+}$ (m/z 523.3) to y8 ion (m/z 545.3) for lysozyme. Internal calibration curve was constructed by the weighted (1/x or 1/x²) linear regression using the peak area plotted against the concentrations. The concentration in mouse plasma was calculated from the calibration curve using the analytical software Masslynx Ver.4.1 (Waters). The time course of antibody concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figure 21.

[0579] Effect of pI and Fc gamma R binding on myostatin concentration in vivo

After administration of MS1032LO06-SG1, plasma total myostatin concentration at 7 hours decreased 5 fold compared to plasma total myostatin concentration at 5 minutes. In contrast, after administration of MS1032LO06-MY101, MS1032LO06-MY201 and MS1032LO06-MY205, plasma total myostatin concentration at 7 hours decreased 28-200 fold compared to plasma total myostatin concentration at 5 minutes. Furthermore, after administration of MS1032LO06-PK2, MS1032LO06-MY351, MS1032LO06-MY344 and MS1032LO06-MY335, plasma

total myostatin concentration at 7 hours decreased 361-419 fold compared to plasma total myostatin concentration at 5 minutes. On the other hands, the difference in each antibody's concentration at each sampling point compared to MS1032LO06-SG1's was approximately within 2 fold, and pI variants did not increase antibody elimination from plasma. Both human Fc gamma RIIb binding enhanced antibodies and pI-increasing substitutions increased elimination of myostatin, but not antibodies.

[0580] High pI variants have more positive charge in plasma. Since this positive charge interacts with cell surface of negative charge, antigen-antibody immune complex of high pI variants get closer to cell surface, resulted in increased cellular uptake of antigen-antibody immune complex of high pI variants.

Example 25

[0581] Evaluation of clearance of myostatin

using Fc gamma RIIb-enhanced Fc variants in monkey

The effect of enhanced binding of Fc variants developed in Example 23 to cynoFc gamma RIIb on myostatin sweeping was evaluated in cynomolgus monkey. And the combination effect with pI-increasing substitutions were also evaluated.

[0582] Preparation and profile of tested variants

The tested 14 antibodies and their binding profiles are summarized in Table 25. It has been reported that Fc variant with enhanced binding to FcRn at acidic pH improve the antibody half-life in vivo (J. Biol. Chem. 2006 281:23514-23524 (2006); Nat. Biotechnol. 28:157-159 (2010), Clin Pharm. & Thera. 89(2):283-290 (2011)). To improve the antibody half-life without binding to rheumatoid factor we combined these substitutions with Fc gamma RIIb enhanced and pI-increased Fc variants.

[0583] The heavy chain, MS103205H795-SG1012, MS103205H795-SG1029, MS103205H795-SG1031, MS103205H795-SG1033, MS103205H795-SG1034 were prepared by introducing a N434A substitution into MS103205H795-MY101, MS103205H795-MY344, MS103205H795-MY351, MS103205H795-MY201, MS103205H795-MY335, respectively. MS103205H795-SG1016 was prepared by introducing pI-increasing substitutions (Q311R/D399K) into MS103205H795-SG1012. MS103240H795-SG1071 and MS103240H795-SG1079 were prepared by introducing M428L/N434A/Y436T/ Q438R/S440E substitutions and N434A/Q438R/S440E substitutions into MS103240 H795-MY344 respectively (MS103240H795: VH, SEQ ID NO; 92).

[0584] MS103240H795-SG1074 and MS103240H795-SG1077 were prepared by introducing pI-increasing substitutions Q311R/P343R and M428L/N434A/Y436T/Q438R/S440E substitutions into MS103240H795-MY209 and MS103240H795-MY518, respectively. MS103240H795-SG1080 and

MS103240H795-SG1081 were prepared by introducing pI-increasing substitutions Q311R/P343R and N434A/Q438R/S440E substitutions into MS103240H795-MY209 and MS103240H795-MY518, respectively. MS103240H795-SG1071 was prepared by introducing pI-increasing substitutions Q311R/D413K and M428L/N434A/Y436T/Q438R/S440E substitutions into MS103240H795-MY205. MS103240H795-SG1079 was prepared by introducing pI-increasing substitutions Q311R/D413K and N434A/Q438R/S440E substitutions into MS103240H795-MY205. These MS1032LO06 variants and MS1032LO19 variants were expressed with M103202L889-SK1 and M103202L1045-SK1 respectively (M103202L1045: VL, SEQ ID NO: 97) as light chain according to the method shown in Example 30 and their affinities to human and cynoFc gamma Rs were evaluated using the method in Example 23. In this example, the value of KD fold for each Fc variant was calculated by dividing the KD value of the parent SG1 by the KD value of the variant for each Fc gamma R. For example, the values of KD fold for MS1032LO06-SG1012 and MS1032LO19-SG1071 were calculated by dividing the KD values of MS1032LO06-SG1 and MS1032LO19-SG1 by the KD values of MS1032LO06-SG1012 and MS1032LO19-SG1071 respectively.

[0585]

[Table 25]

Heavy chain name	CH	SEQ ID NO	mutation	KD (M) for cynoFcγRIIIb						KD (M) for humanFcγRIIIb												
				FcγRIIIa	FcγRIIIb	FcγRIIIc	FcγRIIIa/FcγRIIIb	FcγRIIIa/FcγRIIIc	FcγRIIIb/FcγRIIIc	FcγRIIIa	FcγRIIIb	FcγRIIIc	FcγRIIIa/FcγRIIIb	FcγRIIIa/FcγRIIIc	FcγRIIIb/FcγRIIIc							
M103205H195-SG1	SG1	9		4.8E-08	4.7E-08	8.5E-08	1.9E-07	2.8E-07	8.9E-07	1.5E-06	4.7E-06	5.2E-07	1.0	1.0	1.0	1.0	1.0	1.0	1.0			
M103205H195-SG1012	SG1012	236	G235N/H166E/A330K/P298M/N434A	1.1E-08	1.6E-08	2.3E-08	2.7E-07	2.1E-08	5.0E-07	1.5E-07	4.5E-07	3.8E-08	4.4	4.2	3.8	2.2	0.13	1.3	1.4	9.6	0.11	
M103205H195-SG1016	SG1016	237	G235N/H166E/C311R/A330K/P298M/N434A	1.3E-08	1.1E-08	2.0E-08	3.8E-07	2.4E-08	6.0E-07	2.7E-07	5.3E-07	1.0E-08	3.8	4.1	3.9	6.0	0.12	1.3	1.2	8.7	0.09	
M103205H195-SG1029	SG1029	238	G235N/H166D/C295S/C311R/A330K/D413K/N434A	1.8E-08	1.5E-08	3.1E-08	4.0E-07	5.3E-08	7.9E-07	1.3E-06	9.0E-07	2.0E-08	3.5	3.1	2.8	4.9	0.09	1.1	0.8	5.3	0.09	
M103205H195-SG1031	SG1031	239	G235N/H166D/C311R/A330K/D413K/N434A	1.8E-08	1.5E-08	2.8E-08	5.0E-07	4.4E-08	1.3E-06	8.0E-07	1.3E-06	1.5E-08	2.6	3.1	3.1	3.5	0.06	0.7	1.3	3.8	0.04	
M103205H195-SG1033	SG1033	240	G235N/H166D/A330K/N434A	1.8E-08	1.5E-08	3.0E-08	5.0E-07	4.4E-08	1.2E-06	1.0E-06	1.2E-06	1.1E-08	2.6	3.0	2.9	3.9	0.06	0.7	1.0	3.9	0.03	
M103205H195-SG1034	SG1034	241	G235T/H298D/C311R/A330K/D413K/N434A	3.1E-08	2.7E-08	4.3E-08	8.8E-07	2.4E-08	3.1E-07	2.5E-07	7.4E-08	7.1E-08	1.5	1.7	2.0	2.2	0.13	2.9	4.1	1.8	0.09	
M103240H195-SG1	SG1	9		3.8E-08	4.1E-08	6.6E-08	1.7E-06	2.4E-07	9.7E-07	3.6E-07	3.8E-08	5.8E-07	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
M103240H195-SG1071	SG1071	242	G235N/H168D/C292L/C311R/A330K/D413K/N434A/N435T/Q438R/S446E	1.2E-08	1.3E-08	2.1E-08	3.3E-07	3.8E-08	6.9E-07	1.2E-06	6.8E-07	1.4E-08	3.0	3.2	3.2	5.3	0.07	1.4	0.8	5.6	0.04	
M103240H195-SG1074	SG1074	243	G235N/H168D/C292L/C311R/A330K/D413K/N434A/N435T/Q438R/S446E	7.9E-07	6.8E-07	1.1E-06	1.6E-06	1.4E-06	4.5E-07	3.4E-07	3.9E-07	4.5E-08	5.4	6.1	5.2	11.1	0.19	2.3	1.8	10.2	0.13	
M103240H195-SG1077	SG1077	244	L232W/G288N/H268D/C311R/A330K/D413K/N434A/N435T/Q438R/S446E	1.4E-08	1.3E-08	2.0E-08	3.2E-07	2.9E-08	9.3E-07	9.5E-07	3.1E-07	3.4E-08	2.7	3.1	3.1	3.4	0.09	1.4	1.4	7.3	0.11	
M103240H195-SG1079	SG1079	245	G235N/H168D/C292S/C311R/A330K/D413K/N434A/Q438R/S446E	1.1E-08	1.2E-08	2.1E-08	3.9E-07	3.3E-08	6.7E-07	1.2E-06	6.9E-07	3.2E-08	3.4	3.4	3.2	5.7	0.08	1.4	0.8	5.6	0.18	
M103240H195-SG1080	SG1080	246	G235N/H168D/C292S/C311R/A330K/D413K/N434A/Q438R/S446E	6.5E-07	6.8E-07	1.1E-06	1.4E-07	1.4E-07	4.5E-07	3.7E-07	4.8E-08	5.8	6.1	6.1	12.6	0.19	2.1	1.7	10.5	0.13		
M103240H195-SG1081	SG1081	247	L232W/G288N/H268D/C292L/C311R/A330K/D413K/N434A/Q438R/S446E	1.4E-08	1.3E-08	2.1E-08	2.9E-07	2.0E-08	9.9E-07	5.0E-07	3.4E-08	2.7	2.2	3.1	3.1	0.09	1.0	1.4	7.7	0.17		

[0586] The SPR analysis results are summarized in Table 25. Among these variants, SG1012, SG1016, SG1074 and SG1080 show the strongest affinity to human Fc gamma RIIb, which has 10 fold enhanced affinity to human Fc gamma RIIb compared to SG1.

[0587] 29.2. PK study in monkey

In vivo test using cynomolgus monkey

The accumulation of endogenous myostatin was assessed in vivo upon administration of anti-latent myostatin antibody in 2-4 year old *Macaca fascicularis* (cynomolgus monkey) from Cambodia (Shin Nippon Biomedical Laboratories Ltd., Japan). A dose level of 30mg/kg was injected into the cephalic vein of the forearm using a disposable syringe, extension tube, indwelling needle, and infusion pump. The dosing speed was 30 minutes per body. Blood was collected before the start of dosing and either 5 minutes, 7 hours and 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 and 56 days after the end of dosing, or 5 minutes and 2, 4, and 7 hours and 1, 2, 3, 7, 14, 21, 28, 35, 42, 49 and 56 days after the end of dosing. Blood was drawn from the femoral vein with a syringe containing heparin sodium. The blood was immediately cooled on ice, and plasma was obtained by centrifugation at 4 degrees C, 1700xg for 10 minutes. The plasma samples were stored in a deep freezer (acceptable range: -70 degrees C or below) until measurement. The anti-latent myostatin antibodies used were MS1032LO00-SG1, MS1032LO06-SG1012, MS1032LO06-SG1016, MS1032LO06-SG1029, MS1032LO06-SG1031, MS1032LO06-SG1033, and MS1032LO06-SG1034 (herein, SG1012, SG1016, SG1029, SG1031, SG1033, and SG1034 are the heavy chain constant regions constructed based on SG1 as described below).

[0588] A dose level of 2mg/kg was administered into the cephalic vein of the forearm or saphenous vein using a disposable syringe, and indwelling needle for the anti-latent myostatin antibodies MS1032LO19-SG1079, MS1032LO19-SG1071, MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081, and MS1032LO19-SG1077 (herein, SG1079, SG1071, SG1080, SG1074, SG1081, and SG1077 are the heavy chain constant regions constructed based on SG1 as described below). Blood was collected before the start of dosing and 5 minutes and 2, 4, and 7 hours and 1, 2, 3, 7, 14 days after the end of dosing. The blood was processed as described above. Plasma samples were stored in a deep freezer (acceptable range: -70 degrees C or below) until measurement.

[0589] Measurement of total myostatin concentration in plasma by electrochemiluminescence (ECL)

The concentration of total myostatin in monkey plasma was measured by ECL as described in Example 20. The time course of plasma total myostatin concentration after intravenous administration of anti-latent myostatin antibody as measured by this

method is shown in Figure 22.

[0590] Measurement of ADA in monkey plasma using electrochemiluminescence (ECL) Biotinylated drug was coated onto a MULTI-ARRAY 96-well streptavidin plate (Meso Scale Discovery) and incubated in low cross buffer (Candor) for 2 hours at room temperature. Monkey plasma samples were diluted 20 fold in low cross buffer before addition to the plate. Samples were incubated overnight at 4°C. On the next day, the plate was washed three times with wash buffer before addition of SULFO TAG labelled anti monkey IgG secondary antibody (Thermo Fisher Scientific). After incubating for an hour at room temperature, the plate was washed three times with wash buffer. Read Buffer T (x4) (Meso Scale Discovery) was immediately added to the plate and signal was detected using a SECTOR Imager 2400 (Meso Scale Discovery).

[0591] Effect of pH-dependent and Fc engineering on myostatin accumulation in monkey in vivo

In cynomolgus monkey, administration of non pH-dependent antibody (MS1032LO00-SG1) resulted in at least 60 fold increase in myostatin concentration from baseline at day 28. At day 28, pH-dependent anti-latent myostatin antibodies MS1032LO06-SG1012 and MS1032LO06-SG1033 resulted in 3 fold and 8 fold increase from baseline respectively. The strong sweeping was mainly contributed by the increase in affinity to cynomolgus monkey Fc gamma RIIb. At day 28, pH-dependent anti-latent myostatin antibodies MS1032LO06-SG1029, MS1032LO06-SG1031 and MS1032LO06-SG1034 could sweep antigen to below baseline. The reason for strong sweeping of MS1032LO06-SG1029, MS1032LO06-SG1031 and MS1032LO06-SG1034 are an increase in non-specific uptake in the cell due to increase in positive charge cluster of the antibody and an increase in Fc gamma R-mediated cellular uptake due to enhanced binding to Fc gamma R.

[0592] Administration of pH-dependent anti-latent myostatin antibodies MS1032LO19-SG1079, MS1032LO19-SG1071, MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081 and MS1032LO19-SG1077 reduced myostatin concentration to below the detection limit (<0.25ng/mL) from day 1 in cynomolgus monkey. On day 14, the concentration of myostatin increased above the detection limit for MS1032LO19-SG1079 and MS1032LO19-SG1071 while the concentration of myostatin remained below the detection limit for MS1032LO19-SG1080, MS1032LO19-SG1074, MS1032LO19-SG1081 and MS1032LO19-SG1077. The weaker suppression of MS1032LO19-SG1079 and MS1032LO19-SG1071 could be due to difference in pI mutations.

[0593] The data suggests that strong sweeping of myostatin from the plasma could be achieved by mutations that increase binding to Fc gamma RIIb or combining mutations

that increase positive charge of the antibody and increase binding to Fc gamma RIIb. It is expected that strong sweeping of myostatin could be achieved in human by combining mutations that increase positive charge of the antibody and increase binding to Fc gamma R.

Example 26

[0594] Screening of pI-increased substitutions to enhance clearance of myostatin.

To enhance the clearance of myostatin, pI increased substitutions in Fc portion of antibody were evaluated in this example. The method of adding amino acid substitutions to the antibody constant region to increase pI is not particularly limited, but for example, it can be performed by the method described in WO 2014/145159. As in the case with the variable region, amino acid substitutions introduced into the constant region are preferably those that decrease the number of negatively charged amino acids (such as aspartic acid and glutamic acid) while increasing the positively charged amino acids (such as arginine and lysine). Furthermore, amino acid substitutions may be introduced at any position in the antibody constant region, and may be a single amino acid substitution or a combination of multiple amino acid substitutions. Without particular limitation, the sites for introducing amino acid substitutions are preferably positions where amino acid side chains may be exposed on the antibody molecule surface. Particularly preferable examples include the method of introducing a combination of multiple amino acid substitutions at such positions that may be exposed on the antibody molecule surface. Alternatively, the multiple amino acid substitutions introduced here are preferably positioned so that they are structurally close to each other. Furthermore, without particular limitation, the multiple amino acid substitutions introduced herein are preferably substitutions to positively charged amino acids, so that preferably they result in a state where multiple positive charges are present at structurally proximal positions.

[0595] Preparation and profile of tested variants

The tested antibodies are summarized in Table 26. The heavy chain, MS103205H795-SG141 was prepared by introducing pI-increasing substitutions Q311R/D399R into MS103205H795-SG1. Other heavy chain variants were also prepared by introducing respective substitutions represented in Table 26 into MS103205H795-SG1. All the MS1032LO06 variants were expressed with M103202L889-SK1 as light chain according to the method shown in Example 30.

[0596] Mouse Fc gamma RII-binding assay of pI-increased Fc variants using BIACORE (registered trademark)

Regarding the produced Fc region variant-containing antibodies, binding assays between soluble mouse Fc gamma RII and antigen-antibody complexes were

performed using BIACORE (registered trademark) T200 (GE Healthcare). Soluble mouse Fc gamma RII was produced in the form of a His-tagged molecule by a method known to those skilled in the art. An appropriate amount of an anti-His antibody was fixed onto Sensor chip CM5 (GE Healthcare) by the amine coupling method using a His capture kit (GE Healthcare) to capture mouse Fc gamma RII. Next, an antibody-antigen complex and a running buffer (as a reference solution) were injected, and interaction was allowed to take place with the mouse Fc gamma RII captured onto the sensor chip. 20 mM N-(2-Acetamido)-2-aminoethanesulfonic acid, 150 mM NaCl, 1.2 mM CaCl₂, and 0.05% (w/v) Tween 20 at pH7.4 was used as the running buffer, and the respective buffer was also used to dilute the soluble mouse Fc gamma RII. To regenerate the sensor chip, 10 mM glycine-HCl at pH1.5 was used. All measurements were carried out at 25 degrees C. Analyses were performed based on binding (RU) calculated from sensorgrams obtained by the measurements, and relative values when the binding amount of SG1 was defined as 1.00 are shown. To calculate the parameters, the BIACORE (registered trademark) T100 Evaluation Software (GE Healthcare) was used

[0597] The SPR analysis results are summarized in Table 26. A few Fc variants were shown to have enhanced affinity toward mouse Fc gamma RII fixed on the BIACORE (registered trademark) sensor chip.

[0598] While not being restricted to a particular theory, this result can be explained as follows. The BIACORE (registered trademark) sensor chip is known to be negatively charged, and this charged state can be considered to resemble the cell membrane surface. More specifically, the affinity of an antigen-antibody complex for mouse Fc gamma RII fixed onto the negatively charged BIACORE (registered trademark) sensor chip is surmised to resemble the manner in which the antigen-antibody complex binds to mouse Fc gamma RII present on a similarly negatively charged cell membrane surface.

[0599]

[Table 26]

Summary of pI-increased Fc variants

Heavy chain name	Substitutions	cellular uptake	biacore IC binding
M103205H795-SG1		1.00	1.00
M103205H795-SG141	Q311R/D399R	4.42	1.64
M103205H795-P1375m	Q311R/D413K	3.43	1.21
M103205H795-P1378m	S400R/D413K	3.66	1.23
M103205H795-P1383m	Q311R/S400R/D413K	5.68	1.41
M103205H795-P1454m	Q311R/D312R	0.00	1.33
M103205H795-P1465m	Q311R/N315R	1.88	1.29
M103205H795-P1486m	Q311R/N315K	1.52	1.20
M103205H795-P1487m	Q311R/N384R	1.23	1.46
M103205H795-P1488m	Q311R/N384K	1.45	1.43
M103205H795-P1489m	Q311R/E318R	1.68	1.24
M103205H795-P1490m	Q311R/E318K	1.33	1.28
M103205H795-P1491m	Q311R/E338R	1.37	1.05
M103205H795-P1492m	Q311R/E338K	1.13	0.88
M103205H795-P1493m	Q311R/T335R	0.99	1.10
M103205H795-P1494m	Q311R/T335K	1.12	1.14
M103205H795-P1495m	Q311R/S337R	1.76	1.30
M103205H795-P1496m	Q311R/S337K	1.69	1.28
M103205H795-P1497m	Q311R/Q342R	1.35	1.49
M103205H795-P1498m	Q311R/Q342K	1.56	1.38
M103205H795-P1499m	Q311R/P343R	3.61	1.98
M103205H795-P1500m	Q311R/P343K	1.82	1.32
M103205H795-P1501m	Q311R/D413R	2.40	1.82
M103205H795-P1522m	Q311R/H285R	2.13	1.24
M103205H795-P1523m	Q311R/H285K	1.91	1.19
M103205H795-P1524m	Q311R/G341R	3.66	1.40
M103205H795-P1525m	Q311R/G341K	3.55	1.31
M103205H795-P1526m	Q311R/G385R	1.20	1.04
M103205H795-P1527m	Q311R/G385K	0.92	0.98
M103205H795-P1528m	Q311R/E388R	3.02	1.12
M103205H795-P1529m	Q311R/E388K	2.86	1.08
M103205H795-P1530m	Q311R/N390R	3.12	1.09
M103205H795-P1531m	Q311R/N390K	2.35	1.01
M103205H795-P1532m	Q311R/D401R	4.16	1.23
M103205H795-P1533m	Q311R/D401K	3.52	1.18
M103205H795-P1534m	Q311R/G402R	3.12	1.12
M103205H795-P1535m	Q311R/G402K	2.49	1.11
M103205H795-P1536m	Q311R/G420R	2.05	1.16
M103205H795-P1537m	Q311R/V422R	2.77	1.32
M103205H795-P1538m	Q311R/V422K	1.64	1.11
M103205H795-P1539m	Q311R/A431R	3.20	0.90
M103205H795-P1540m	D401R/D413K	7.64	1.73
M103205H795-P1541m	D401K/D413K	7.17	1.57
M103205H795-P1542m	G402R/D413K	3.32	1.21
M103205H795-P1543m	G402K/D413K	3.70	1.19
M103205H795-P1544m	Q311R/D401R/D413K	7.66	2.04
M103205H795-P1545m	Q311R/D401K/D413K	7.73	1.80
M103205H795-P1546m	Q311R/G402R/D413K	5.10	1.41
M103205H795-P1547m	Q311R/G402K/D413K	4.85	1.33
M103205H795-P1548m	Q311R/G385R/D401R	2.30	1.37
M103205H795-P1549m	Q311R/G385R/G402R	2.03	1.22
M103205H795-P1550m	Q311R/E388R/D401R	6.43	1.63
M103205H795-P1551m	Q311R/E388R/G402R	2.91	1.33
M103205H795-P1552m	G385R/D401R/D413K	4.44	2.19
M103205H795-P1553m	G385R/G402R/D413K	2.66	1.47
M103205H795-P1555m	E388R/G402R/D413K	3.71	2.01

[0600] Here, the antibodies produced by introducing pI-increasing modifications into the Fc

region are antibodies in which the charge of the Fc region is more towards the positive side when compared with before introduction of the modifications. Therefore, the Coulombic interaction between the Fc region (positive charge) and the sensor chip surface (negative charge) can be considered to have been strengthened by the pI-increasing amino acid modifications. Furthermore, such effects are expected to take place similarly on the same negatively charged cell membrane surface; therefore, they are also expected to show an effect of accelerating the speed of uptake into cells in vivo.

[0601] Among the pI increased Fc variants with two amino acid substitution from SG1, the antigen-antibody complex made by SG141, P1499m, P1501m and P1540m shows highest binding to human Fc gamma RIIb. The amino acid substitutions on Q311R/D399R, Q311R/P343R, Q311R/D413R and D401R/D413K are supposed to have strong charge effect on binding to human Fc gamma RIIb on the sensor chip.

[0602] Cellular uptake of pI-increased Fc variants

To evaluate the rate of intracellular uptake into a human Fc gamma RIIb-expressing cell line, following assay was performed. An MDCK (Madin-Darby canine kidney) cell line that constitutively expresses human Fc gamma RIIb was produced by known methods. Using these cells, intracellular uptake of antigen-antibody complexes was evaluated.

[0603] Specifically, pHrodoRed (Life Technologies) was used to label human latent Myostatin (antigen) according to an established protocol, and antigen-antibody complexes were formed in a culture solution with the antibody concentration being 10 mg/mL and the antigen concentration being 2.5 mg/mL. The culture solution containing the antigen-antibody complexes was added to culture plates of the above-mentioned MDCK cells which constitutively express human Fc gamma RIIb and incubated for one hour, and then the fluorescence intensity of the antigen taken up into the cells was quantified using InCell Analyzer 6000 (GE healthcare). The amount of antigen taken up was presented as relative values to the SG1 value which is taken as 1.00.

[0604] The quantification results of cellular uptake were summarized in Table 26. Strong fluorescence derived from the antigen in the cells was observed in several Fc variants.

[0605] While not being restricted to a particular theory, this result can be explained as follows.

[0606] The antigen and antibodies added to the cell culture solution form antigen-antibody complexes in the culture solution. The antigen-antibody complexes bind to human Fc gamma RIIb expressed on the cell membrane via the antibody Fc region, and are taken up into the cells in a receptor-dependent manner. Antibodies used in this experiment binds to antigen in a pH-dependent manner; therefore, the antibody can dissociate from

the antigen in the endosomes (acidic pH conditions) inside the cells. Since the dissociated antigen is labeled with pHrodoRed as described earlier, it fluoresces in the endosomes. Thus, a strong fluorescence intensity inside the cell is thought to indicate that the uptake of the antigen-antibody complexes into the cells is taking place more quickly or in larger amounts.

[0607] Among the pI increased Fc variants with two amino acid substitution from SG1, the antigen-antibody complex made by SG141, P1375m, P1378m, P1499m, P1524m, P1525m, P1532m, P1533m, P1540m, P1541m and P1543m shows stronger antigen uptake into the cells. The amino acid substitutions on Q311R/D399R, Q311R/D413K, S400R/D413K, Q311R/P343R, Q311R/G341R, Q311R/G341K, Q311R/D401R, Q311R/D401K, D401R/D413K, D401K/D413K and G402K/D413K are supposed to have strong charge effect on antigen antibody complex uptake into the cells.

[0608] PK study in human FcRn transgenic mouse

In vivo test using human FcRn transgenic mice

The elimination of myostatin and anti-latent myostatin antibody were assessed in vivo upon co-administration of anti-latent myostatin antibody and latent myostatin in human FcRn transgenic mice in which mouse FcRn was substituted with human FcRn. An anti-latent myostatin antibody (0.1 mg/ml) and mouse latent myostatin (0.05 mg/ml) were administered at a single dose of 10 ml/kg into the caudal vein in the experiment PK-2 (described in Figure 23). An anti-latent myostatin antibody (0.3 mg/ml), human latent myostatin (0.05 mg/ml) and human normal immunoglobulin (CSL Behring AG) (100 mg/ml) were administered at a single dose of 10 ml/kg into the caudal vein in the experiment PK-4 (described in Figure 24). Blood was collected at 5 minutes, 15min, 1 hour, 4 hours, 7 hours, 1 day, 2days, 7 days, 14 days, 21 days, and 28 days after administration in the experiment PK-2. Blood was collected at 5 minutes, 1 hour, 4 hours, 7 hours, 1 day, 7 days, 14 days, 21 days, and 30 days after administration in the experiment PK-4. The collected blood was centrifuged immediately at 15,000 rpm in 4 degrees C for 5 minutes to separate the plasma. The separated plasma was stored at or below -20 degrees C until measurement. The anti-latent myostatin antibodies used were MS1032LO06-SG1, MS1032LO06-P1375m, MS1032LO06-P1378m, MS1032LO06-P1383m in the experiment PK-2, and MS1032LO06-P1375m, MS1032LO06-P1499m in the experiment PK-4.

[0609] Measurement of total myostatin concentration in plasma by electrochemiluminescence (ECL)

The concentration of total myostatin in mouse plasma was measured by ECL as described in Example 24 (Ravetch PK). The time course of total myostatin concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figures 23A and 24A.

[0610] Measurement of anti-latent myostatin antibody concentration in plasma by enzyme-linked immunosorbent assay (ELISA)

The concentration of anti-latent myostatin antibody in mouse plasma was measured by ELISA in the experiment PK-2. Anti-human IgG (gamma-chain specific) F(ab')₂ antibody fragment (Sigma) was dispensed onto a Nunc-ImmunoPlate MaxiSorp (Nalge Nunc International) and allowed to stand overnight at 4 degrees C to prepare anti-human IgG-immobilized plates. Calibration curve samples having plasma concentrations of 2.5, 1.25, 0.625, 0.313, 0.156, 0.078, and 0.039 micro g/ml, and mouse plasma samples diluted 100-fold or more were prepared. Then, the samples were dispensed onto the anti-human IgG-immobilized plates, and allowed to stand for 1 hour at room temperature. Subsequently, Goat Anti-Human IgG (gamma-chain specific) Biotin conjugate (Southern Biotech) was added to react for 1 hour at room temperature. Then, Streptavidin-PolyHRP80 (Stereospecific Detection Technologies) was added to react for one hour at room temperature, and chromogenic reaction was carried out using TMB One Component HRP Microwell Substrate (BioFX Laboratories) as a substrate. After stopping the reaction with 1 N sulfuric acid (Showa Chemical), the absorbance at 450 nm was measured by a microplate reader. The concentration in mouse plasma was calculated from the absorbance of the calibration curve using the analytical software SOFTmax PRO (Molecular Devices). The time course of antibody concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figure 23B.

[0611] The concentration of anti-latent myostatin antibody in mouse plasma was measured by a Gyrolab Bioaffy™ CD (Gyros) in the experiment PK-4. Biotinylated anti-human IgG Fc antibody was flowed over the streptavidin bead column within the microstructure of the CDs. Calibration curve samples having plasma concentrations of 0.5, 1, 2, 4, 8, 16, and 32 micro g/ml spiking plasma concentrations of 5 mg/mL of human normal immunoglobulin (CSL Behring AG) and 200 micro g/ml of mouse latent myostatin, and mouse plasma samples diluted 25-fold or more spiking plasma concentrations of 200 micro g/ml of mice latent myostatin were prepared. Then the samples were added into CDs and flowed over the bead column. Subsequently, Alexa-labeled Goat anti-human IgG polyclonal antibody (BETHYL) was added into CDs and flowed over the bead column. The concentration in mouse plasma was calculated from the response of the calibration curve using the Gyrolab Evaluator Program. The time course of antibody concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figure 24B.

[0612] Effect of pI on myostatin concentration in vivo

After administration of MS1032LO06-SG1, plasma total myostatin concentration at 7 hours decreased 12 fold compared to plasma total myostatin concentration at 5 minutes in the experiment PK-2. In contrast, after administration of MS1032LO06-P1375m, MS1032LO06-P1378m and MS1032LO06-P1383m, plasma total myostatin concentration at 7 hours decreased 26-67 fold compared to plasma total myostatin concentration at 5 minutes in the experiment PK-2. Antibody concentration of MS1032LO06-P1378m and MS1032LO06-P1383m decreased more than 3 fold compared to that of MS1032LO06-SG1, although the difference in MS1032LO06-P1375m's concentration at each sampling point compared to MS1032LO06-SG1's was within 2 fold in the experiment PK-2. pI variants including the amino acid substitutions on Q311R/D413K showed enhancement of myostatin elimination from plasma without enhancement of antibody elimination from plasma.

[0613] Furthermore, total myostatin concentration and antibody concentration after administration of MS1032LO06-P1499m were evaluated under co-administration of human normal immunoglobulin to mimic human plasma. After administration of MS1032LO06-P1375m and MS1032LO06-P1499m, plasma total myostatin concentration at 7 hours decreased 3.4 and 5.3 fold compared to plasma total myostatin concentration at 5 minutes, and total myostatin concentration and antibody concentration at each sampling point in MS1032LO06-P1499m was within 1.5 fold compared to that in MS1032LO06-P1375m in the experiment PK-4. pI variants including the amino acid substitutions on Q311R/P343R also showed enhancement of myostatin elimination from plasma without enhancement of antibody elimination from plasma.

[0614] High pI variants have more positive charge in plasma. Since this positive charge interacts with cell surface of negative charge, antigen-antibody immune complex of high pI variants get closer to cell surface, resulted in increased cellular uptake of antigen-antibody immune complex of high pI variants.

Example 27

[0615] PI-increased substitutions in combination with Fc gamma RIIb-enhanced Fc variant
The effect of clearance of myostatin by Fc gamma RIIb-enhanced Fc variant in combination with other pI-increasing substitutions were evaluated in human Fc gamma RIIb transgenic mice. Human Fc gamma RIIb transgenic mice were generated by microinjection of BAC (bacterial artificial chromosome) vector containing all the exons of human FCGR2B gene into the pronucleus of fertilized eggs of C57BL/6N by standard techniques (see, e.g., J. Immunol., 2015 Oct 1; 195(7): 3198-205). Mouse Fc gamma RIIb deficient mice were generated using zinc finger nucleases (ZFNs) which was designed to target exon 1. The Humanized Fc gamma RIIb mice were established

by crossing human Fc gamma RIIb transgenic mice with mouse Fc gamma RIIb KO mice. Using this mouse, the combination effect of affinity enhancement to human Fc gamma RIIb and pI increase on clearance of soluble antigen can be evaluated.

[0616] Preparation and profile of tested variants

The tested 7 antibodies and their binding profiles are summarized in Table 27. The heavy chain, MS103205H795-MY352, MS103205H795-PK55, MS103205H795-PK56, MS103205H795-PK57, were prepared by introducing pI-increasing substitutions Q311R/D413R, Q311R/P343R, Q311R/P343R/D413R, Q311R/N384R/D413R, respectively into MS103205H795-MY201. All the MS1032LO06 variants were expressed with M103202L889-SK1 as light chain according to the method shown in Example 30 and their affinities to human and cynoFc gamma Rs were evaluated using the method in Example 23.

[0617]

[0618] Based on the SPR analysis summarized in Table 27, it was confirmed that the pI-increasing substitutions do not affect the Fc gamma R binding of Fc gamma RIIb-enhanced Fc variants. MY201 and MY351, which was prepared by introducing Q311R/D413K into MY201, show 6-fold and 5-fold enhanced human Fc gamma RIIb binding, respectively. With respect to other human and cynoFc gamma Rs, they show almost the same binding profile. Similarly, MY352, PK55, PK56 and PK57 showed similar binding profile with parent MY201 (Table 27). These results indicates that either pair of pI-increasing substitutions does not affect the affinities against human and cynoFc gamma Rs.

[0619] PK study in human Fc gamma RIIb transgenic mice

In vivo test using human Fc gamma RIIb transgenic mice

The elimination of myostatin and anti-latent myostatin antibody were assessed in vivo upon co-administration of anti-latent myostatin antibody and human latent myostatin in human Fc gamma RIIb transgenic mice in which mouse Fc gamma RII was substituted with human Fc gamma RIIb. An anti-latent myostatin antibody (0.3 mg/ml) and latent myostatin (0.05 mg/ml) were administered at a single dose of 10 ml/kg into the caudal vein. Blood was collected at 5 minutes, 1 hour, 4 hours, 7 hours, 1 day, 7 days, 14 days, 21 days, and 28 days after administration. The collected blood was centrifuged immediately at 15,000 rpm in 4 degrees C for 5 minutes to separate the plasma. The separated plasma was stored at or below -20 degrees C until measurement. The anti-latent myostatin antibodies used were MS1032LO06-SG1, MS1032LO06-MY201, MS1032LO06-MY351, MS1032LO06-MY352, MS1032LO06-PK55, MS1032LO06-PK56 and MS1032LO06-PK57.

[0620] Measurement of total myostatin concentration in plasma by electrochemiluminescence

The concentration of total myostatin in mouse plasma was measured by electrochemiluminescence (ECL) as described in Example 24. The time course of total myostatin concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figure 25.

[0621] Measurement of anti-latent myostatin antibody concentration in plasma by enzyme-linked immunosorbent assay (ELISA)

The concentration of anti-latent myostatin antibody in mouse plasma was measured by ELISA. Anti-human IgG (gamma-chain specific) F(ab')₂ antibody fragment (Sigma) was dispensed onto a Nunc-ImmunoPlate MaxiSorp (Nalge Nunc International) and allowed to stand overnight at 4 degrees C to prepare anti-human IgG-immobilized plates. Calibration curve samples having plasma concentrations of 2.5, 1.25, 0.625, 0.313, 0.156, 0.078, and 0.039 micro g/ml, and mouse plasma samples

diluted 100-fold or more were prepared. Then, the samples were dispensed onto the anti-human IgG-immobilized plates, and allowed to stand for 1 hour at room temperature. Subsequently, Goat Anti-Human IgG (gamma-chain specific) Biotin conjugate (Southern Biotech) was added to react for 1 hour at room temperature. Then, Streptavidin-PolyHRP80 (Stereospecific Detection Technologies) was added to react for one hour at room temperature, and chromogenic reaction was carried out using TMB One Component HRP Microwell Substrate (BioFX Laboratories) as a substrate. After stopping the reaction with 1 N sulfuric acid (Showa Chemical), the absorbance at 450 nm was measured by a microplate reader. The concentration in mouse plasma was calculated from the absorbance of the calibration curve using the analytical software SOFTmax PRO (Molecular Devices). The time course of antibody concentration in plasma after intravenous administration of anti-latent myostatin antibody and latent myostatin measured by this method is shown in Figure 26.

[0622] Effect of pI and Fc gamma R binding on myostatin concentration in vivo

After administration of MS1032LO06-MY201, plasma total myostatin concentration at 7 hours decreased 8 fold compared to plasma total myostatin concentration at 5 minutes. In contrast, after administration of MS1032LO06-PK57, plasma total myostatin concentration at 7 hours decreased 376 fold compared to plasma total myostatin concentration at 5 minutes. Other high pI variants showed similar enhancement of myostatin elimination from plasma. Antibody concentration of high pI variants at 28 days decreased 2-3 fold compared to antibody concentration of MS1032LO06-SG1, and pI variants showed slight enhancement of antibody elimination from plasma.

[0623] High pI variants have more positive charge in plasma. Since this positive charge interacts with cell surface of negative charge, antigen-antibody immune complex of high pI variants get closer to cell surface, resulted in increased cellular uptake of antigen-antibody immune complex of high pI variants.

Example 28

[0624] Development of human Fc gamma RIIb-enhanced Fc variants

Human Fc gamma RIIb-enhanced Fc variants with anti-myostatin variable region were constructed and their affinity for human Fc gamma Rs was evaluated. Specifically, human Fc gamma RIIb-enhanced Fc variants were constructed by introducing substitutions into MS103240H795-SG1 (VH, SEQ ID NO: 92; CH, SEQ ID NO: 9) in combination with T250V/T307P substitutions. In addition, substitutions (Q311R/D413K or Q311R/P343R) were also introduced. The variants were expressed using M103202L1045-SK1 as light chain and their affinity to human Fc gamma Rs was analyzed according to the method shown in Example 30. Table 28 shows the result

of kinetic analysis against human and cynoFc gamma Rs. The KD values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis.

[0625] All the variants evaluated showed enhanced affinity to human Fc gamma RIIb and reduced binding to human Fc gamma RIIaR, Fc gamma RIIaH, Fc gamma RIIIaV compared to SG1. The affinity to human Fc gamma RIIb varies between 4.1-fold and 30.5-fold increase compared to SG1. The affinity to human Fc gamma RIIaR was between 0.02-fold and 0.22-fold. The affinities to human Fc gamma RIIaH and human Fc gamma RIIIaV were less than 0.04-fold and 0.012-fold, respectively. It was revealed that the substitutions (T250V/T307P) does not affect the binding profile to human Fc gamma Rs by comparing the affinities of MY009 (P238D) and MY214 (P238D/T250V/T307P). On the other hand, both pair of pI-increasing substitutions (Q311R/D413K and Q311R/P343R) decreased the binding affinity about 0.5-fold compared to the variants which does not contain the pI-increasing substitutions. For example, although TT14 showed 30.5-fold higher affinity to human Fc gamma RIIb, it showed only 16.1-fold and 14.5-fold increase in combination with Q311R/D413K (TT33) and Q311R/P343R (TT32), respectively.

[0626] Furthermore, the substitutions used in Example 25 for improving antibody half-life and reducing binding to rheumatoid factor were introduced into human Fc gamma RIIb-enhanced Fc variants and their affinity against human Fc gamma Rs were analyzed (Table 29). In this SPR analysis, all the data were obtained using mouse anti-human IgG kappa light chain for capturing the antibodies of interest. Table 30 shows the result and the KD values in cells filled in gray were calculated using [Equation 2] since their affinity was too weak to be correctly determined by kinetic analysis.

[0627]

[Table 28]

Binding profile of the human Fc gamma RIIB-enhanced Fc variant

Heavy chain name	CH	SEQ ID NO	Substitutions	KD (M) for humanFcRs						KD fold for humanFcRs (SG1 = 1)							
				FcgRIIaH	FcgRIIaR	FcgRIIb	FcgRIIIaV	FcgRIIIaH	FcgRIIIaR	FcgRIIIb	FcgRIIIaV	FcgRIIIaH	FcgRIIIaR	FcgRIIIb	FcgRIIIaV		
MS103240H795-SG1	SG1	9		7.5E-07	1.1E-06	5.8E-06	8.1E-07	1.000	1.000	1.00	1.0	1.000					
MS103240H795-MY009	MY009	252	P238D	7.3E-05	2.3E-05	1.3E-06	2.2E-04	0.010	0.05	4.5	0.004						
MS103240H795-MY214	MY214	253	P238D/T250V/T307P	3.2E-05	2.1E-05	1.0E-06	1.5E-04	0.023	0.05	5.8	0.005						
MS103240H795-TT08	TT08	254	P238D/T250V/T307P/A330K	5.5E-05	1.6E-05	6.8E-07	9.6E-05	0.014	0.07	8.5	0.008						
MS103240H795-TT09	TT09	255	P238D/T250V/V264I/T307P/A330K	4.4E-05	1.4E-05	2.9E-07	1.7E-04	0.017	0.08	20.0	0.005						
MS103240H795-TT10	TT10	256	P238D/T250V/S267A/T307P/A330K	5.6E-05	8.7E-06	6.3E-07	7.9E-04	0.013	0.13	9.2	0.001						
MS103240H795-TT11	TT11	257	L234Y/P238D/T250V/T307P/A330K	2.4E-05	1.0E-05	5.2E-07	1.7E-04	0.031	0.11	11.2	0.005						
MS103240H795-TT12	TT12	258	L234Y/P238D/T250V/S267A/T307P/A330K	2.0E-05	5.0E-06	4.9E-07	1.3E-04	0.038	0.22	11.8	0.006						
MS103240H795-TT13	TT13	259	P238D/T250V/V264I/S267A/T307P/A330K	4.5E-05	9.8E-06	3.2E-07	1.4E-04	0.017	0.11	18.1	0.006						
MS103240H795-TT14	TT14	260	L234Y/P238D/T250V/V264I/T307P/A330K	1.8E-05	7.6E-06	1.9E-07	1.5E-04	0.042	0.14	30.5	0.005						
MS103240H795-TT15	TT15	261	L234Y/P238D/T250V/V264I/S267A/T307P/A330K	2.9E-05	6.1E-06	2.5E-07	1.3E-04	0.026	0.18	23.2	0.006						
MS103240H795-TT20	TT20	262	P238D/T250V/T307P/Q311R/A330K/P343R	9.1E-05	2.8E-05	1.4E-06	8.4E-05	0.008	0.04	4.1	0.010						
MS103240H795-TT21	TT21	263	P238D/T250V/T307P/Q311R/A330K/D413K	5.6E-05	2.0E-05	1.3E-06	8.5E-05	0.013	0.06	4.5	0.010						
MS103240H795-TT22	TT22	264	P238D/T250V/V264I/T307P/Q311R/A330K/P343R	6.0E-05	2.1E-05	5.9E-07	7.2E-05	0.013	0.05	9.8	0.011						
MS103240H795-TT23	TT23	265	P238D/T250V/V264I/T307P/Q311R/A330K/D413K	1.0E-04	4.8E-05	5.5E-07	4.5E-04	0.007	0.02	10.5	0.002						
MS103240H795-TT24	TT24	266	P238D/T250V/S267A/T307P/Q311R/A330K/P343R	4.9E-05	1.3E-05	1.2E-06	2.6E-04	0.015	0.08	4.8	0.003						
MS103240H795-TT25	TT25	267	P238D/T250V/S267A/T307P/Q311R/A330K/D413K	2.2E-05	1.3E-05	1.0E-06	1.4E-04	0.034	0.08	5.8	0.006						
MS103240H795-TT26	TT26	268	L234Y/P238D/T250V/T307P/Q311R/A330K/P343R	6.9E-05	2.1E-05	1.1E-06	2.0E-04	0.011	0.05	5.3	0.004						
MS103240H795-TT27	TT27	269	L234Y/P238D/T250V/T307P/Q311R/A330K/D413K	5.2E-05	1.4E-05	8.2E-07	1.3E-04	0.014	0.08	7.1	0.006						
MS103240H795-TT28	TT28	270	L234Y/P238D/T250V/S267A/T307P/Q311R/A330K/P343R	4.8E-05	7.7E-06	8.5E-07	8.2E-05	0.016	0.14	6.8	0.010						
MS103240H795-TT29	TT29	271	L234Y/P238D/T250V/S267A/T307P/Q311R/A330K/D413K	3.7E-05	7.5E-06	8.1E-07	8.9E-05	0.020	0.15	7.2	0.009						
MS103240H795-TT30	TT30	272	P238D/T250V/V264I/S267A/T307P/Q311R/A330K/P343R	1.5E-04	1.4E-05	5.7E-07	6.6E-05	0.005	0.08	10.2	0.012						
MS103240H795-TT31	TT31	273	P238D/T250V/V264I/S267A/T307P/Q311R/A330K/D413K	1.1E-04	1.9E-05	5.6E-07	2.9E-04	0.007	0.06	10.4	0.003						
MS103240H795-TT32	TT32	274	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/P343R	5.0E-05	1.2E-05	4.0E-07	1.1E-04	0.015	0.09	14.5	0.007						
MS103240H795-TT33	TT33	275	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/D413K	4.2E-05	1.2E-05	3.6E-07	4.4E-04	0.018	0.09	16.1	0.002						
MS103240H795-TT34	TT34	276	L234Y/P238D/T250V/V264I/S267A/T307P/Q311R/A330K/P343R	2.2E-05	8.9E-06	4.9E-07	9.6E-05	0.034	0.12	11.8	0.008						
MS103240H795-TT35	TT35	277	L234Y/P238D/T250V/V264I/S267A/T307P/Q311R/A330K/D413K	2.5E-05	9.0E-06	4.3E-07	1.8E-04	0.030	0.12	13.5	0.004						

[0628] [Table 29]

Amino acid sequences of heavy chain constant regions comprising human Fc gamma RIIB-enhanced Fc variants (shown as SEQ ID NOs)

CH	-	+N434A +Q438R +S440E	+N434A +Y436T +Q438R +S440E	+M428L +N434A +Y436T +Q438R +S440E	+M428L +N434A +Q438R +S440E
MY009	252	278	304	330	356
MY214	253	279	305	331	357
TT08	254	280	306	332	358
TT09	255	281	307	333	359
TT10	256	282	308	334	360
TT11	257	283	309	335	361
TT12	258	284	310	336	362
TT13	259	285	311	337	363
TT14	260	286	312	338	364
TT15	261	287	313	339	365
TT20	262	288	314	340	366
TT21	263	289	315	341	367
TT22	264	290	316	342	368
TT23	265	291	317	343	369
TT24	266	292	318	344	370
TT25	267	293	319	345	371
TT26	268	294	320	346	372
TT27	269	295	321	347	373
TT28	270	296	322	348	374
TT29	271	297	323	349	375
TT30	272	298	324	350	376
TT31	273	299	325	351	377
TT32	274	300	326	352	378
TT33	275	301	327	353	379
TT34	276	302	328	354	380
TT35	277	303	329	355	381

[0629]

[Table 30]

Binding profile of the human Fc gamma RIIB-enhanced Fc variants

Heavy chain name	CH	SEQ ID NO	Substitutions	KD (M) for human Fcγ1s				KD fold for human Fcγ1s (SG1 = 1)				
				FcγRIIaH	FcγRIIaB	FcγRIIb	FcγRIIaV	FcγRIIaH	FcγRIIaB	FcγRIIaR	FcγRIIb	
MS103240H795-SG1	SG1	9	-	9.7E-07	1.2E-06	4.7E-06	7.2E-07	1.000	1.00	1.00	1.0	1.000
MS103240H795-TT33	TT33	275	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/D413K	3.5E-05	2.3E-05	3.0E-07	4.0E-04	0.028	0.05	0.05	15.7	0.002
MS103240H795-TT66	TT66	288	P238D/T250V/T307P/Q311R/A330K/P343R/N434A/Q438R/S440E	1.3E-04	3.2E-05	1.0E-06	5.9E-04	0.007	0.04	0.04	4.7	0.001
MS103240H795-TT67	TT67	340	P238D/T250V/T307P/Q311R/A330K/P343R/N428L/N434A/Y436T/Q438R/S440E	1.2E-04	2.8E-05	1.7E-06	6.1E-04	0.008	0.04	0.04	3.9	0.001
MS103240H795-TT68	TT68	289	P238D/T250V/T307P/Q311R/A330K/D413K/N434A/Q438R/S440E	2.1E-04	6.1E-05	9.6E-07	4.8E-04	0.005	0.02	0.02	4.9	0.001
MS103240H795-TT69	TT69	341	P238D/T250V/T307P/Q311R/A330K/D413K/M428L/N434A/Y436T/Q438R/S440E	1.3E-04	3.4E-05	1.1E-06	5.3E-04	0.008	0.04	0.04	4.3	0.001
MS103240H795-TT70	TT70	290	P238D/T250V/V264I/T307P/Q311R/A330K/P343R/N434A/Q438R/S440E	7.2E-05	4.0E-05	3.7E-07	3.9E-04	0.013	0.03	0.03	12.7	0.002
MS103240H795-TT71	TT71	342	P238D/T250V/V264I/T307P/Q311R/A330K/P343R/M428L/N434A/Y436T/Q438R/S440E	9.6E-05	2.7E-05	4.2E-07	4.0E-04	0.010	0.04	0.04	11.2	0.002
MS103240H795-TT72	TT72	291	P238D/T250V/V264I/T307P/Q311R/A330K/D413K/N434A/Q438R/S440E	7.9E-05	2.4E-05	4.0E-07	5.0E-04	0.012	0.05	0.05	11.8	0.001
MS103240H795-TT73	TT73	343	P238D/T250V/V264I/T307P/Q311R/A330K/D413K/M428L/N434A/Y436T/Q438R/S440E	7.4E-05	1.9E-05	4.2E-07	5.6E-04	0.013	0.06	0.06	11.7	0.001
MS103240H795-TT90	TT90	300	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/P343R/N434A/Q438R/S440E	2.9E-05	2.5E-05	3.0E-07	3.6E-04	0.033	0.05	0.05	15.7	0.002
MS103240H795-TT91	TT91	352	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/P343R/M428L/N434A/Y436T/Q438R/S440E	4.6E-05	3.0E-05	3.2E-07	4.5E-04	0.021	0.04	0.04	14.7	0.002
MS103240H795-TT92	TT92	301	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/D413K/N434A/Q438R/S440E	4.0E-05	2.0E-05	2.8E-07	4.9E-04	0.024	0.06	0.06	16.8	0.001
MS103240H795-TT93	TT93	353	L234Y/P238D/T250V/V264I/T307P/Q311R/A330K/D413K/M428L/N434A/Y436T/Q438R/S440E	5.2E-05	2.4E-05	3.1E-07	4.7E-04	0.019	0.05	0.05	15.2	0.002

SG1 and TT33 were evaluated again in this measurement in which capturing method was different from that in Table 28. As a result, "KD fold" values of TT33 were consistent with those obtained with Table 28 (16.1-fold in Table 28 and 15.7-fold in Table 30 against human Fc gamma RIIb). TT92 and TT93, which were constructed by introducing N434A/Q438R/S440E and M428L/N434A/Y436T/Q438R/S440E into TT33, showed comparable binding profile to TT33. Similarly, TT90 and TT91 derived from TT32, TT72 and TT73 derived from TT31, TT70 and TT71 derived from TT30, TT68 and TT69 derived from TT21, and TT66 and TT67 derived from TT20 show comparable binding profile to those of parental antibodies shown in Table 28. These results indicate that substitutions for improving antibody half-life and reducing binding to rheumatoid factor do not affect binding profile of human Fc gamma RIIb-enhanced variants against human Fc gamma Rs.

Example 29

[0630] Cell imaging analysis of Fc gamma RIIb-enhanced Fc variants

To evaluate the intracellular uptake of antigen-antibody complex formed by the antibody described in Example 28, cell imaging assay described in Example 26 was performed. To avoid the signal saturation, the antigen-antibody complexes were formed in a culture solution with the antibody concentration being 1.25 mg/mL and the antigen concentration being 0.34 mg/mL in this example.

[0631] Assay results are shown in Figure 27. By increasing the binding affinity to human Fc gamma RIIb, cellular uptake of antigen-antibody complex were increased. In case of TT14, which has 30 fold enhanced binding affinity to human Fc gamma RIIb compared with SG1, the antigen florescent intensity inside cells was 7.5 fold increased as that of SG1.

[0632] Although pI-increasing substitutions (Q311R/D413K and Q311R/P343R) decreased the binding affinity to human Fc gamma RIIb about 0.5-fold compared to the variants which does not contain the pI-increasing substitutions, the cellular uptake of antigen antibody complex of Fc variants with pI increased substitutions was increased compared to Fc variants without pI increased substitutions. TT33 shows 36 fold increase in antigen antibody uptake into the cells compared to SG1, while its parent TT14 shows 7.5 fold increase in cellular uptake. Furthermore, TT33 shows comparable cellular uptake of antigen-antibody complex into the cells compared to SG1071, SG1074, SG1077, SG1079, SG1080 and SG1081 which shows strong sweeping in Cynomolugus monkey. These results suggest that combining of pI increased substitutions with Fc gamma RIIb enhanced Fc variants is the powerful tool for antigen sweeping.

Example 30

[0633] Construction of antibody expression vectors;
and expression and purification of antibodies

Synthesis of full-length genes encoding the nucleotide sequences of the H chain and L chain of the antibody variable regions was carried out by production methods known to those skilled in the art using Assemble PCR and such. Introduction of amino acid substitutions was carried out by methods known to those skilled in the art using PCR or such. The obtained plasmid fragment was inserted into an animal cell expression vector, and the H-chain expression vector and L-chain expression vector were produced. The nucleotide sequence of the obtained expression vector was determined by methods known to those skilled in the art. The produced plasmids were introduced transiently into the HEK293H cell line derived from human embryonic kidney cancer cells (Invitrogen) or into FreeStyle293 cells (Invitrogen) for antibody expression. The obtained culture supernatant was collected, and then passed through a 0.22 micrometer MILLEX(R)-GV filter (Millipore), or through a 0.45 micrometer MILLEX(R)-GV filter (Millipore) to obtain the culture supernatant. Antibodies were purified from the obtained culture supernatant by methods known to those skilled in the art using rProtein A Sepharose Fast Flow (GE Healthcare) or Protein G Sepharose 4 Fast Flow (GE Healthcare). For the concentration of the purified antibodies, their absorbance at 280 nm was measured using a spectrophotometer. From the obtained value, the extinction coefficient calculated by the methods such as PACE was used to calculate the antibody concentration (Protein Sci. 4:2411-2423 (1995)).

[0634] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

CLAIMS:

1. An isolated antibody that binds to latent myostatin, wherein the antibody inhibits activation of myostatin, wherein the antibody blocks the spontaneous release of mature myostatin from latent myostatin, and wherein the antibody binds to the same epitope as an antibody comprising the VH sequence of SEQ ID NO: 12 and the VL sequence of SEQ ID NO: 14.
2. The antibody of claim 1, wherein the antibody:
 - (a) blocks the release of mature myostatin from latent myostatin;
 - (b) blocks the proteolytic release of mature myostatin; and/or
 - (c) does not bind to mature myostatin; or binds to an epitope within a fragment consisting of amino acids 21-100 of myostatin propeptide (SEQ ID NO: 78).
3. The antibody of claim 1 or 2, which binds to latent myostatin with higher affinity at neutral pH than at acidic pH, or which binds to latent myostatin with higher affinity at pH7.4 than at pH5.8.
4. The antibody of any one of claims 1 to 3, which is (a) a monoclonal antibody, (b) a human, humanized, or chimeric antibody; (c) a full length IgG antibody or (d) an antibody fragment that binds to myostatin.
5. An isolated nucleic acid encoding the antibody of any one of claims 1 to 4.
6. A host cell comprising the nucleic acid of claim 5.
7. A method of producing an anti-myostatin antibody comprising:
 - (a) culturing the host cell of claim 6 so that the antibody is produced; or

(b) immunizing an animal against a polypeptide, wherein the polypeptide comprises the region corresponding to amino acids at positions 21 to 100 of myostatin propeptide (SEQ ID NO: 78).

8. A pharmaceutical formulation comprising the antibody of any one of claims 1 to 4 and a pharmaceutically acceptable carrier.

9. An anti-myostatin antibody produced by the method of claim 7.

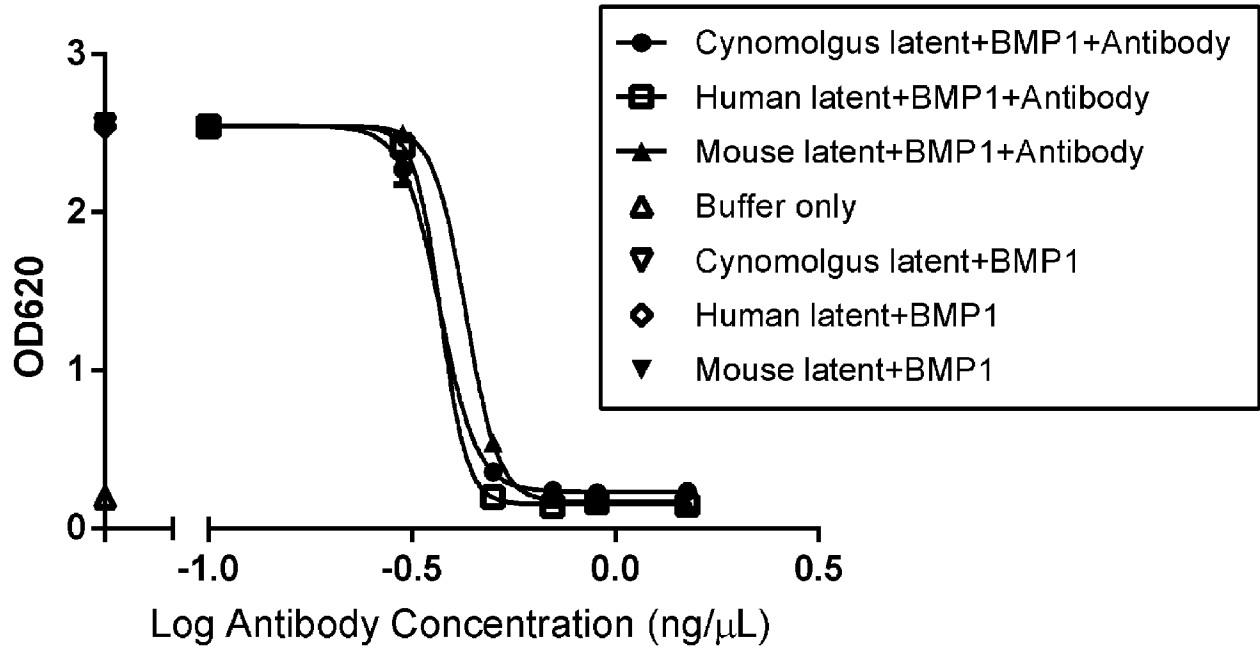
Chugai Seiyaku Kabushiki Kaisha

Patent Attorneys for the Applicant/Nominated Person

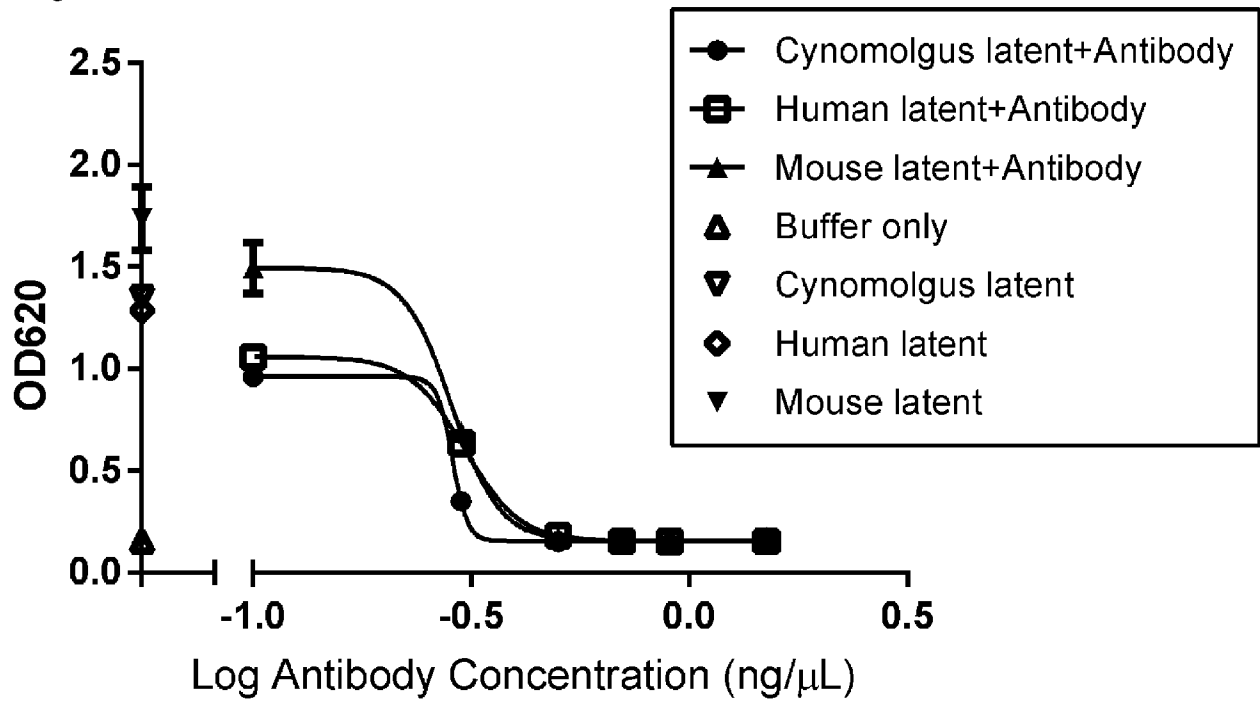
SPRUSON & FERGUSON

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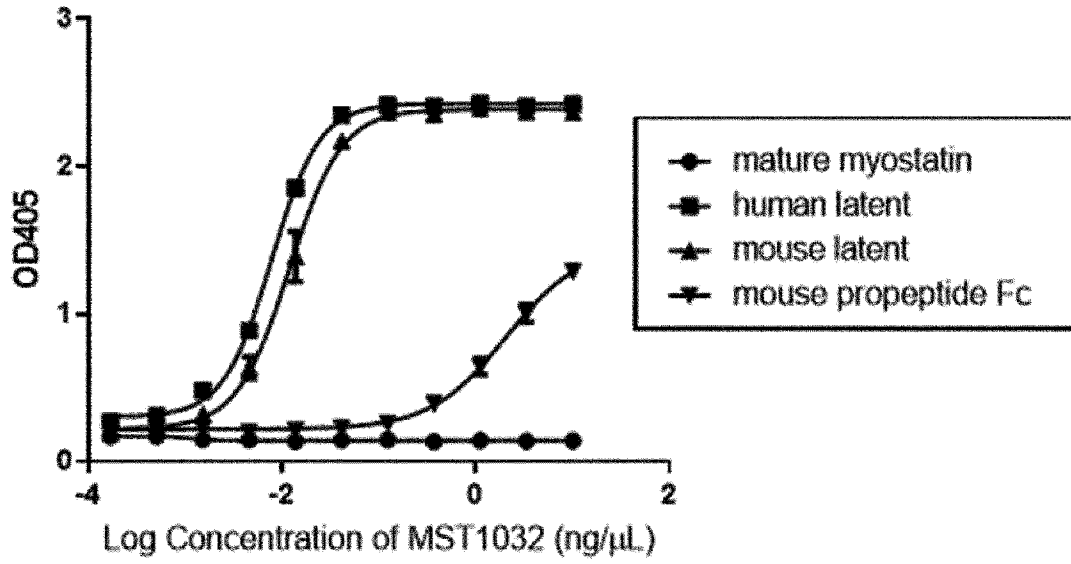
[Fig. 1]



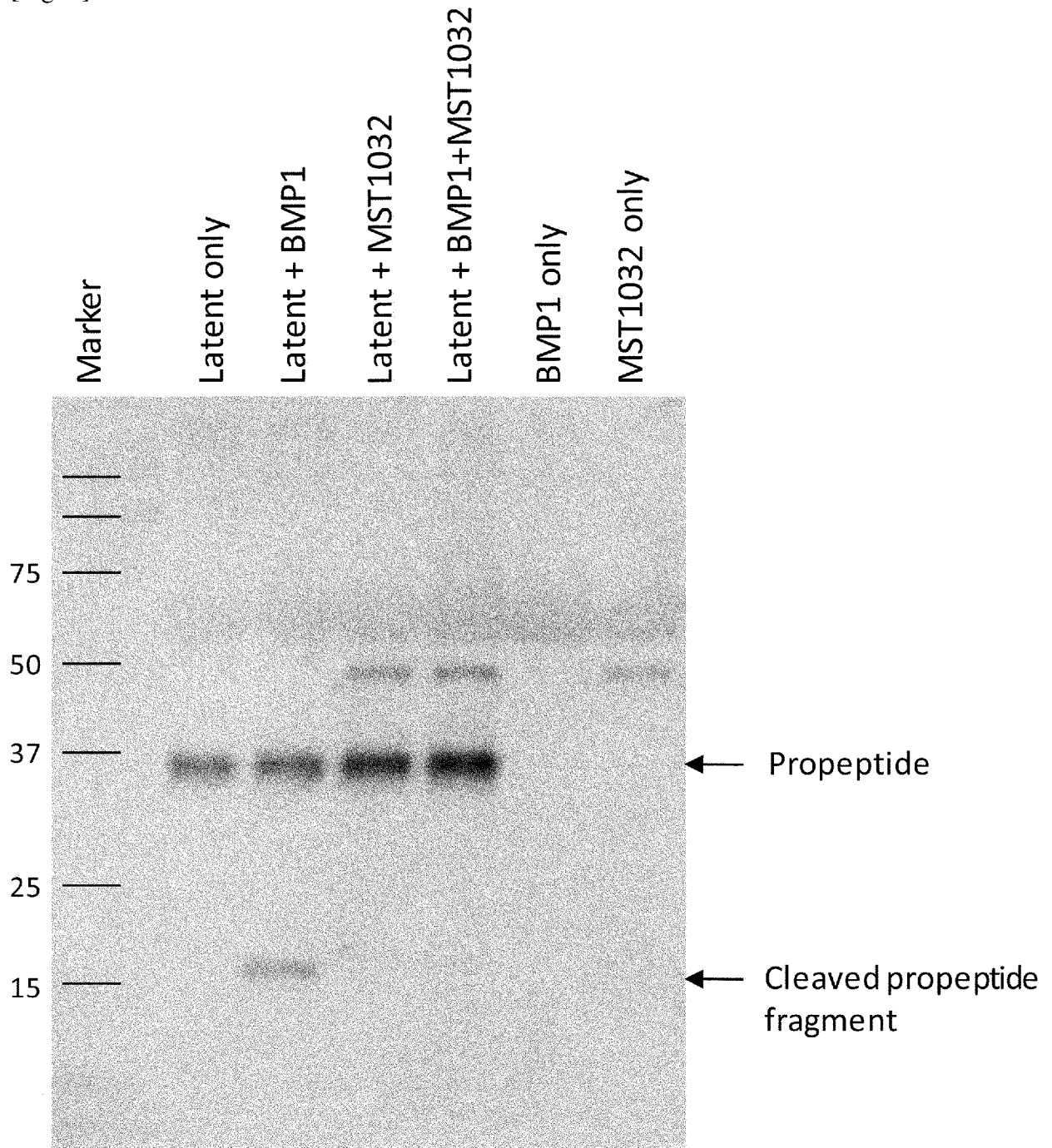
[Fig. 2]



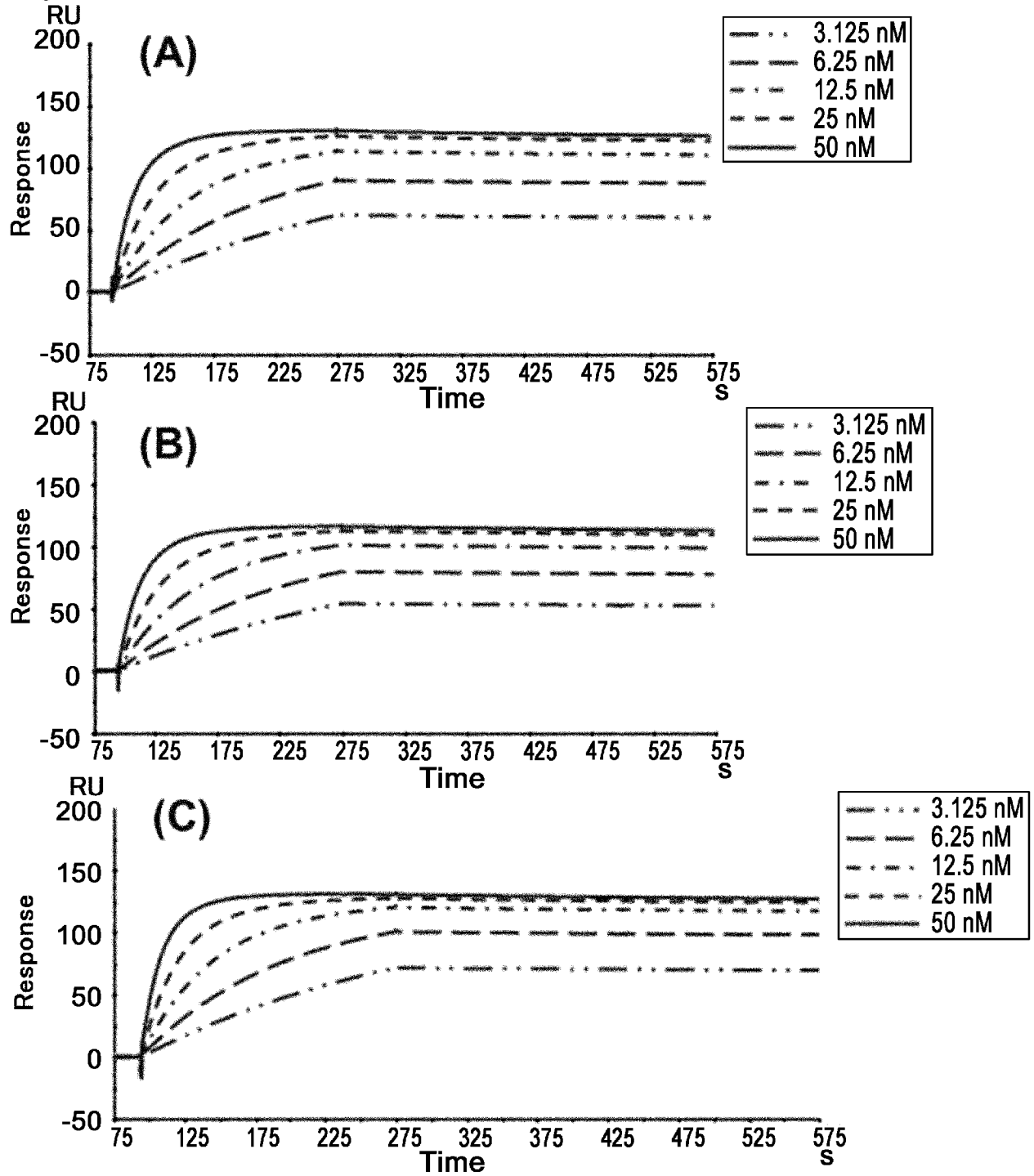
[Fig. 3]



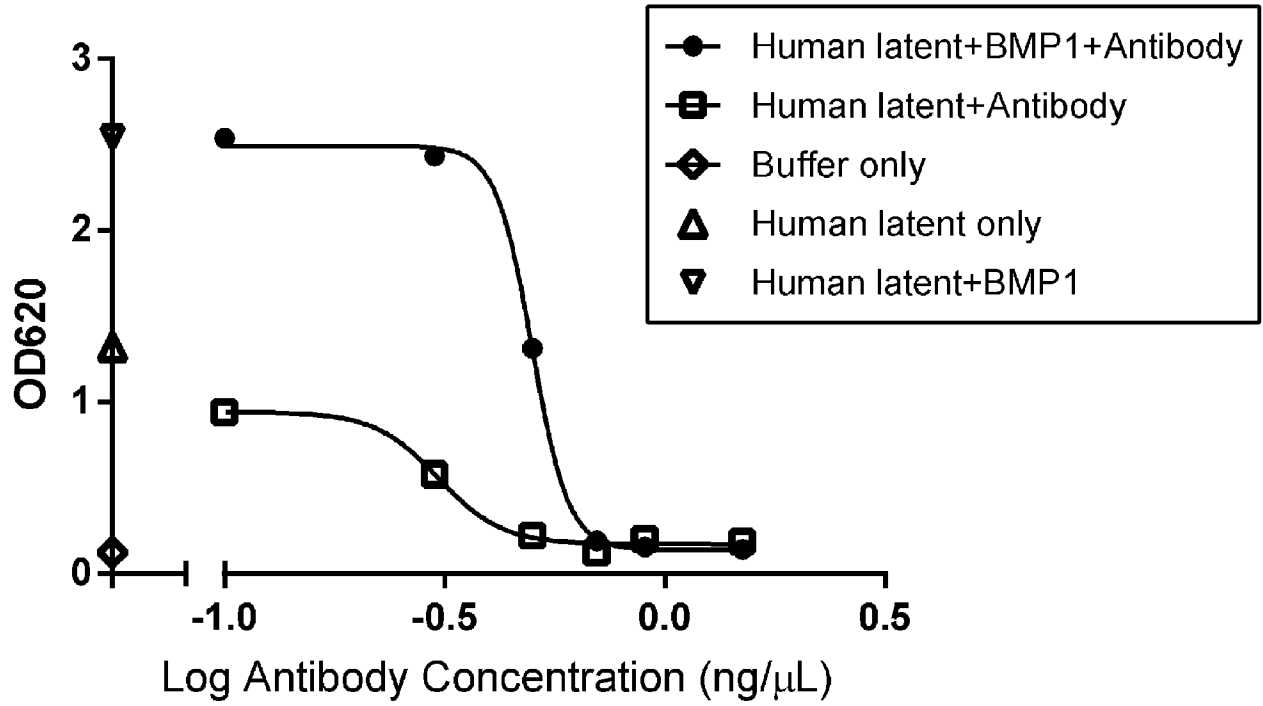
[Fig. 4]



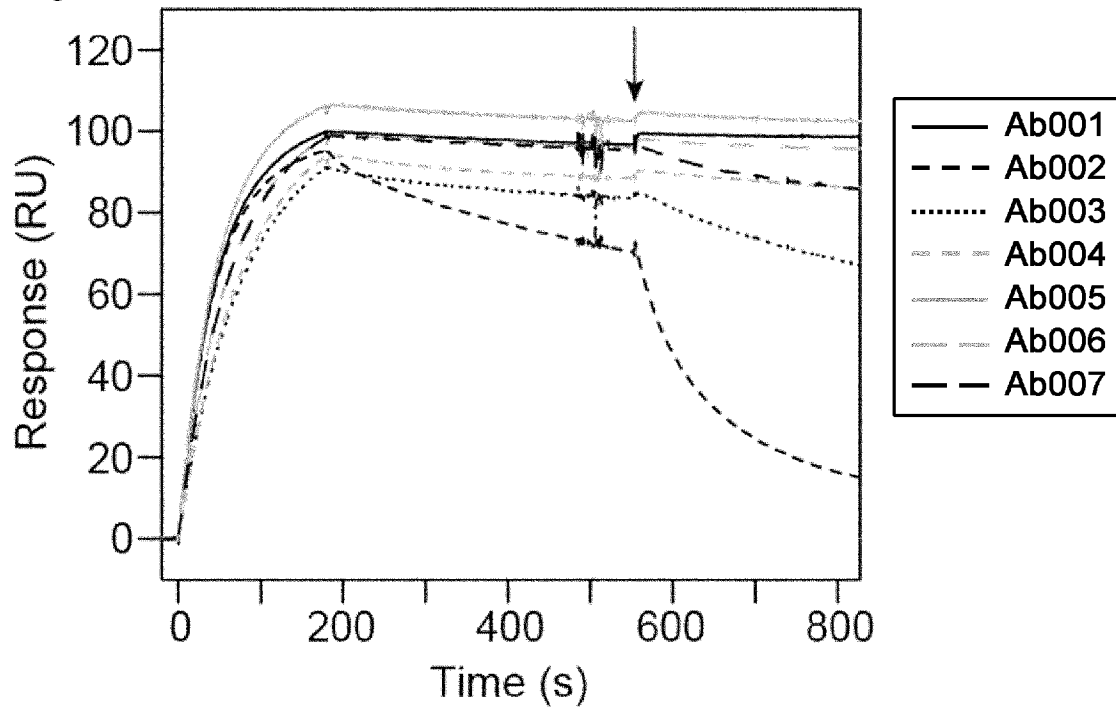
[Fig. 5]



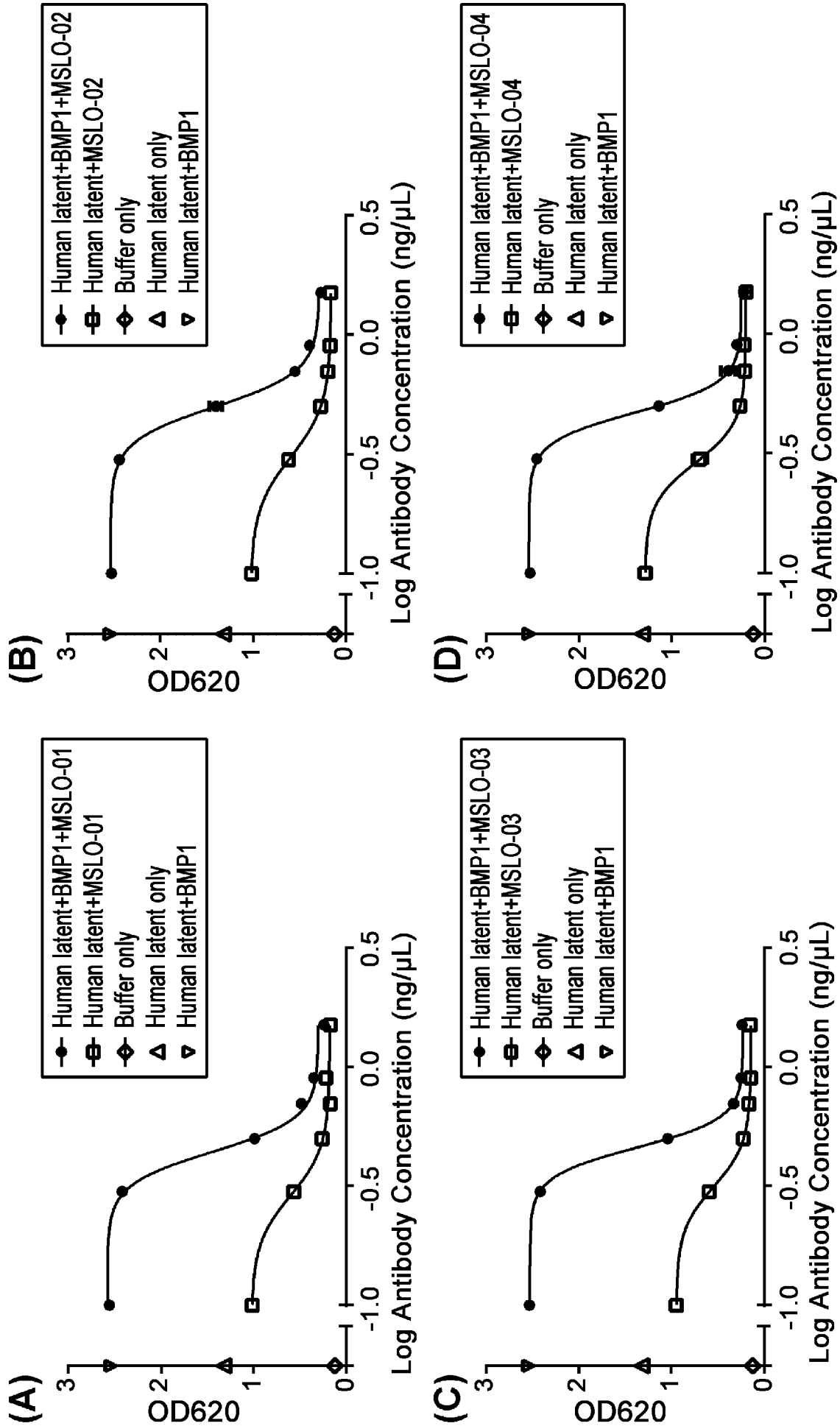
[Fig. 6]



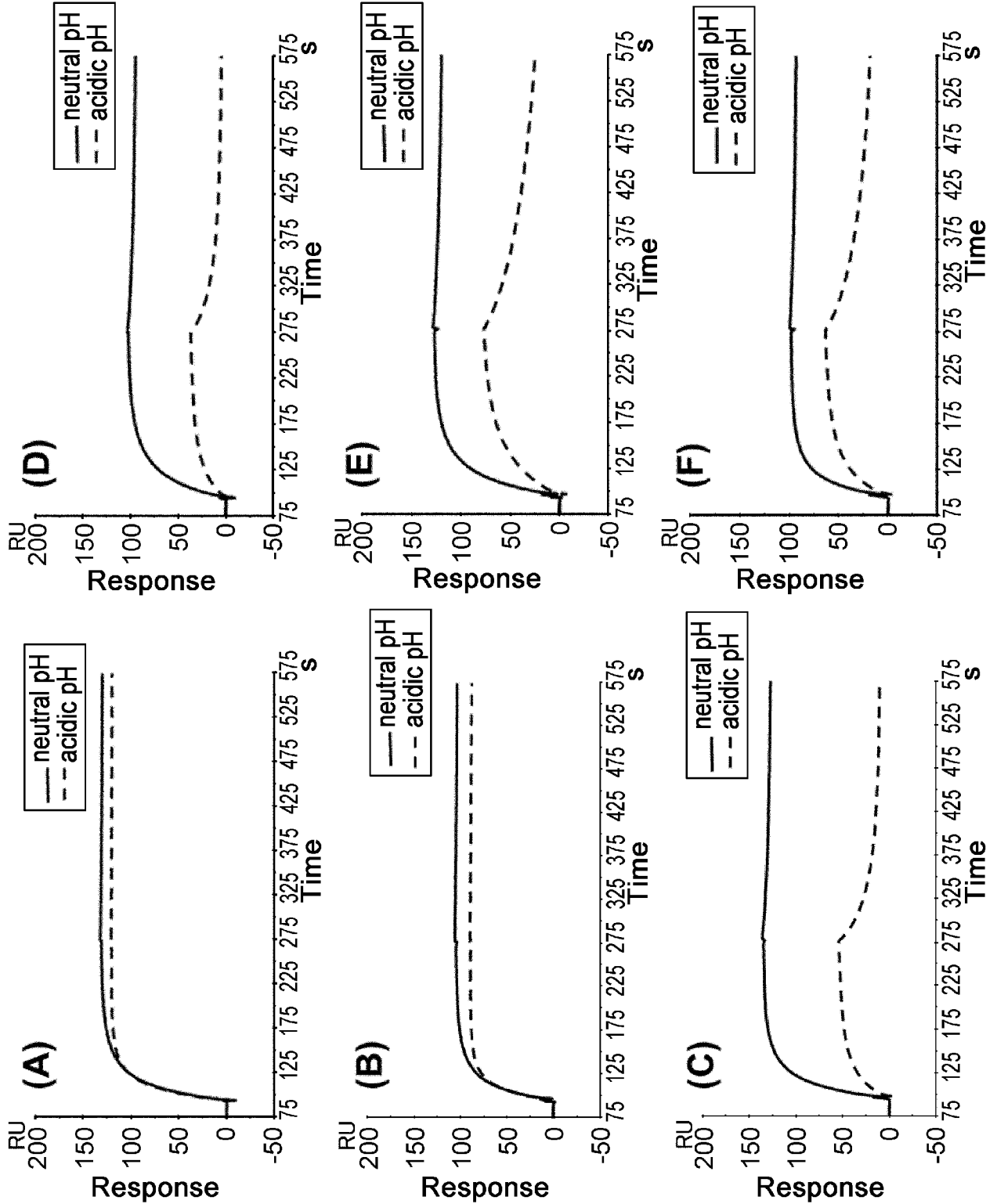
[Fig. 7]



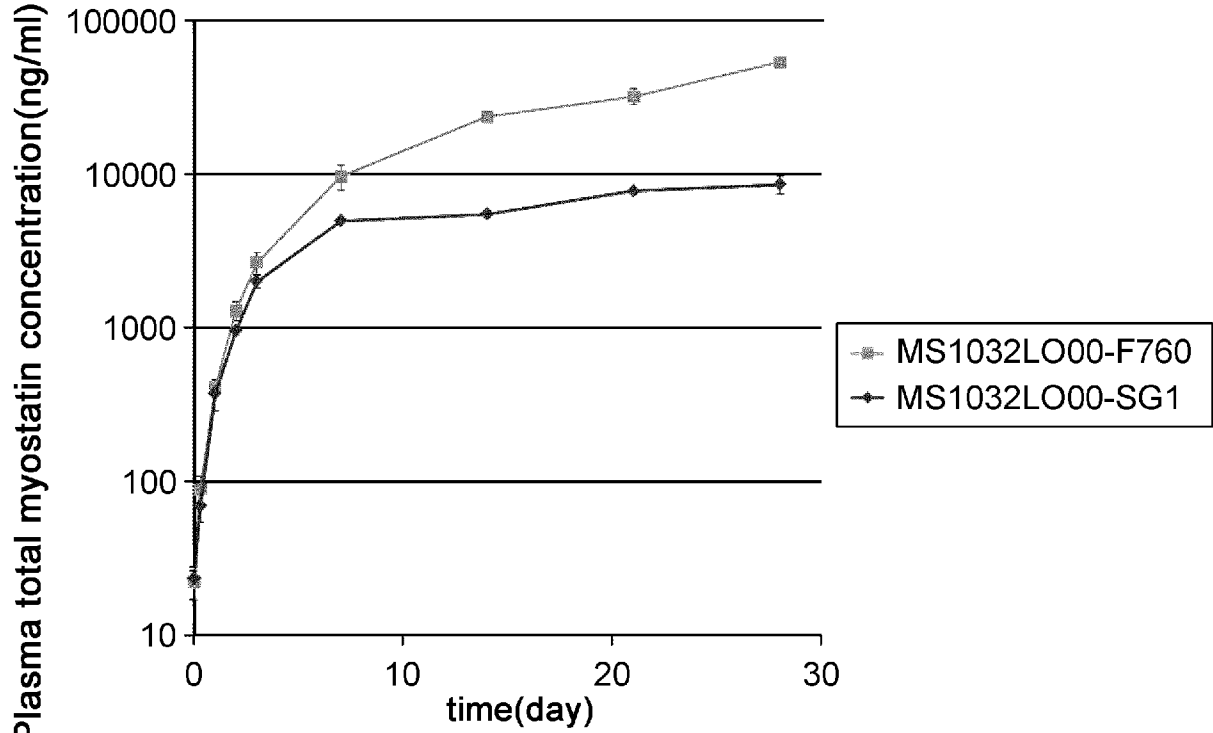
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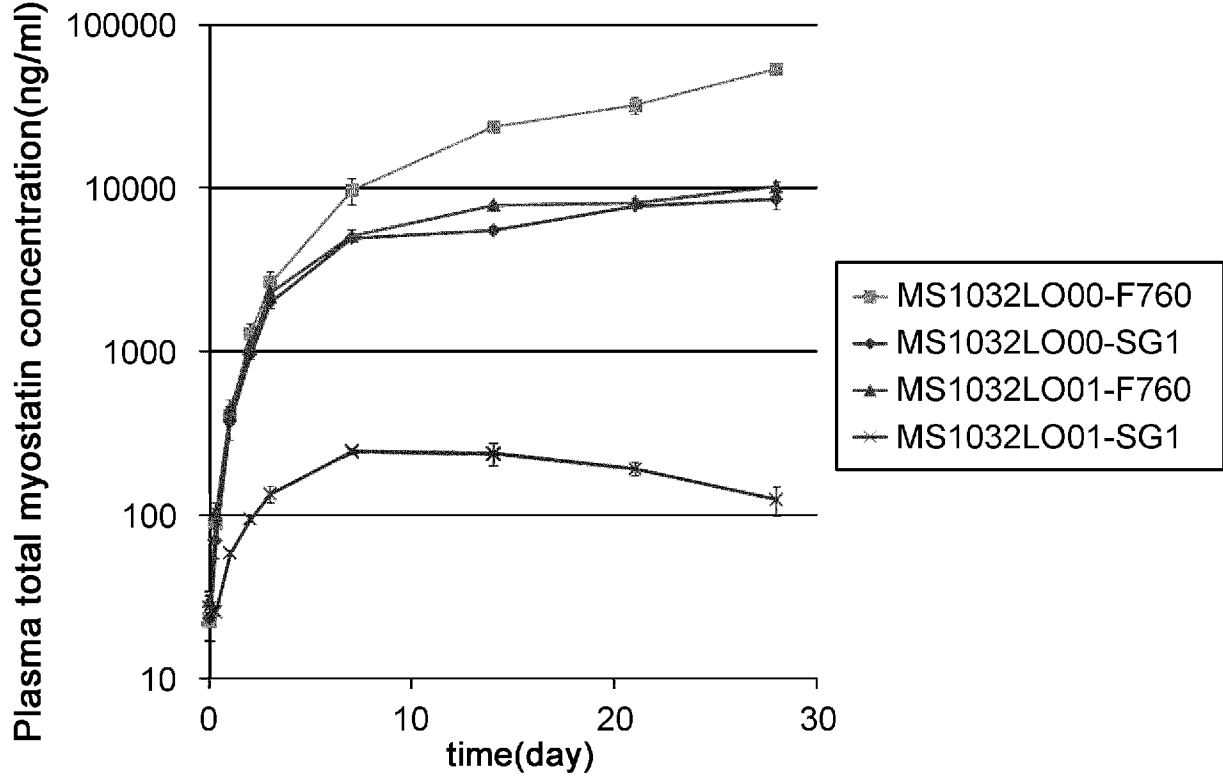
[Fig. 9]



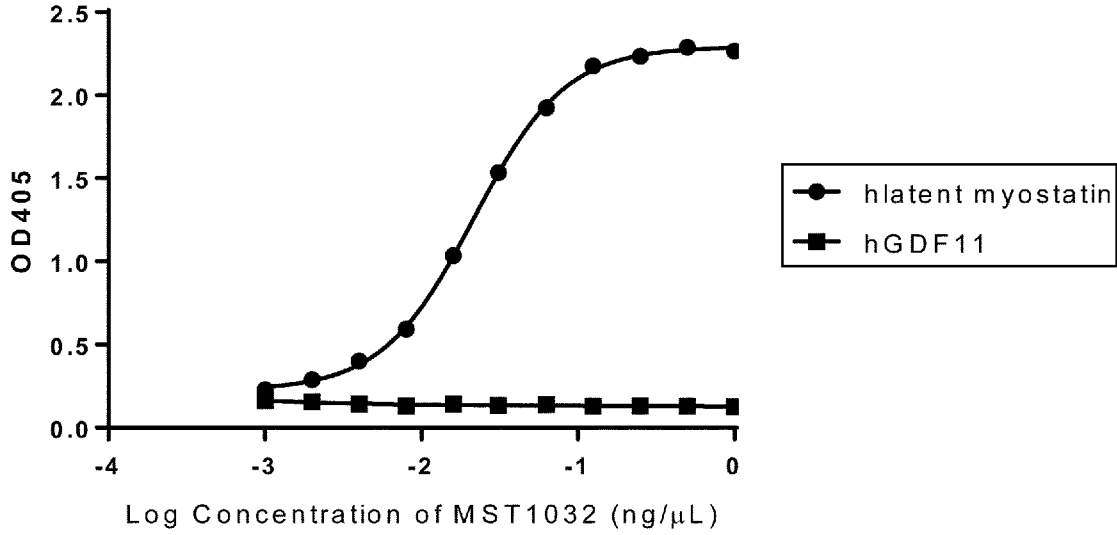
[Fig. 10]



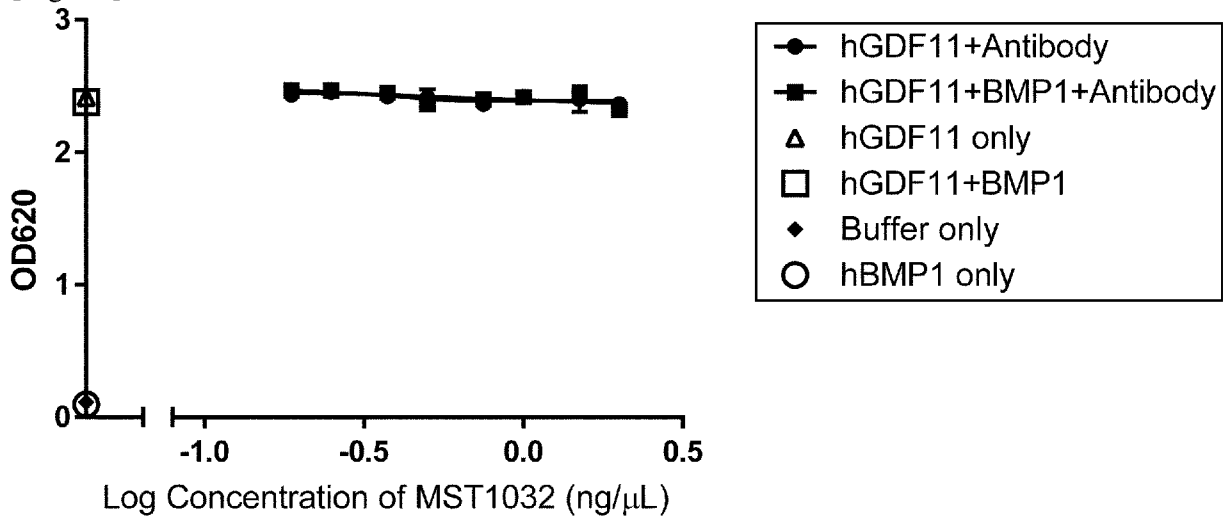
[Fig. 11]



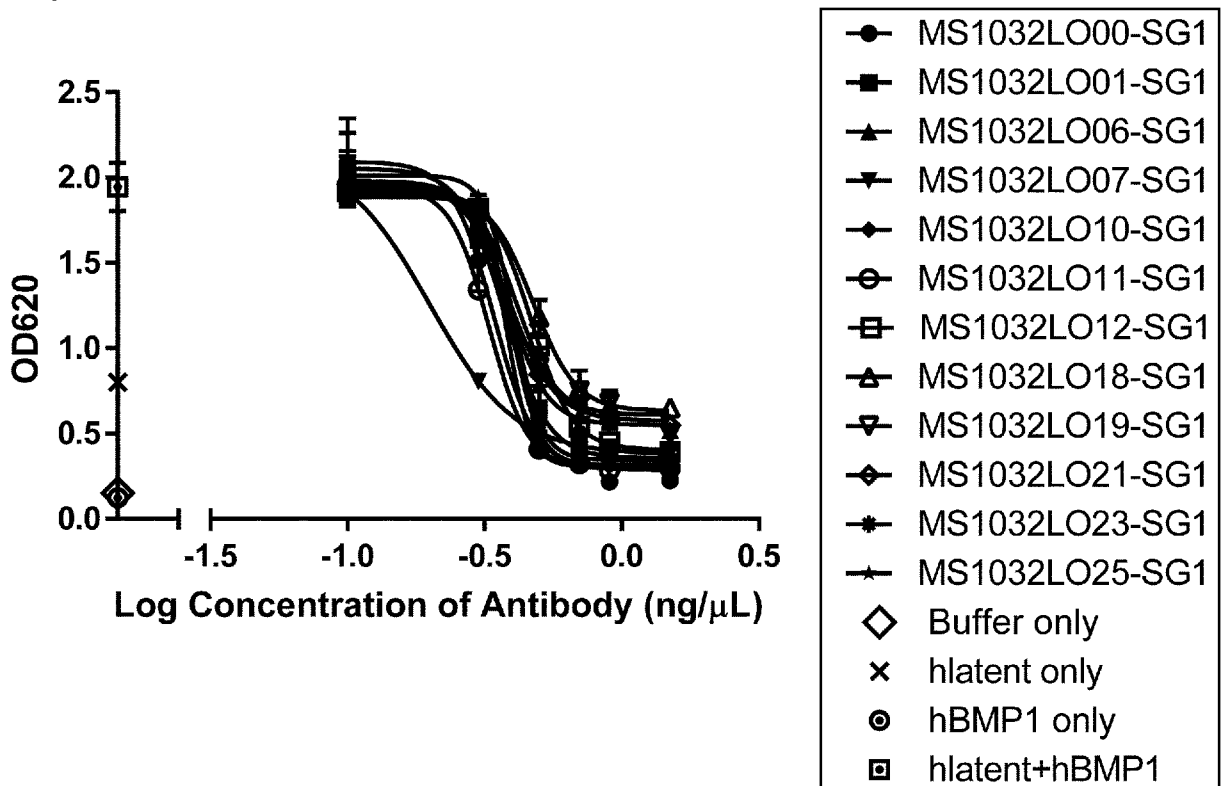
[Fig. 12]



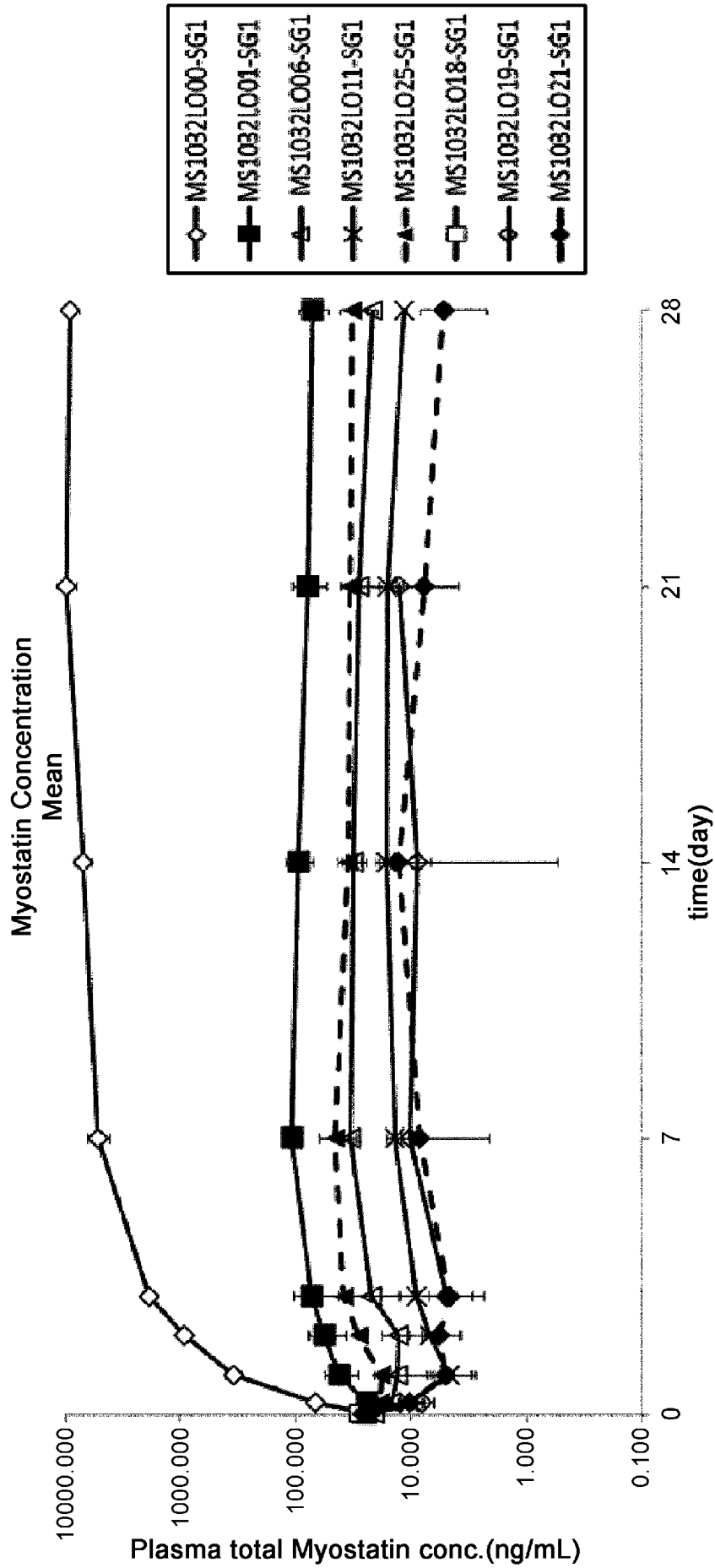
[Fig. 13]



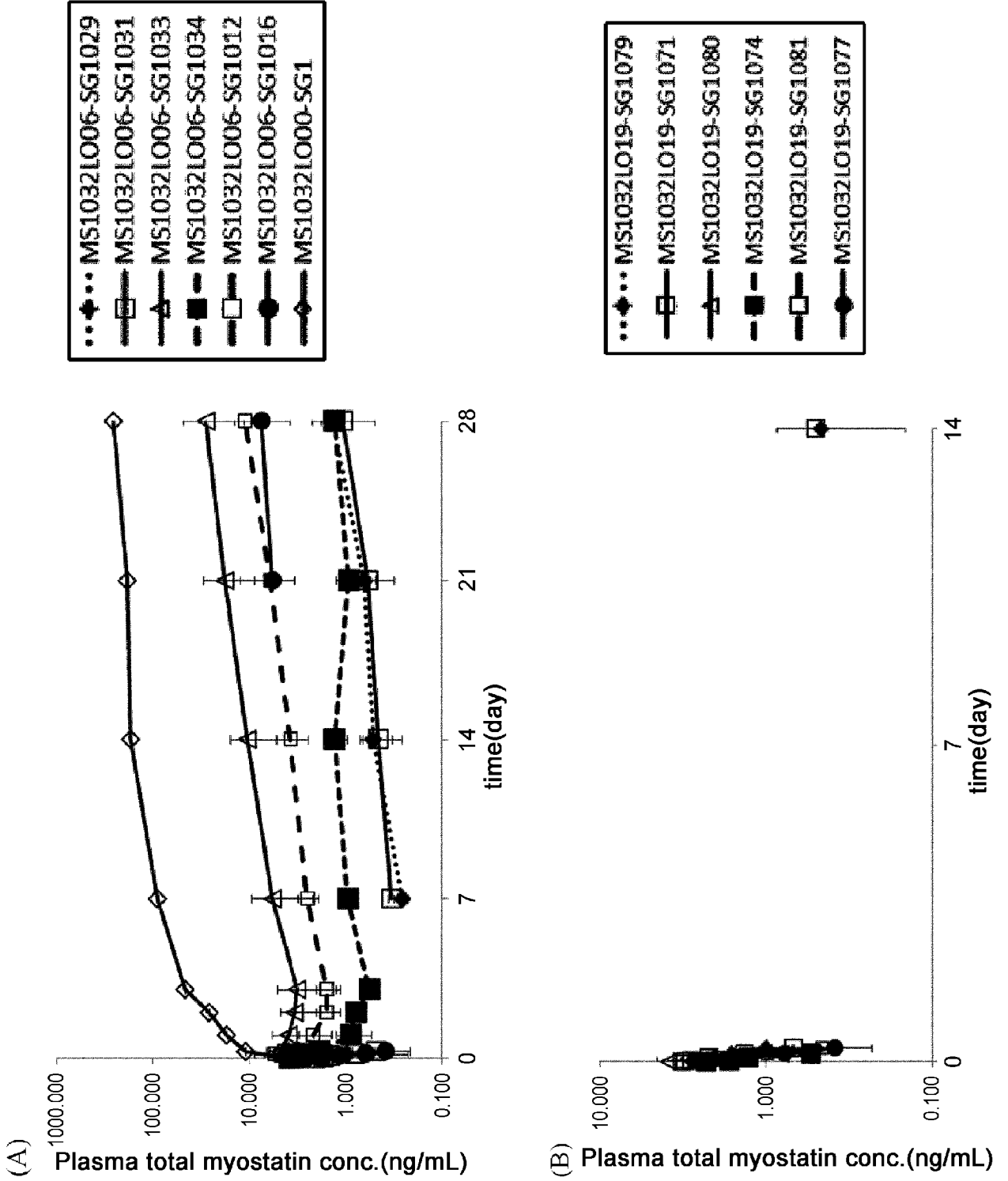
[Fig. 14]



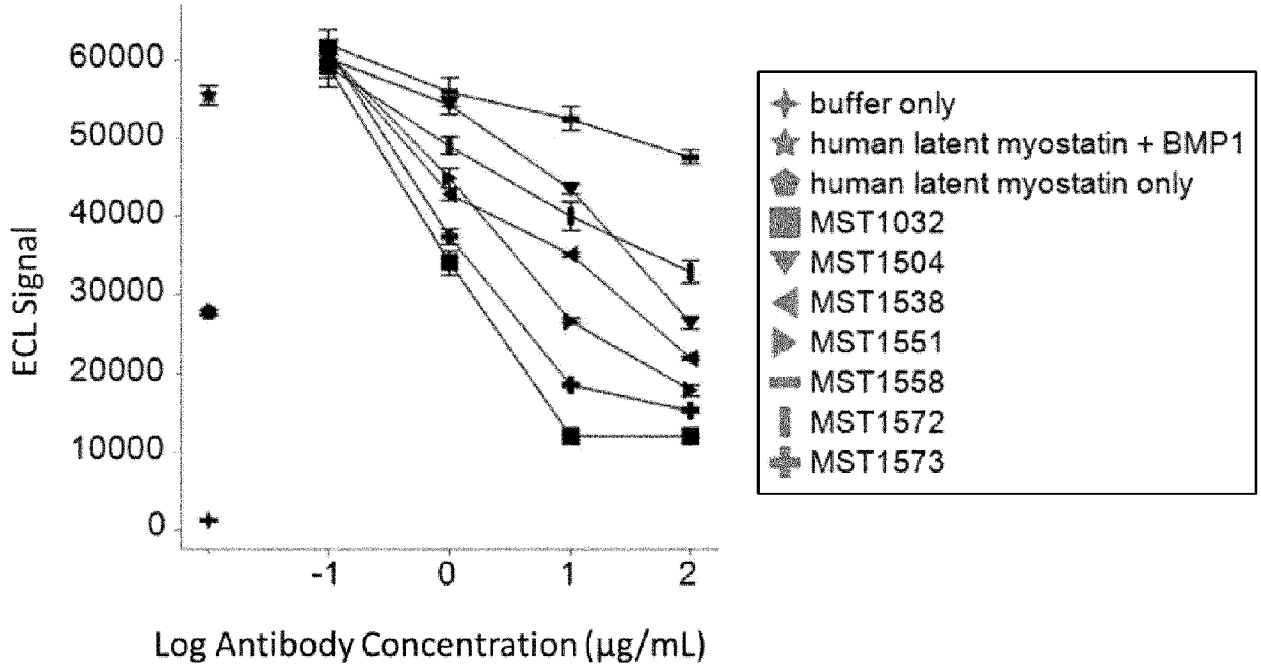
[Fig. 15]



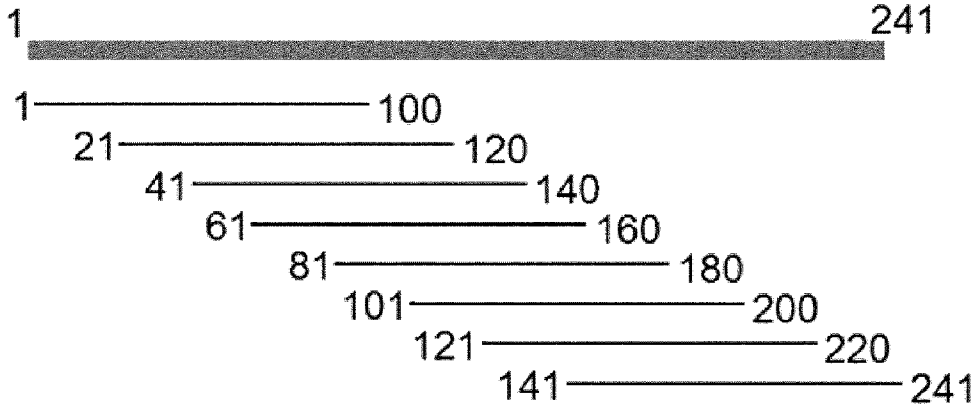
[Fig. 16]



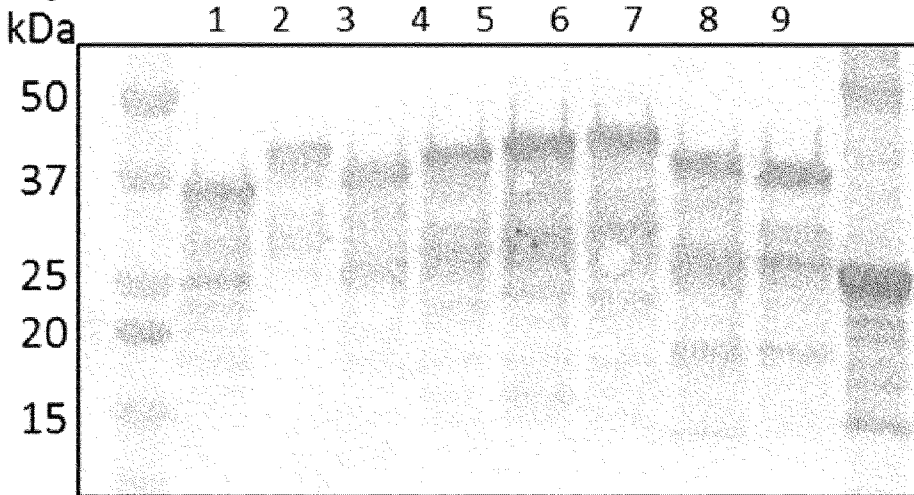
[Fig. 17]



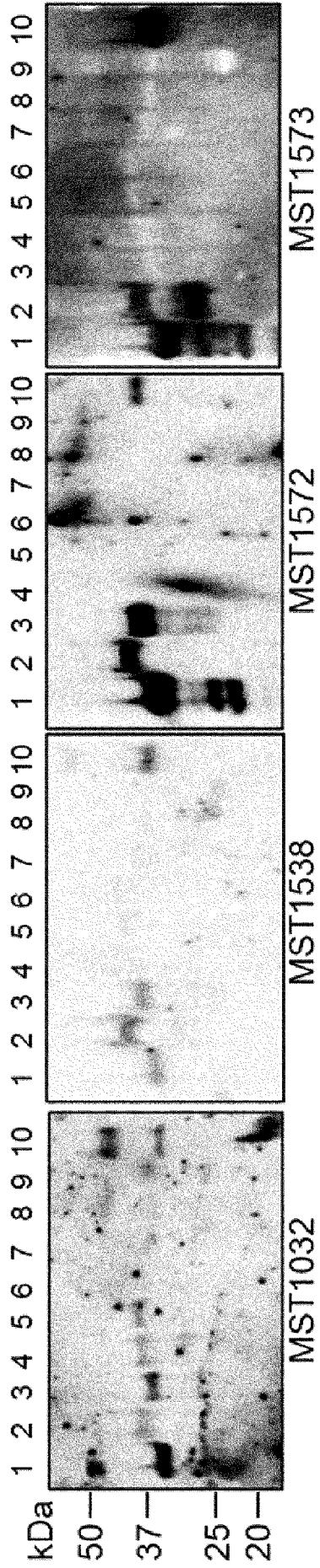
[Fig. 18A]



[Fig. 18B]



[Fig. 18C]



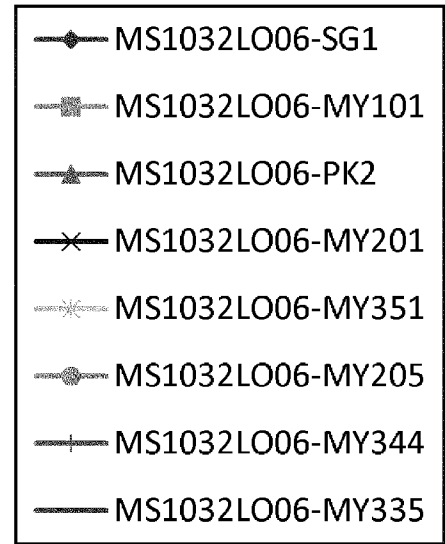
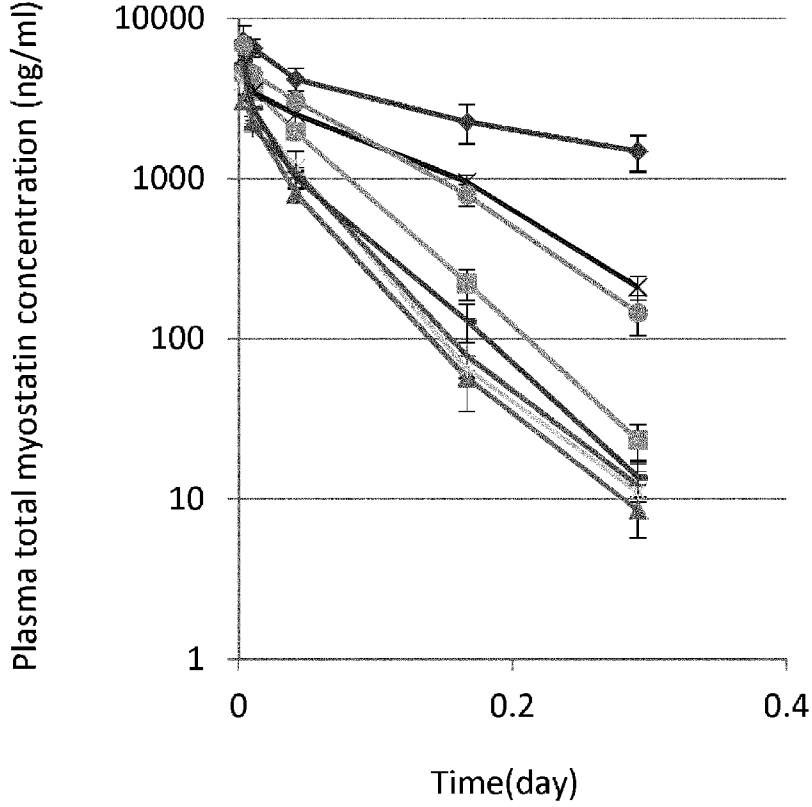
[Fig. 18D]

Ab	Main epitope	fragments							
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MST1572	41-60	■	■	■					
MST1573	21-40	■	■						

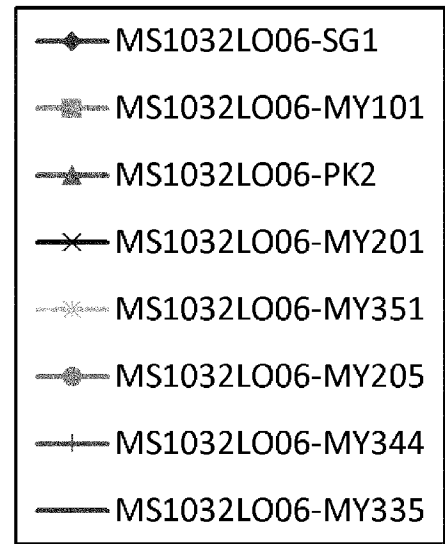
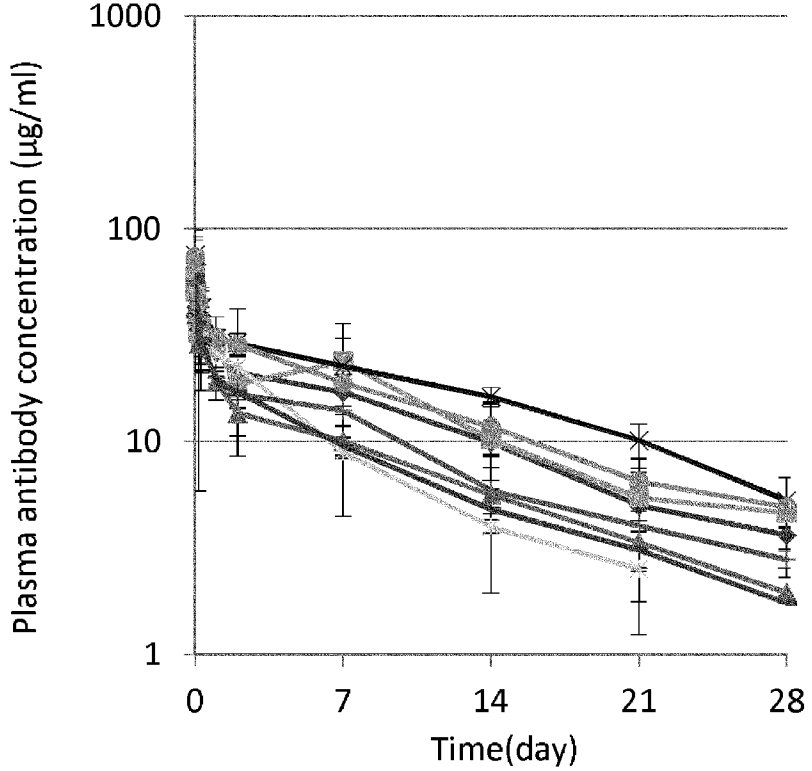
[Fig. 19]

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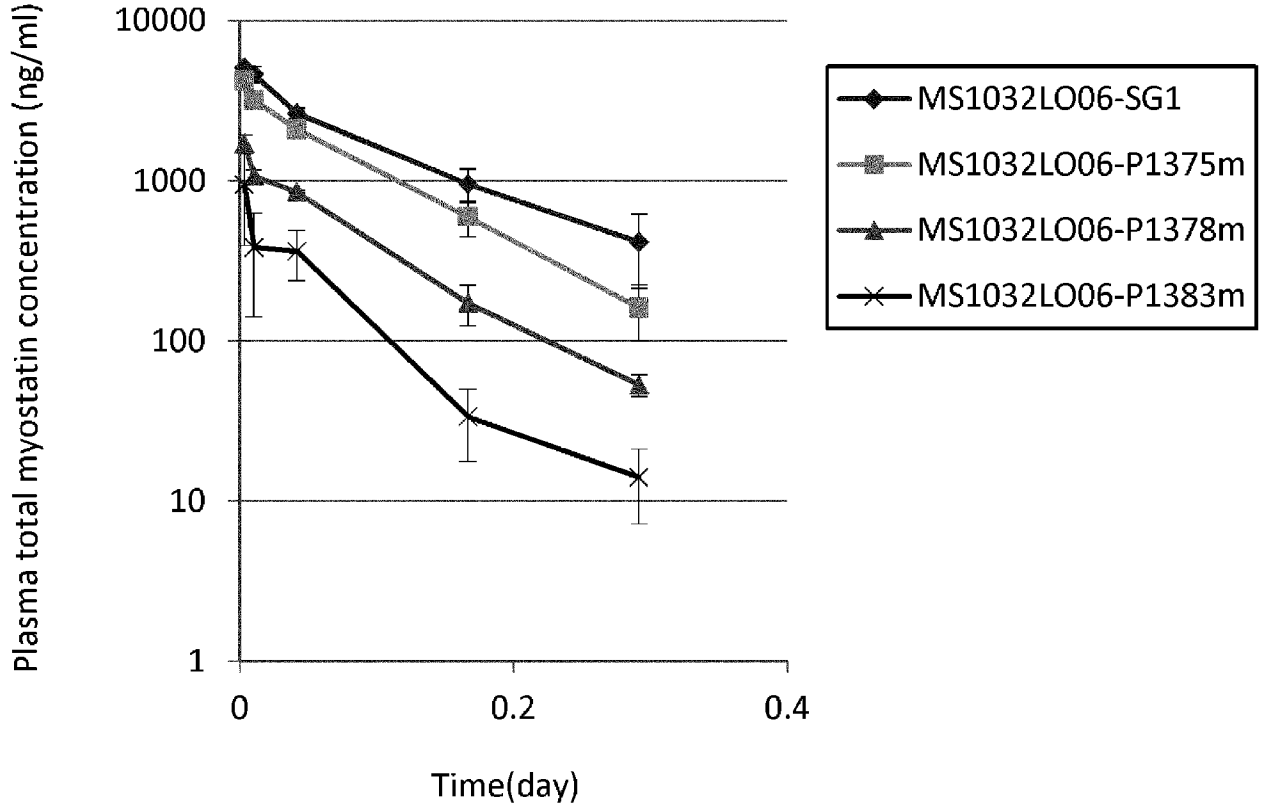
[Fig. 20]



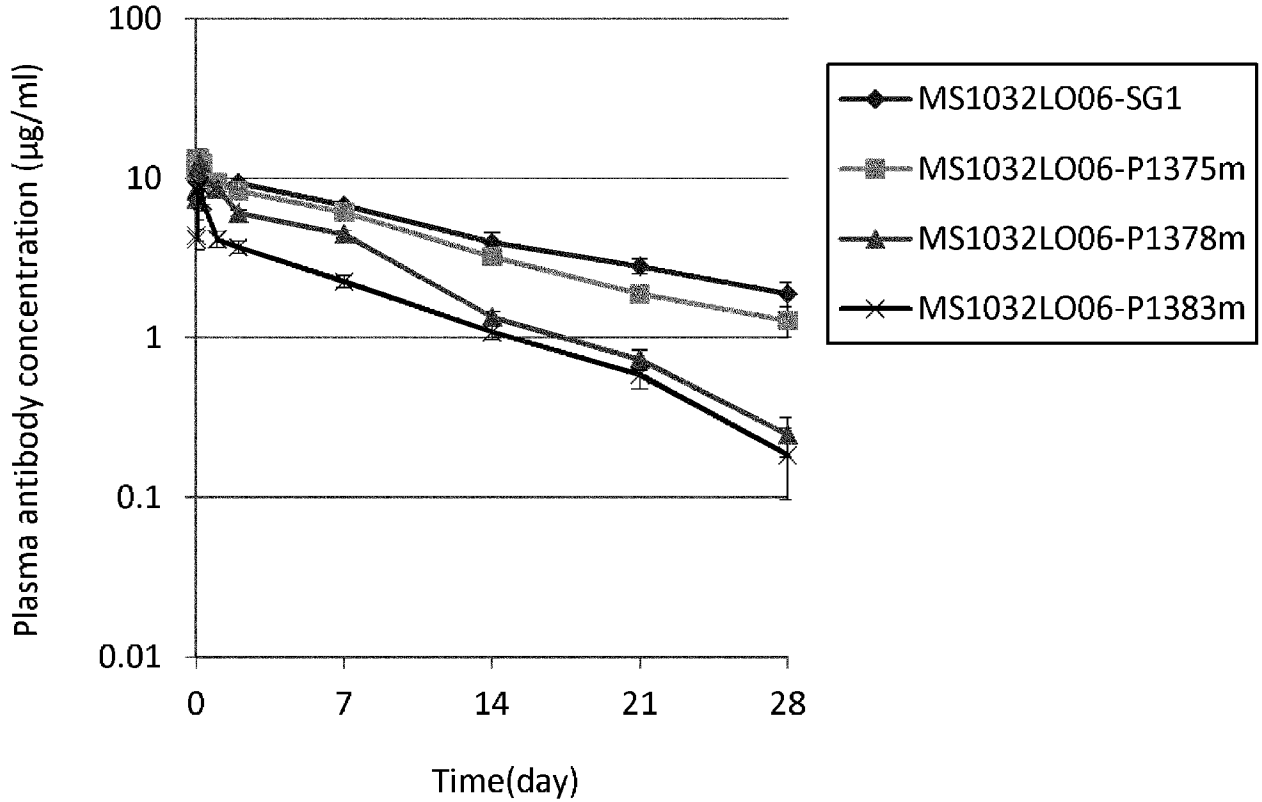
[Fig. 21]



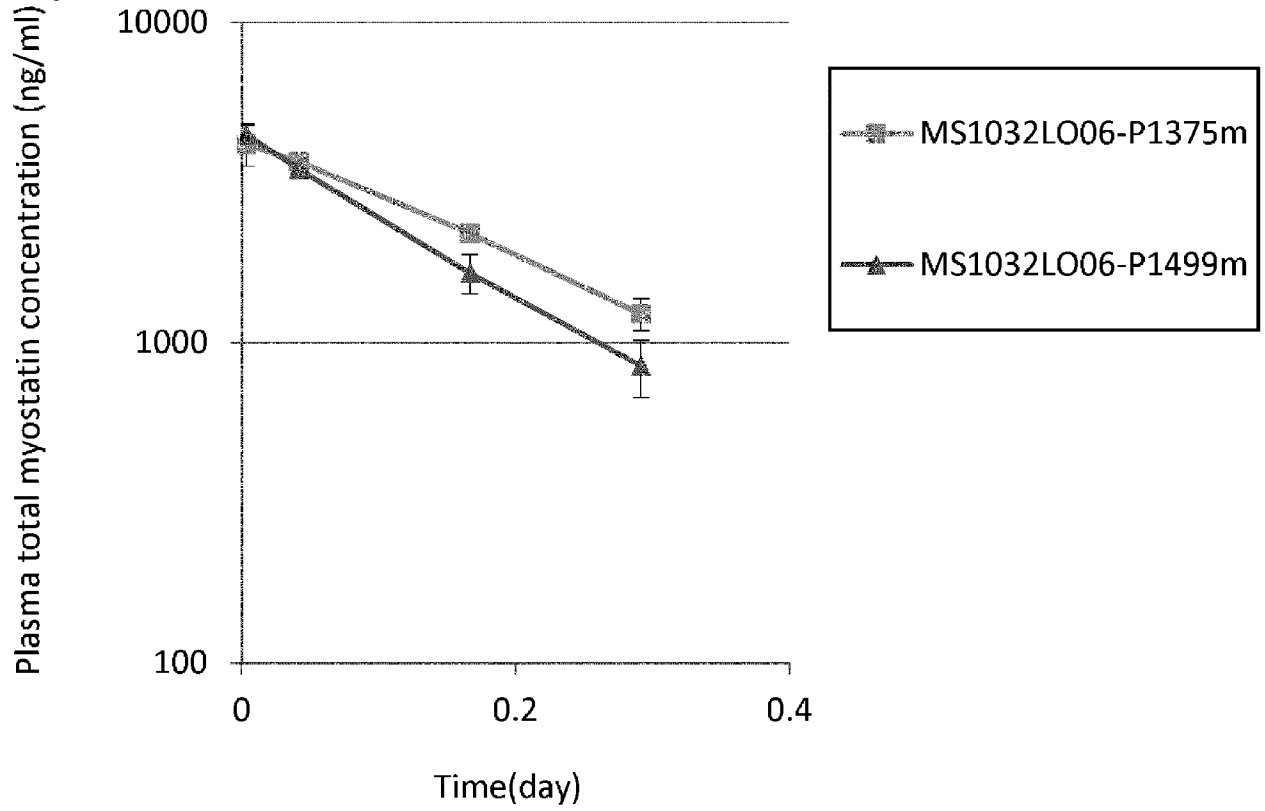
[Fig. 23A]



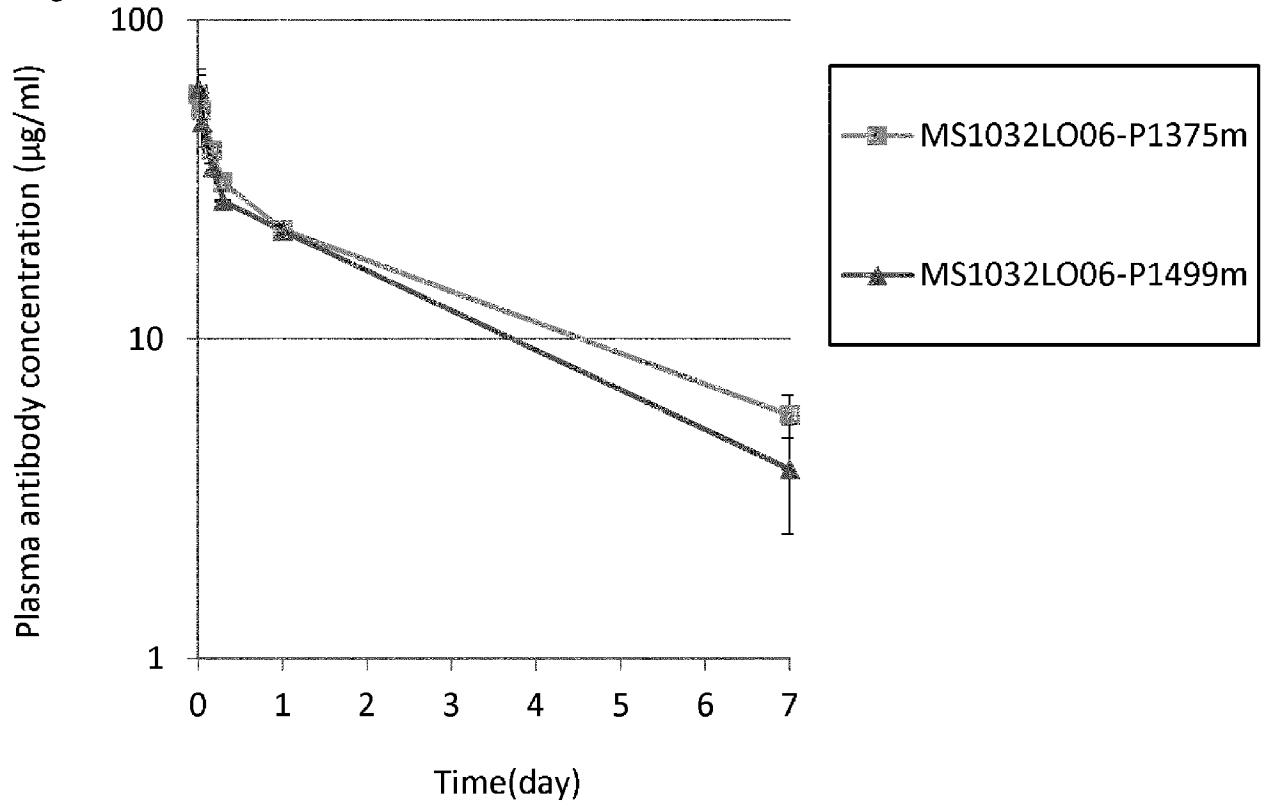
[Fig. 23B]



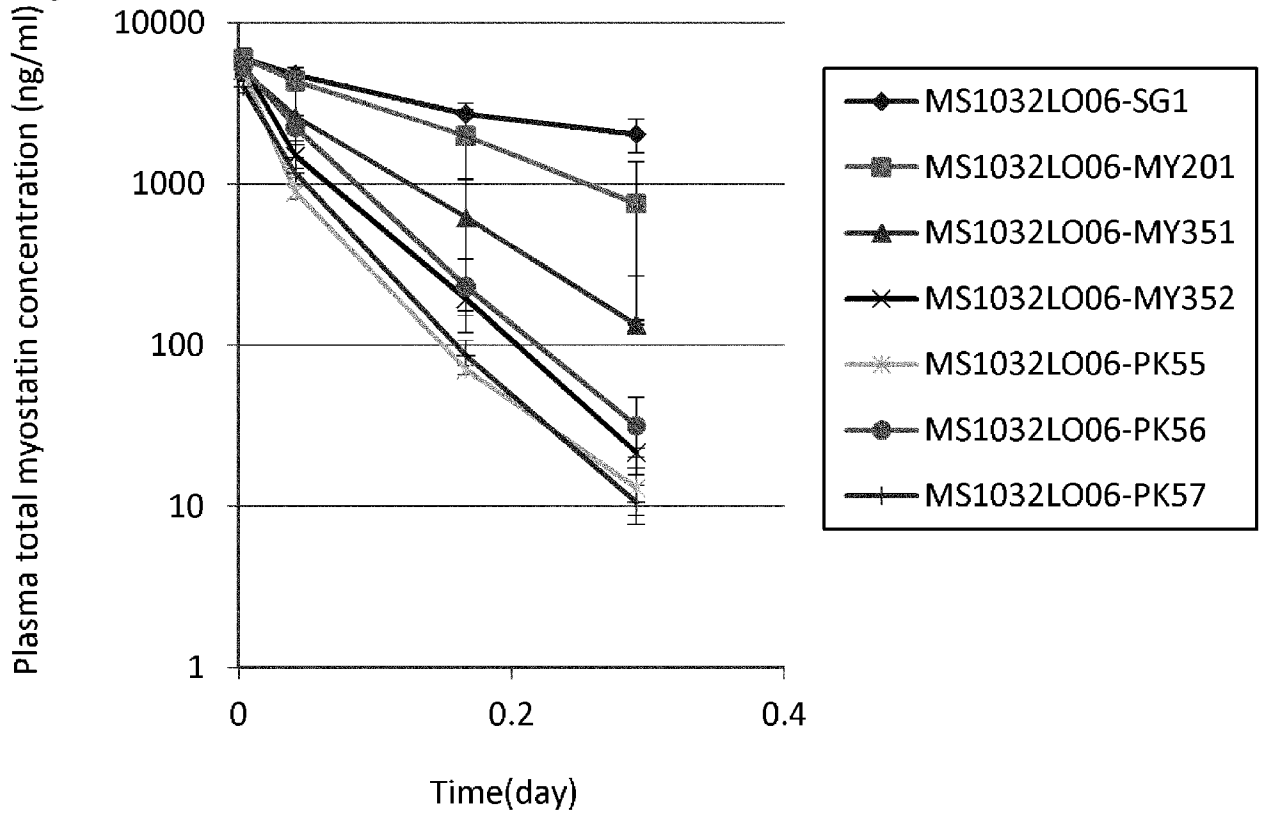
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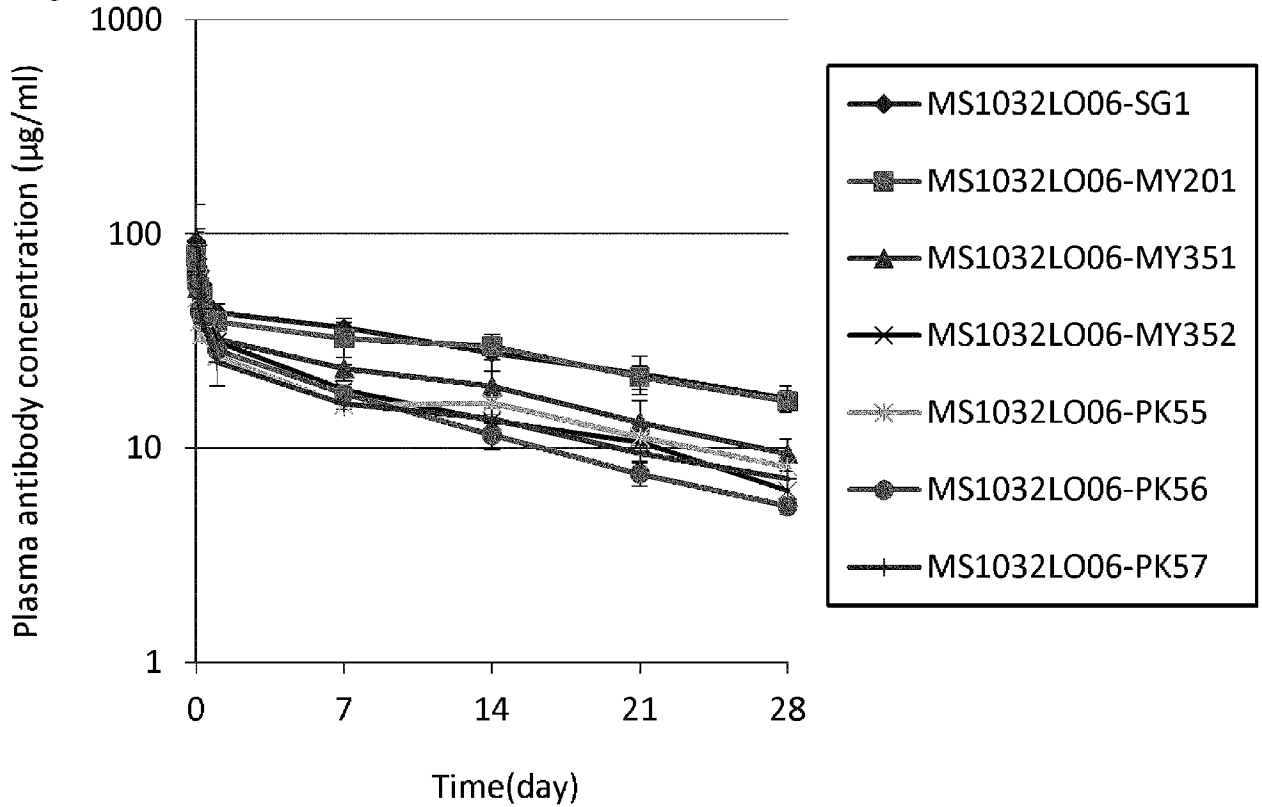
[Fig. 24B]



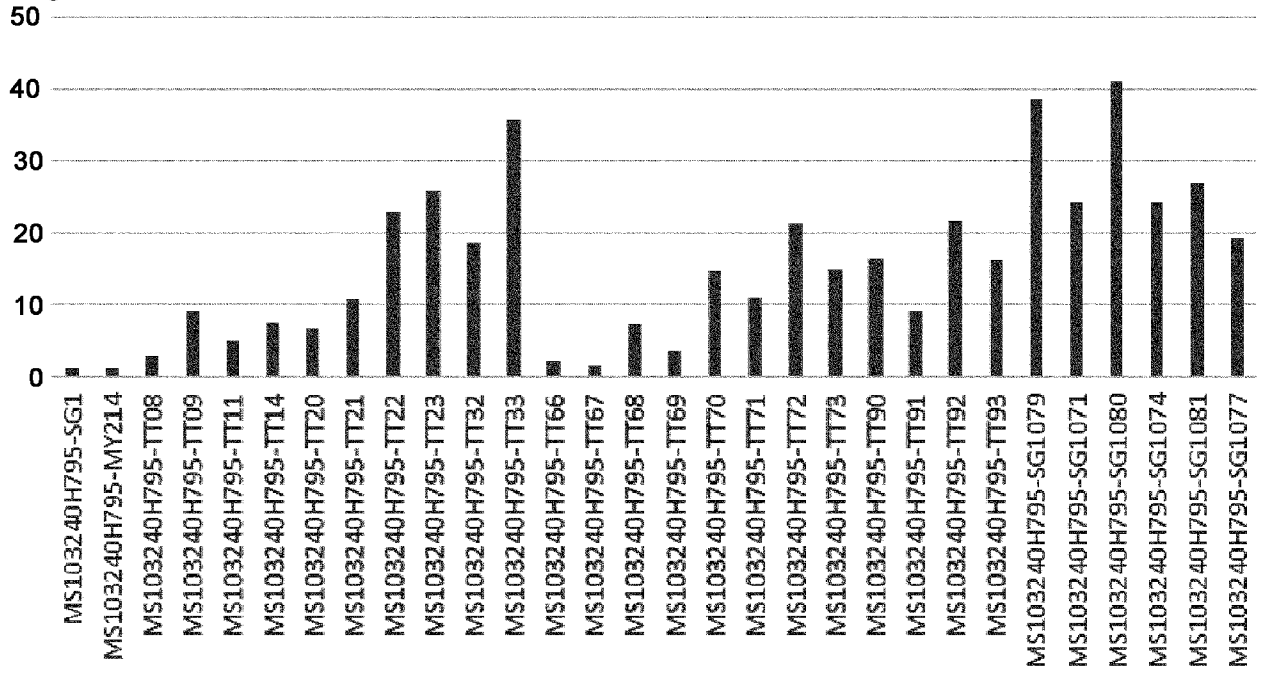
[Fig. 25]



[Fig. 26]



[Fig. 27]



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T y r P r o H i s T h r H i s L e u V a l H i s G l n A l a A s n P r o A r g G l y S e r A l a
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G l y P r o C y s C y s T h r P r o T h r L y s M e t S e r P r o I l e A s n M e t L e u T y r
 340 345 350

P h e A s n G l y L y s G l u G l n I l e I l e T y r G l y L y s I l e P r o A l a M e t V a l
 355 360 365

V a l A s p A r g C y s G l y C y s S e r
 370 375

<210> 4
 <211> 109
 <212> PRT
 <213> Macaca fascicularis

<400> 4

A s p P h e G l y L e u A s p C y s A s p G l u H i s S e r T h r G l u S e r A r g C y s C y s
 1 5 10 15

A r g T y r P r o L e u T h r V a l A s p P h e G l u A l a P h e G l y T r p A s p T r p I l e
 20 25 30

JPOXMLDOC01-seq1

I l e A l a P r o L y s A r g T y r L y s A l a A s n T y r C y s S e r G l y G l u C y s G l u
 35 40 45

P h e V a l P h e L e u G l n L y s T y r P r o H i s T h r H i s L e u V a l H i s G l n A l a
 50 60

A s n P r o A r g G l y S e r A l a G l y P r o C y s C y s T h r P r o T h r L y s M e t S e r
 65 70 75 80

P r o I l e A s n M e t L e u T y r P h e A s n G l y L y s G l u G l n I l e I l e T y r G l y
 85 90 95

L y s I l e P r o A l a M e t V a l V a l A s p A r g C y s G l y C y s S e r
 100 105

<210> 5
 <211> 376
 <212> PRT
 <213> Mus muscul us

<400> 5

M e t M e t G l n L y s L e u G l n M e t T y r V a l T y r I l e T y r L e u P h e M e t L e u
 1 5 10 15

I l e A l a A l a G l y P r o V a l A s p L e u A s n G l u G l y S e r G l u A r g G l u G l u
 20 25 30

A s n V a l G l u L y s G l u G l y L e u C y s A s n A l a C y s A l a T r p A r g G l n A s n
 35 40 45

T h r A r g T y r S e r A r g I l e G l u A l a I l e L y s I l e G l n I l e L e u S e r L y s
 50 55 60

L e u A r g L e u G l u T h r A l a P r o A s n I l e S e r L y s A s p A l a I l e A r g G l n
 65 70 75 80

L e u L e u P r o A r g A l a P r o P r o L e u A r g G l u L e u I l e A s p G l n T y r A s p
 85 90 95

V a l G l n A r g A s p A s p S e r S e r A s p G l y S e r L e u G l u A s p A s p A s p T y r
 100 105 110

H i s A l a T h r T h r G l u T h r I l e I l e T h r M e t P r o T h r G l u S e r A s p P h e
 115 120 125

L e u M e t G l n A l a A s p G l y L y s P r o L y s C y s C y s P h e P h e L y s P h e S e r
 130 135 140

S e r L y s I l e G l n T y r A s n L y s V a l V a l L y s A l a G l n L e u T r p I l e T y r
 145 150 155 160

L e u A r g P r o V a l L y s T h r P r o T h r T h r V a l P h e V a l G l n I l e L e u A r g

JPOXMLDOC01-seq1

165

170

175

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

Leu Lys Leu Asp Met Ser Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp
195 200 205

Val Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu
210 215 220

Gly Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val
225 230 235 240

Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val
245 250 255

Lys Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp
260 265 270

Cys Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr
275 280 285

Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg
290 295 300

Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln
305 310 315 320

Lys Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser
325 330 335

Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu
340 345 350

Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met
355 360 365

Val Val Asp Arg Cys Gly Cys Ser
370 375

<210> 6
<211> 109
<212> PRT
<213> Mus musculus

<400> 6

Asp Phe Gly Leu Asp Cys Asp Glu His Ser Thr Glu Ser Arg Cys Cys
1 5 10 15

Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
20 25 30

JPOXMLDOC01-seq1

I l e A l a P r o L y s A r g T y r L y s A l a A s n T y r C y s S e r G l y G l u C y s G l u
35 40 45

P h e V a l P h e L e u G l n L y s T y r P r o H i s T h r H i s L e u V a l H i s G l n A l a
50 55 60

A s n P r o A r g G l y S e r A l a G l y P r o C y s C y s T h r P r o T h r L y s M e t S e r
65 70 75 80

P r o I l e A s n M e t L e u T y r P h e A s n G l y L y s G l u G l n I l e I l e T y r G l y
85 90 95

L y s I l e P r o A l a M e t V a l V a l A s p A r g C y s G l y C y s S e r
100 105

<210> 7
<211> 328
<212> PRT
<213> A r t i f i c i a l s e q u e n c e

<220>
<223> A n a r t i f i c i a l l y s y n t h e s i z e d s e q u e n c e

<400> 7

A l a S e r T h r L y s G l y P r o S e r V a l P h e P r o L e u A l a P r o S e r S e r L y s
1 5 10 15

S e r T h r S e r G l y G l y T h r A l a A l a L e u G l y C y s L e u V a l L y s A s p T y r
20 25 30

P h e P r o G l u P r o V a l T h r V a l S e r T r p A s n S e r G l y A l a L e u T h r S e r
35 40 45

G l y V a l H i s T h r P h e P r o A l a V a l L e u G l n S e r S e r G l y L e u T y r S e r
50 55 60

L e u S e r S e r V a l V a l T h r V a l P r o S e r S e r S e r L e u G l y T h r G l n T h r
65 70 75 80

T y r I l e C y s A s n V a l A s n H i s L y s P r o S e r A s n T h r L y s V a l A s p L y s
85 90 95

L y s V a l G l u P r o L y s S e r C y s A s p L y s T h r H i s T h r C y s P r o P r o C y s
100 105 110

P r o A l a P r o G l u L e u L e u G l y G l y P r o S e r V a l P h e L e u P h e P r o P r o
115 120 125

L y s P r o L y s A s p T h r L e u M e t I l e S e r A r g T h r P r o G l u V a l T h r C y s
130 135 140

JPOXMLDOC01-seq1

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

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

<220>
<223> An artificially synthesized sequence

<400> 8

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

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

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

JPOXMLDOC01-seq1

Ser Gly Asn Ser Gl n Gl u Ser Val Thr Gl u Gl n Asp Ser Lys Asp Cys
 50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Al a Asp Tyr Gl u
 65 70 75 80

Lys Hi s Lys Val Tyr Al a Cys Gl u Val Thr Hi s Gl n Gly Leu Ser Ser
 85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Gl u Cys
 100 105

<210> 9
 <211> 328
 <212> PRT
 <213> Arti ficial sequence

<220>
 <223> An arti ficial ly synthesi zed sequence

<400> 9

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Il e Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Il e Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

JPOXMLDOC01-seq1

Tyr Val Asp Gly Val₁₆₅ Glu Val His Asn Ala₁₇₀ Lys Thr Lys Pro Arg Glu₁₇₅

Glu Gln Tyr Asn₁₈₀ Ser Thr Tyr Arg Val₁₈₅ Val Ser Val Leu Thr₁₉₀ Val Leu

His Gln Asp₁₉₅ Trp Leu Asn Gly Lys₂₀₀ Glu Tyr Lys Cys Lys₂₀₅ Val Ser Asn

Lys Ala₂₁₀ Leu Pro Ala Pro Ile₂₁₅ Glu Lys Thr Ile₂₂₀ Ser Lys Ala Lys Gly

Gln Pro Arg Glu Pro Gln₂₃₀ Val Tyr Thr Leu Pro₂₃₅ Pro Ser Arg Glu Glu₂₄₀

Met Thr Lys Asn₂₄₅ Gln Val Ser Leu Thr Cys₂₅₀ Leu Val Lys Gly Phe Tyr₂₅₅

Pro Ser Asp Ile₂₆₀ Ala Val Glu Trp Glu₂₆₅ Ser Asn Gly Gln Pro₂₇₀ Glu Asn

Asn Tyr Lys₂₇₅ Thr Thr Pro Pro Val₂₈₀ Leu Asp Ser Asp Gly₂₈₅ Ser Phe Phe

Leu Tyr Ser Lys Leu Thr Val₂₉₅ Asp Lys Ser Arg Trp₃₀₀ Gln Gln Gly Asn

Val Phe Ser Cys Ser Val₃₁₀ Met His Glu Ala₃₁₅ Leu His Asn His Tyr Thr₃₂₀

Gln Lys Ser Leu Ser₃₂₅ Leu Ser Pro

<210> 10

<211> 107

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 10

Arg Thr Val Ala₅ Ala Pro Ser Val Phe Ile₁₀ Phe Pro Pro Ser Asp Glu₁₅

Gln Leu Lys Ser₂₀ Gly Thr Ala Ser Val₂₅ Val Cys Leu Leu Asn₃₀ Asn Phe

Tyr Pro Arg₃₅ Glu Ala Lys Val Gln Trp Lys Val Asp Asn₄₅ Ala Leu Gln

Ser Gly₅₀ Asn Ser Gln Glu Ser₅₅ Val Thr Glu Gln Asp₆₀ Ser Lys Asp Ser

JPOXMLDOC01-seq1

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

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 11
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 11

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Arg Gly Gly Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

JPOXMLDOC01-seq1

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

- <210> 12
- <211> 116
- <212> PRT
- <213> Artificial sequence

- <220>
- <223> An artificially synthesized sequence

<400> 12

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

Leu Thr Val Thr Cys Arg Val Ser Gly Ile Asp Leu Ser Ser Tyr Asp
 20 25 30

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

Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
 50 55 60

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

JPOXMLDOC01-seq1

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

Pro Ala Tyr Ser Thr Gly Gly Asp Leu Trp Gly Pro Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 13
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 13

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 14
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 14

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

JPOXMLDOC01-seqI

Gly Thr Val Thr Ile Asn Cys Gln Ser Ser Gln Ser Val Tyr Asp Asn
20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
35 40 45

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

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

Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

Gly Leu Tyr Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 15
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence
<400> 15

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

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

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

Gly Leu Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 16
<211> 119
<212> PRT
<213> Artificial sequence

JPOXMLDOC01-seqI

<220>

<223> An artificial ly synthesized sequence

<400> 16

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 17

<211> 119

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 17

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

JPOXMLDOC01-seq1

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 18
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 18

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 19
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 19

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

JPOXMLDOC01-seq1

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 20
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 20

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

JPOXMLDOC01-seq1

<210> 21
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence
<400> 21

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 22
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence
<400> 22

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

JPOXMLD0C01-seq1

Gly Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gl n Val Val Leu
65 70 75 80

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Gly Val Pro Ala His Ser Thr Gly Gly Asp Leu Trp Gly Gl n Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 23
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 23

Gl n Val Thr Leu Lys Gl u Ser Gly Pro Val Leu Val Lys Pro Thr Gl u
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
20 25 30

Asp Ile Ser Trp Val Arg Gl n Ala Pro Gly Lys Gly Leu Gl u Trp Val
35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

Gly Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gl n Val Val Leu
65 70 75 80

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Gly Val Pro Ala His Ser Thr Gly Gly Asp Leu Trp Gly Gl n Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 24
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

JPOXMLDOC01-seq1

<400> 24

Gln Val Thr Leu Lys Glu Ser Gly Pro Val Leu Val Lys Pro Thr Glu
 1 5 10 15
 Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
 20 25 30
 Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60
 Gly Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val Leu
 65 70 75 80
 Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95
 Arg Gly Val Pro Ala Tyr Ser His Gly Gly Asp Leu Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115

<210> 25

<211> 119

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 25

Gln Val Thr Leu Lys Glu Ser Gly Pro Val Leu Val Lys Pro Thr Glu
 1 5 10 15
 Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
 20 25 30
 Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60
 Gly Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val Leu
 65 70 75 80
 Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

JPOXMLDOC01-seq1

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 26
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 26

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

Arg Gly Val Pro Ala His Ser His Gly Gly Asp Leu Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 27
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 27

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
 20 25 30

JPOXMLDOC01-seq1

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 28
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 28

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

Arg Gly Val Pro Ala His Ser His Gly Gly Asp Leu Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 29
 <211> 119

JPOXMLDOC01-seq1

<212> PRT
 <213> Artificial sequence

<220>
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<400> 29

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

Arg Gly Val Pro Ala His Ser His Gly Gly Asp Leu Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> 30
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 30

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

JPOXMLDOC01-seqI

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Gly Val Pro Ala His Ser His Gly Gly Asp Leu Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 31
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 31

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

Glu Arg Ala Thr Leu Ser Cys Gln Ser Ser Gln Ser Val Tyr His Asn
20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

Gly Leu Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 32
<211> 119
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 32

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Thr
20 25 30

JPOXMLDOC01-seq1

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 33
<211> 119
<212> PRT
<213> Artificial sequence

<220>
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<400> 33

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Thr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Met Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

JPOXMLDOC01-seq1

<210> 34
 <211> 119
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 34

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Tyr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 35
 <211> 110
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 35

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

Glu Arg Ala Thr Leu Ser Cys Thr Ser Ser Gln Ser Val Tyr His Asn
 20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
 35 40 45

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

JPOXMLDOC01-seq1

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

Gly Arg Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 36
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 36

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

Glu Arg Ala Thr Leu Ser Cys Gln Ser Ser Gln Ser Val Tyr His Asn
20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

Gly Leu Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 37
<211> 110
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 37

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

Glu Arg Ala Thr Leu Ser Cys Gln Thr Ser Gln Ser Val Tyr His Asp
20 25 30

JPOXMLDOC01-seq1

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
 35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
 85 90 95

Gly Arg Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 38
 <211> 110
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 38

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

Glu Arg Ala Thr Leu Ser Cys Thr Ser Ser Gln Ser Val Tyr His Asp
 20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
 35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
 85 90 95

Gly Leu Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 39
 <211> 348
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 39

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JPOXMLDOC01-seq1

tgcagagtct ctggaatcga cctcagtagt tacgacatca gctgggtccg ccaggctcca 120
 gggaaggggc tggagtggat cggaatcatt agttatgctg gtagcacata ctacgcgagc 180
 tgggcaaaag gccgattcac catctcaaaa acctcgacca cgggtgatct gaaaatgacc 240
 agtctgacaa ccgaggacac ggccacctat ttctgtgcca gaggtgtgcc tgcttatagt 300
 actggtggtg acttgtgggg cccaggcacc ctggtcaccg tctcctcc 348

<210> 40
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 40
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 acctgcacag tgagtgggat cgacctgagc agctacgaca tctcctgggt gcggcaggca 120
 cccgaaagg gcctggaatg ggtcggcatc attagctacg ccgggagcac atactatgcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcctt 300
 gcttactcta ccggagggga tctgtgggga caggaaccc tgggtgacagt ctctagt 357

<210> 41
 <211> 330
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 41
 gcgcaagtgc tgaccagac tgcatcatcc gtgtctgcag ctgtgggagg cacagtcacc 60
 atcaattgcc agtccagtca gagtgtttat gataacaact ggttatcctg gtttcagcag 120
 aaaccagggc agcctccaa gtcctgatc tattgggcat cactctggc atctggggtc 180
 ccatcgcggt tcaaaggcag tggatctggg acacagttca ctctacccat cagcgacctg 240
 gagtgtgacg atgctgccac ttactactgt gcaggcgggt atggtggtg tctgtatgct 300
 ttcggcggag ggaccaaggt ggagatcaaa 330

<210> 42
 <211> 330
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 42
 gacattgtga tgactcagtc tctgccact ctgtcactga gccctggcga gcgagcaacc 60
 ctgtcttgcc agagcagcca gtccgtgtac gacaacaatt ggctgagctg gttccagcag 120

JPOXMLD0C01-seqI

aagccagggc agccccctaa actgctgac tattgggcat caaactggc cagcggcgtc 180
 ccctccagat tctccgacg tggcagtggg actgacttta ccctgacat cagcagcctc 240
 cagcccagg atgccgctac ctactattgt gctggcgggt acggaggcgg gctgtatgca 300
 ttggacagg gcacaaagg ggaaatcaaa 330

<210> 43
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 43
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 acctgcacag tgagtgggat cgacctgagc cacaccgaca tctcctgggt gcggcaggca 120
 cccgaaagg gcctggaatg ggtcggcatc attagctacg ccgggagcac atactatgcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcctc 300
 gcttactctc acggagggga tctgtgggga caggaacc tggtgacagt ctctagt 357

<210> 44
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 44
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 acctgcacag tgagtgggat cgacctgagc cacaccgaca tctcctgggt gcggcaggca 120
 cccgaaagg gcctggaatg ggtcggcatc attagctacg ccgggagcac atactatag 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcctc 300
 gcttactctc acggagggga tctgtgggga caggaacc tggtgacagt ctctagt 357

<210> 45
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 45
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 acctgcacag tgagtgggat cgacctgagc cactacgaca tctcctgggt gcggcaggca 120
 cccgaaagg gcctggaatg ggtcggcatc attagctacg ccgggagcac atactatgcc 180

JPOXMLD0C01-seq1

agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
actatgacca atatggaccc cgtggataca gcaacttact attgtgccag gggcgtcct 300
gcttactctc acggagggga tctgtgggga caggaaccc tggtagacagt ctctagt 357

<210> 46
<211> 330
<212> DNA
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 46
gacattgtga tgactcagtc tctgccact ctgtcactga gccctggcga gcgagcaacc 60
ctgtcttgca ccagcagcca gtccgtgtac cacaacaatt ggctgagctg gttccagcag 120
aagccagggc agccccctaa actgctgac tattgggcat caaactggc ctacggcgtc 180
ccctccagat tctccgatc tggcagtggg actgacttta ccctgacat cagcagcctc 240
cagcccagg atgccgtac ctactattgt gctggcgggt acggaggcgg gcggtatgca 300
tttgacagg gcacaaaggt ggaaatcaaa 330

<210> 47
<211> 330
<212> DNA
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 47
gacattgtga tgactcagtc tctgccact ctgtcactga gccctggcga gcgagcaacc 60
ctgtcttgcc agagcagcca gtccgtgtac cacaacaatt ggctgagctg gttccagcag 120
aagccagggc agccccctaa actgctgac tattgggcat caaactggc cttcggcgtc 180
ccctccagat tctccgatc tggcagtggg actgacttta ccctgacat cagcagcctc 240
cagcccagg atgccgtac ctactattgt gctggcgggt acggaggcgg gctgtatgca 300
tttgacagg gcacaaaggt ggaaatcaaa 330

<210> 48
<211> 330
<212> DNA
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 48
gacattgtga tgactcagtc tctgccact ctgtcactga gccctggcga gcgagcaacc 60
ctgtcttgcc agaccagcca gtccgtgtac cagacaatt ggctgagctg gttccagcag 120
aagccagggc agccccctaa actgctgac tattgggcat caaactggc cagcggcgtc 180
ccctccagat tctccgatc tggcagtggg actgacttta ccctgacat cagcagcctc 240

JPOXMLDOC01-seq1

cagcccgagg atgccgctac ctactattgt gctggcgggt acggaggcgg gcggtatgca 300
 ttggacagg gcacaaaggt ggaaatcaaa 330

<210> 49
 <211> 330
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 49
 gacattgtga tgactcagtc tcctgccact ctgtcactga gccctggcga gcgagcaacc 60
 ctgtcttgca ccagcagcca gtccgtgtac cagcacaatt ggctgagctg gttccagcag 120
 aagccagggc agccccctaa actgctgac tattgggcat caaactggc ctacggcgctc 180
 ccctccagat tctccggatc tggcagtggg actgacttta ccctgaccat cagcagcctc 240
 cagcccgagg atgccgctac ctactattgt gctggcgggt acggaggcgg gctgtatgca 300
 ttggacagg gcacaaaggt ggaaatcaaa 330

<210> 50
 <211> 987
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 50
 gcttccacca agggcccatc ggtcttcccc ctggcaccct cctccaagtc cacctctggg 60
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 tggaaactcag gcgccctgac ctccggcgtg cacaccttcc cggctgtcct acagtcctca 180
 ggactctact ccctctctc cgtggtgacc gtgccctcct cgtccttggg caccagacc 240
 tacatctgca acgtgaatca caagccctc aacaccaagg tggacaagaa agttgagccc 300
 aatcttgtg acaaaactca cacatgccca ccgtgccag cacctgaact cctgggggga 360
 ccgtcagtct tcctcttccc ccaaaaacc aaggacacc tcatgatctc ccggaccct 420
 gaggtacat gcgtgggtgt ggacgtgtcc cacgaagacc ctgaggtcaa gttcaactgg 480
 tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 540
 tccacgtacc gtgtggtctc cgtcctcacc gtctgcacc aggactggct gaatggcaag 600
 gagtacaagt gcaaggtctc caacaagcc ctcccagccc ccatcgagaa aaccatctcc 660
 aaagccaaag ggcagccccg agaaccacag gtgtacacc tgccccatc ccgggaggaa 720
 atgaccaaga accaggtctc cctgacctgc ctggtaaaag gcttctatcc ctccgacatc 780
 gccgtggagt gggagtcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 840
 ctggactccg acggctcctt cttcctctac tccaagctca ccgtggacaa gtccaggtgg 900
 cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacag 960

JPOXMLDOC01-seq1

cagaagtcgc tctccctgtc tccgtag 987

<210> 51
 <211> 984
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 51
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 tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca 180
 ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg caccagacc 240
 tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc 300
 aaatcttgtg acaaaactca cacatgccca ccgtgccag cacctgaact ccggggggga 360
 ccgaaagtct tcctcttccc ccaaaacc aaggacacc tcatgatctc ccggaccct 420
 gaggtcacat gcgtgggtgt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg 480
 tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 540
 agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag 600
 gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 660
 aaagccaaag ggcagccccg agaaccacag gtgtacacc tgccccatc ccgggatgag 720
 ctgaccaaga accaggtcag cctgacctgc ctgggtcaaag gcttctatcc cagcgacatc 780
 gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg 840
 ctggactccg acggctcctt cttcctctac agcaagctca ccgtggacaa gagcaggtgg 900
 cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa cactacacg 960
 cagaagagcc tctccctgtc tccg 984

<210> 52
 <211> 987
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 52
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 tggaactcag gcgccctgac cagtggcgtg cacaccttcc cggctgtcct acagtcctca 180
 ggactctact ccctcagtag tgtggtgacc gtgccctcca gtagtttggg caccagacc 240
 tacatctgca acgtgaatca caagcccagt aacaccaagg tggacaagaa agttgagccc 300
 aaatcttgtg acaaaactca cacatgccca ccgtgccag cacctgagct cctggggggga 360

JPOXMLDOC01-seq1

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccct 420
gaggtcacat gcgtgggtgg ggacgtgagt cacgaagacc ctgaggtcaa gttcaactgg 480
tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac 540
agtacgtacc gtgtggtcag tgtcctcacc gtcctgcacc aggactggct gaatggcaag 600
gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc 660
aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgccccatc ccgggaggag 720
atgaccaaga accaggtcag tctgacctgc ctgggtcaaag gcttctatcc cagtgcacatc 780
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ctggactccg acggctcctt cttcctctac agtaagctca ccgtggacaa gagtaggtgg 900
cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa cactacacg 960
cagaagagtc tctccctgtc tccgtga 987

<210> 53
<211> 324
<212> DNA
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 53
cgtacgggtg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct 60
ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120
tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac 180
tccaaggact gcacctactc cctctctcc accctgacgc tgtccaaagc agactacgag 240
aacacaaaag tctacgcctg cgaagtcacc catcagggcc tgtcctcgcc cgtcaciaag 300
tccttcaaca ggggagagtg ttga 324

<210> 54
<211> 324
<212> DNA
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 54
cgtacgggtg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct 60
ggtaccgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120
tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac 180
agtaaggaca gtacctacag tctcagtagt accctgacgc tgtccaaagc agactacgag 240
aacacaaaag tctacgcctg cgaagtcacc catcagggcc tgtcctcgcc cgtcaciaag 300
tccttcaaca ggggagagtg ttga 324

JPOXMLDOC01-seqI

<210> 55
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 55

Ser Tyr Asp Ile Ser
1 5

<210> 56
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 56

His Tyr Asp Ile Ser
1 5

<210> 57
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> An artificially synthesized sequence

<400> 57

His Thr Asp Ile Ser
1 5

<210> 58
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 58

Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 59
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 59

Ile Ile Ser His Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

JPOXMLDOC01-seqI

<210> 60
<211> 16
<212> PRT
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<220>
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<400> 60

Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Met Ser Trp Ala Lys Gly
1 5 10 15

<210> 61
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence
<400> 61

Gly Val Pro Ala Tyr Ser Thr Gly Gly Asp Leu
1 5 10

<210> 62
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<400> 62

Gly Val Pro Ala His Ser Thr Gly Gly Asp Leu
1 5 10

<210> 63
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence
<400> 63

Gly Val Pro Ala Tyr Ser His Gly Gly Asp Leu
1 5 10

<210> 64
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<400> 64

JPOXMLD0C01-seq1

Gly Val Pro Ala His Ser His Gly Gly Asp Leu
 1 5 10

<210> 65
 <211> 13
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 65

Gln Ser Ser Gln Ser Val Tyr Asp Asn Asn Trp Leu Ser
 1 5 10

<210> 66
 <211> 13
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 66

Gln Ser Ser Gln Ser Val Tyr His Asn Asn Trp Leu Ser
 1 5 10

<210> 67
 <211> 13
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 67

Thr Ser Ser Gln Ser Val Tyr His Asn Asn Trp Leu Ser
 1 5 10

<210> 68
 <211> 13
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 68

Gln Thr Ser Gln Ser Val Tyr His Asp Asn Trp Leu Ser
 1 5 10

<210> 69
 <211> 13
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 69

Thr Ser Ser Gln Ser Val Tyr His Asp Asn Trp Leu Ser
1 5 10

<210> 70

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 70

Trp Ala Ser Thr Leu Ala Ser
1 5

<210> 71

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 71

Trp Ala Ser Thr Leu Ala Tyr
1 5

<210> 72

<211> 7

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 72

Trp Ala Ser Thr Leu Ala Phe
1 5

<210> 73

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 73

Ala Gly Gly Tyr Gly Gly Gly Leu Tyr Ala
1 5 10

<210> 74

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 74

Ala Gly Gly Tyr Gly Gly Gly Arg Tyr Ala
1 5 10

<210> 75

<211> 242

<212> PRT

<213> Homo sapiens

<400> 75

Glu Asn Ser Glu Gln Lys Glu Asn Val Glu Lys Glu Gly Leu Cys Asn
1 5 10 15

Ala Cys Thr Trp Arg Gln Asn Thr Lys Ser Ser Arg Ile Glu Ala Ile
20 25 30

Lys Ile Gln Ile Leu Ser Lys Leu Arg Leu Glu Thr Ala Pro Asn Ile
35 40 45

Ser Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg
50 55 60

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly
65 70 75 80

Ser Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr
85 90 95

Met Pro Thr Glu Ser Asp Phe Leu Met Gln Val Asp Gly Lys Pro Lys
100 105 110

Cys Cys Phe Phe Lys Phe Ser Ser Lys Ile Gln Tyr Asn Lys Val Val
115 120 125

Lys Ala Gln Leu Trp Ile Tyr Leu Arg Pro Val Glu Thr Pro Thr Thr
130 135 140

Val Phe Val Gln Ile Leu Arg Leu Ile Lys Pro Met Lys Asp Gly Thr
145 150 155 160

Arg Tyr Thr Gly Ile Arg Ser Leu Lys Leu Asp Met Asn Pro Gly Thr
165 170 175

Gly Ile Trp Gln Ser Ile Asp Val Lys Thr Val Leu Gln Asn Trp Leu
180 185 190

Lys Gln Pro Glu Ser Asn Leu Gly Ile Glu Ile Lys Ala Leu Asp Glu
195 200 205

Asn Gly His Asp Leu Ala Val Thr Phe Pro Gly Pro Gly Glu Asp Gly

JPOXMLDOC01-seq1
220

210

215

Leu Asn Pro Phe Leu Glu Val Lys Val Thr Asp Thr Pro Lys Arg Ser
225 230 235 240

Arg Arg

<210> 76
<211> 242
<212> PRT
<213> Macaca fascicularis

<400> 76

Glu Asn Ser Glu Gln Lys Glu Asn Val Glu Lys Glu Gly Leu Cys Asn
1 5 10 15

Ala Cys Thr Trp Arg Gln Asn Thr Lys Ser Ser Arg Ile Glu Ala Ile
20 25 30

Lys Ile Gln Ile Leu Ser Lys Leu Arg Leu Glu Thr Ala Pro Asn Ile
35 40 45

Ser Lys Asp Ala Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg
50 55 60

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly
65 70 75 80

Ser Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr
85 90 95

Met Pro Thr Glu Ser Asp Phe Leu Met Gln Val Asp Gly Lys Pro Lys
100 105 110

Cys Cys Phe Phe Lys Phe Ser Ser Lys Ile Gln Tyr Asn Lys Val Val
115 120 125

Lys Ala Gln Leu Trp Ile Tyr Leu Arg Pro Val Glu Thr Pro Thr Thr
130 135 140

Val Phe Val Gln Ile Leu Arg Leu Ile Lys Pro Met Lys Asp Gly Thr
145 150 155 160

Arg Tyr Thr Gly Ile Arg Ser Leu Lys Leu Asp Met Asn Pro Gly Thr
165 170 175

Gly Ile Trp Gln Ser Ile Asp Val Lys Thr Val Leu Gln Asn Trp Leu
180 185 190

Lys Gln Pro Glu Ser Asn Leu Gly Ile Glu Ile Lys Ala Leu Asp Glu
195 200 205

JPOXMLDOC01-seq1

Asn Gly His Asp Leu Ala Val Thr Phe Pro Gly Pro Gly Glu Asp Gly
 210 215 220

Leu Asn Pro Phe Leu Glu Val Lys Val Thr Asp Thr Pro Lys Arg Ser
 225 230 235 240

Arg Arg

<210> 77
 <211> 242
 <212> PRT
 <213> Mus musculus
 <400> 77

Glu Gly Ser Glu Arg Glu Glu Asn Val Glu Lys Glu Gly Leu Cys Asn
 1 5 10 15

Ala Cys Ala Trp Arg Gln Asn Thr Arg Tyr Ser Arg Ile Glu Ala Ile
 20 25 30

Lys Ile Gln Ile Leu Ser Lys Leu Arg Leu Glu Thr Ala Pro Asn Ile
 35 40 45

Ser Lys Asp Ala Ile Arg Gln Leu Leu Pro Arg Ala Pro Pro Leu Arg
 50 55 60

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly
 65 70 75 80

Ser Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr
 85 90 95

Met Pro Thr Glu Ser Asp Phe Leu Met Gln Ala Asp Gly Lys Pro Lys
 100 105 110

Cys Cys Phe Phe Lys Phe Ser Ser Lys Ile Gln Tyr Asn Lys Val Val
 115 120 125

Lys Ala Gln Leu Trp Ile Tyr Leu Arg Pro Val Lys Thr Pro Thr Thr
 130 135 140

Val Phe Val Gln Ile Leu Arg Leu Ile Lys Pro Met Lys Asp Gly Thr
 145 150 155 160

Arg Tyr Thr Gly Ile Arg Ser Leu Lys Leu Asp Met Ser Pro Gly Thr
 165 170 175

Gly Ile Trp Gln Ser Ile Asp Val Lys Thr Val Leu Gln Asn Trp Leu
 180 185 190

JPOXMLDOC01-seq1

Lys Gln Pro Glu Ser Asn Leu Gly Ile Glu Ile Lys Ala Leu Asp Glu
 195 200 205

Asn Gly His Asp Leu Ala Val Thr Phe Pro Gly Pro Gly Glu Asp Gly
 210 215 220

Leu Asn Pro Phe Leu Glu Val Lys Val Thr Asp Thr Pro Lys Arg Ser
 225 230 235 240

Arg Arg

<210> 78
 <211> 266
 <212> PRT
 <213> Homo sapiens

<400> 78

Met Gln Lys Leu Gln Leu Cys Val Tyr Ile Tyr Leu Phe Met Leu Ile
 1 5 10 15

Val Ala Gly Pro Val Asp Leu Asn Glu Asn Ser Glu Gln Lys Glu Asn
 20 25 30

Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Thr Trp Arg Gln Asn Thr
 35 40 45

Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu
 50 55 60

Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Val Ile Arg Gln Leu
 65 70 75 80

Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val
 85 90 95

Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
 100 105 110

Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu
 115 120 125

Met Gln Val Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser
 130 135 140

Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr Leu
 145 150 155 160

Arg Pro Val Glu Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg Leu
 165 170 175

JPOXMLDOC01-seq1

I l e L y s P r o M e t L y s A s p G l y T h r A r g T y r T h r G l y I l e A r g S e r L e u
 180 185 190

L y s L e u A s p M e t A s n P r o G l y T h r G l y I l e T r p G l n S e r I l e A s p V a l
 195 200 205

L y s T h r V a l L e u G l n A s n T r p L e u L y s G l n P r o G l u S e r A s n L e u G l y
 210 215 220

I l e G l u I l e L y s A l a L e u A s p G l u A s n G l y H i s A s p L e u A l a V a l T h r
 225 230 235 240

P h e P r o G l y P r o G l y G l u A s p G l y L e u A s n P r o P h e L e u G l u V a l L y s
 245 250 255

V a l T h r A s p T h r P r o L y s A r g S e r A r g A r g
 260 265

<210> 79
 <211> 266
 <212> PRT
 <213> Macaca fascicularis

<400> 79

M e t G l n L y s L e u G l n L e u C y s V a l T y r I l e T y r L e u P h e M e t L e u I l e
 1 5 10 15

V a l A l a G l y P r o V a l A s p L e u A s n G l u A s n S e r G l u G l n L y s G l u A s n
 20 25 30

V a l G l u L y s G l u G l y L e u C y s A s n A l a C y s T h r T r p A r g G l n A s n T h r
 35 40 45

L y s S e r S e r A r g I l e G l u A l a I l e L y s I l e G l n I l e L e u S e r L y s L e u
 50 55 60

A r g L e u G l u T h r A l a P r o A s n I l e S e r L y s A s p A l a I l e A r g G l n L e u
 65 70 75 80

L e u P r o L y s A l a P r o P r o L e u A r g G l u L e u I l e A s p G l n T y r A s p V a l
 85 90 95

G l n A r g A s p A s p S e r S e r A s p G l y S e r L e u G l u A s p A s p A s p T y r H i s
 100 105 110

A l a T h r T h r G l u T h r I l e I l e T h r M e t P r o T h r G l u S e r A s p P h e L e u
 115 120 125

M e t G l n V a l A s p G l y L y s P r o L y s C y s C y s P h e P h e L y s P h e S e r S e r
 130 135 140

L y s I l e G l n T y r A s n L y s V a l V a l L y s A l a G l n L e u T r p I l e T y r L e u

JPOXMLDOC01-seq1

145 150 155 160

Arg Pro Val Glu Thr Pro Thr Thr Val Phe Val Gl n Ile Leu Arg Leu
165 170 175

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

Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gl n Ser Ile Asp Val
195 200 205

Lys Thr Val Leu Gl n Asn Trp Leu Lys Gl n Pro Gl u Ser Asn Leu Gly
210 215 220

Ile Gl u Ile Lys Ala Leu Asp Gl u Asn Gly Hi s Asp Leu Ala Val Thr
225 230 235 240

Phe Pro Gly Pro Gly Gl u Asp Gly Leu Asn Pro Phe Leu Gl u Val Lys
245 250 255

Val Thr Asp Thr Pro Lys Arg Ser Arg Arg
260 265

<210> 80
<211> 267
<212> PRT
<213> Mus muscul us

<400> 80

Met Met Gl n Lys Leu Gl n Met Tyr Val Tyr Ile Tyr Leu Phe Met Leu
1 5 10 15

Ile Ala Ala Gly Pro Val Asp Leu Asn Gl u Gly Ser Gl u Arg Gl u Gl u
20 25 30

Asn Val Gl u Lys Gl u Gly Leu Cys Asn Ala Cys Ala Trp Arg Gl n Asn
35 40 45

Thr Arg Tyr Ser Arg Ile Gl u Ala Ile Lys Ile Gl n Ile Leu Ser Lys
50 55 60

Leu Arg Leu Gl u Thr Ala Pro Asn Ile Ser Lys Asp Ala Ile Arg Gl n
65 70 75 80

Leu Leu Pro Arg Ala Pro Pro Leu Arg Gl u Leu Ile Asp Gl n Tyr Asp
85 90 95

Val Gl n Arg Asp Asp Ser Ser Asp Gly Ser Leu Gl u Asp Asp Asp Tyr
100 105 110

Hi s Ala Thr Thr Gl u Thr Ile Ile Thr Met Pro Thr Gl u Ser Asp Phe
115 120 125

JPOXMLDOC01-seq1

Leu Met Gln Ala Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser
 130 135 140

Ser Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr
 145 150 155 160

Leu Arg Pro Val Lys Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg
 165 170 175

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

Leu Lys Leu Asp Met Ser Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp
 195 200 205

Val Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu
 210 215 220

Gly Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val
 225 230 235 240

Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val
 245 250 255

Lys Val Thr Asp Thr Pro Lys Arg Ser Arg Arg
 260 265

<210> 81
 <211> 407
 <212> PRT
 <213> Homo sapiens
 <400> 81

Met Val Leu Ala Ala Pro Leu Leu Leu Gly Phe Leu Leu Leu Ala Leu
 1 5 10 15

Glu Leu Arg Pro Arg Gly Glu Ala Ala Glu Gly Pro Ala Ala Ala Ala
 20 25 30

Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Val Gly Gly Glu Arg Ser
 35 40 45

Ser Arg Pro Ala Pro Ser Val Ala Pro Glu Pro Asp Gly Cys Pro Val
 50 55 60

Cys Val Trp Arg Gln His Ser Arg Glu Leu Arg Leu Glu Ser Ile Lys
 65 70 75 80

Ser Gln Ile Leu Ser Lys Leu Arg Leu Lys Glu Ala Pro Asn Ile Ser
 85 90 95

JPOXMLDOC01-seq1

Arg Glu Val Val Lys Gln Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln
100 105 110

Ile Leu Asp Leu His Asp Phe Gln Gly Asp Ala Leu Gln Pro Glu Asp
115 120 125

Phe Leu Glu Glu Asp Glu Tyr His Ala Thr Thr Glu Thr Val Ile Ser
130 135 140

Met Ala Gln Glu Thr Asp Pro Ala Val Gln Thr Asp Gly Ser Pro Leu
145 150 155 160

Cys Cys His Phe His Phe Ser Pro Lys Val Met Phe Thr Lys Val Leu
165 170 175

Lys Ala Gln Leu Trp Val Tyr Leu Arg Pro Val Pro Arg Pro Ala Thr
180 185 190

Val Tyr Leu Gln Ile Leu Arg Leu Lys Pro Leu Thr Gly Glu Gly Thr
195 200 205

Ala Gly Gly Gly Gly Gly Gly Arg Arg His Ile Arg Ile Arg Ser Leu
210 215 220

Lys Ile Glu Leu His Ser Arg Ser Gly His Trp Gln Ser Ile Asp Phe
225 230 235 240

Lys Gln Val Leu His Ser Trp Phe Arg Gln Pro Gln Ser Asn Trp Gly
245 250 255

Ile Glu Ile Asn Ala Phe Asp Pro Ser Gly Thr Asp Leu Ala Val Thr
260 265 270

Ser Leu Gly Pro Gly Ala Glu Gly Leu His Pro Phe Met Glu Leu Arg
275 280 285

Val Leu Glu Asn Thr Lys Arg Ser Arg Arg Asn Leu Gly Leu Asp Cys
290 295 300

Asp Glu His Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
305 310 315 320

Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
325 330 335

Lys Ala Asn Tyr Cys Ser Gly Gln Cys Glu Tyr Met Phe Met Gln Lys
340 345 350

Tyr Pro His Thr His Leu Val Gln Gln Ala Asn Pro Arg Gly Ser Ala
355 360 365

JPOXMLDOC01-seq1

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
 370 375 380

Phe Asn Asp Lys Gln Gln Ile Ile Tyr Gly Lys Ile Pro Gly Met Val
 385 390 395 400

Val Asp Arg Cys Gly Cys Ser
 405

<210> 82
 <211> 109
 <212> PRT
 <213> Homo sapiens

<400> 82

Asn Leu Gly Leu Asp Cys Asp Glu His Ser Ser Glu Ser Arg Cys Cys
 1 5 10 15

Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
 20 25 30

Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Gln Cys Glu
 35 40 45

Tyr Met Phe Met Gln Lys Tyr Pro His Thr His Leu Val Gln Gln Ala
 50 55 60

Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
 65 70 75 80

Pro Ile Asn Met Leu Tyr Phe Asn Asp Lys Gln Gln Ile Ile Tyr Gly
 85 90 95

Lys Ile Pro Gly Met Val Val Asp Arg Cys Gly Cys Ser
 100 105

<210> 83
 <211> 274
 <212> PRT
 <213> Homo sapiens

<400> 83

Ala Glu Gly Pro Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
 1 5 10 15

Ala Gly Val Gly Gly Glu Arg Ser Ser Arg Pro Ala Pro Ser Val Ala
 20 25 30

Pro Glu Pro Asp Gly Cys Pro Val Cys Val Trp Arg Gln His Ser Arg
 35 40 45

Glu Leu Arg Leu Glu Ser Ile Lys Ser Gln Ile Leu Ser Lys Leu Arg

JPOXMLDOC01-seq1

50

55

60

Leu Lys Glu Ala Pro Asn Ile Ser Arg Glu Val Val Lys Gln Leu Leu
65 70 75 80

Pro Lys Ala Pro Pro Leu Gln Gln Ile Leu Asp Leu His Asp Phe Gln
85 90 95

Gly Asp Ala Leu Gln Pro Glu Asp Phe Leu Glu Glu Asp Glu Tyr His
100 105 110

Ala Thr Thr Glu Thr Val Ile Ser Met Ala Gln Glu Thr Asp Pro Ala
115 120 125

Val Gln Thr Asp Gly Ser Pro Leu Cys Cys His Phe His Phe Ser Pro
130 135 140

Lys Val Met Phe Thr Lys Val Leu Lys Ala Gln Leu Trp Val Tyr Leu
145 150 155 160

Arg Pro Val Pro Arg Pro Ala Thr Val Tyr Leu Gln Ile Leu Arg Leu
165 170 175

Lys Pro Leu Thr Gly Glu Gly Thr Ala Gly Gly Gly Gly Gly Gly Arg
180 185 190

Arg His Ile Arg Ile Arg Ser Leu Lys Ile Glu Leu His Ser Arg Ser
195 200 205

Gly His Trp Gln Ser Ile Asp Phe Lys Gln Val Leu His Ser Trp Phe
210 215 220

Arg Gln Pro Gln Ser Asn Trp Gly Ile Glu Ile Asn Ala Phe Asp Pro
225 230 235 240

Ser Gly Thr Asp Leu Ala Val Thr Ser Leu Gly Pro Gly Ala Glu Gly
245 250 255

Leu His Pro Phe Met Glu Leu Arg Val Leu Glu Asn Thr Lys Arg Ser
260 265 270

Arg Arg

<210> 84
<211> 298
<212> PRT
<213> Homo sapiens

<400> 84

Met Val Leu Ala Ala Pro Leu Leu Leu Gly Phe Leu Leu Leu Ala Leu
1 5 10 15

JPOXMLDOC01-seq1

Glu Leu Arg Pro Arg Gly Glu Ala Ala Glu Gly Pro Ala Ala Ala Ala
 20 25 30
 Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Val Gly Gly Glu Arg Ser
 35 40 45
 Ser Arg Pro Ala Pro Ser Val Ala Pro Glu Pro Asp Gly Cys Pro Val
 50 55 60
 Cys Val Trp Arg Gln His Ser Arg Glu Leu Arg Leu Glu Ser Ile Lys
 65 70 75 80
 Ser Gln Ile Leu Ser Lys Leu Arg Leu Lys Glu Ala Pro Asn Ile Ser
 85 90 95
 Arg Glu Val Val Lys Gln Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln
 100 105 110
 Ile Leu Asp Leu His Asp Phe Gln Gly Asp Ala Leu Gln Pro Glu Asp
 115 120 125
 Phe Leu Glu Glu Asp Glu Tyr His Ala Thr Thr Glu Thr Val Ile Ser
 130 135 140
 Met Ala Gln Glu Thr Asp Pro Ala Val Gln Thr Asp Gly Ser Pro Leu
 145 150 155 160
 Cys Cys His Phe His Phe Ser Pro Lys Val Met Phe Thr Lys Val Leu
 165 170 175
 Lys Ala Gln Leu Trp Val Tyr Leu Arg Pro Val Pro Arg Pro Ala Thr
 180 185 190
 Val Tyr Leu Gln Ile Leu Arg Leu Lys Pro Leu Thr Gly Glu Gly Thr
 195 200 205
 Ala Gly Gly Gly Gly Gly Gly Arg Arg His Ile Arg Ile Arg Ser Leu
 210 215 220
 Lys Ile Glu Leu His Ser Arg Ser Gly His Trp Gln Ser Ile Asp Phe
 225 230 235 240
 Lys Gln Val Leu His Ser Trp Phe Arg Gln Pro Gln Ser Asn Trp Gly
 245 250 255
 Ile Glu Ile Asn Ala Phe Asp Pro Ser Gly Thr Asp Leu Ala Val Thr
 260 265 270
 Ser Leu Gly Pro Gly Ala Glu Gly Leu His Pro Phe Met Glu Leu Arg
 275 280 285

JPOXMLDOC01-seqI

Val Leu Glu Asn Thr Lys Arg Ser Arg Arg
 290 295

<210> 85
 <211> 409
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 85

Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Ile Ser Gly Ser Ala
 1 5 10 15

Phe Ser Asp Tyr Lys Asp Asp Asp Asp Lys Ala Glu Gly Pro Ala Ala
 20 25 30

Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Val Gly Gly Glu
 35 40 45

Arg Ser Ser Arg Pro Ala Pro Ser Val Ala Pro Glu Pro Asp Gly Cys
 50 55 60

Pro Val Cys Val Trp Arg Gln His Ser Arg Glu Leu Arg Leu Glu Ser
 65 70 75 80

Ile Lys Ser Gln Ile Leu Ser Lys Leu Arg Leu Lys Glu Ala Pro Asn
 85 90 95

Ile Ser Arg Glu Val Val Lys Gln Leu Leu Pro Lys Ala Pro Pro Leu
 100 105 110

Gln Gln Ile Leu Asp Leu His Asp Phe Gln Gly Asp Ala Leu Gln Pro
 115 120 125

Glu Asp Phe Leu Glu Glu Asp Glu Tyr His Ala Thr Thr Glu Thr Val
 130 135 140

Ile Ser Met Ala Gln Glu Thr Asp Pro Ala Val Gln Thr Asp Gly Ser
 145 150 155 160

Pro Leu Cys Cys His Phe His Phe Ser Pro Lys Val Met Phe Thr Lys
 165 170 175

Val Leu Lys Ala Gln Leu Trp Val Tyr Leu Arg Pro Val Pro Arg Pro
 180 185 190

Ala Thr Val Tyr Leu Gln Ile Leu Arg Leu Lys Pro Leu Thr Gly Glu
 195 200 205

JPOXMLDOC01-seq1

Gly Thr Ala Gly Gly Gly Gly Gly Arg Arg His Ile Arg Ile Arg
 210 215 220

Ser Leu Lys Ile Glu Leu His Ser Arg Ser Gly His Trp Gln Ser Ile
 225 230 235 240

Asp Phe Lys Gln Val Leu His Ser Trp Phe Arg Gln Pro Gln Ser Asn
 245 250 255

Trp Gly Ile Glu Ile Asn Ala Phe Asp Pro Ser Gly Thr Asp Leu Ala
 260 265 270

Val Thr Ser Leu Gly Pro Gly Ala Glu Gly Leu His Pro Phe Met Glu
 275 280 285

Leu Arg Val Leu Glu Asn Thr Lys Arg Ser Arg Arg Asn Leu Gly Leu
 290 295 300

Asp Cys Asp Glu His Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu
 305 310 315 320

Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys
 325 330 335

Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Gln Cys Glu Tyr Met Phe Met
 340 345 350

Gln Lys Tyr Pro His Thr His Leu Val Gln Gln Ala Asn Pro Arg Gly
 355 360 365

Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met
 370 375 380

Leu Tyr Phe Asn Asp Lys Gln Gln Ile Ile Tyr Gly Lys Ile Pro Gly
 385 390 395 400

Met Val Val Asp Arg Cys Gly Cys Ser
 405

- <210> 86
- <211> 119
- <212> PRT
- <213> Artificial sequence
- <220>
- <223> An artificially synthesized sequence
- <400> 86

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Asp
 20 25 30

JPOXMLDOC01-seq1

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 87
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<220>
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<400> 87

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Asp
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Met Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

JPOXMLDOC01-seq1

<210> 88
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<220>
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<400> 88

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Thr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Lys Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

Lys Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val Leu
 65 70 75 80

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 89
 <211> 119
 <212> PRT
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<220>
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<400> 89

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Thr
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Lys Lys Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

JPOXMLDOC01-seq1

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 90
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<400> 90

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Thr
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ile Ile Ser Tyr Ala Gly Ser Lys Tyr Lys Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 91
<211> 119
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<400> 91

JPOXMLDOC01-seq1

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser His Asp
 20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Gly Ile Ile Ser Tyr Ala Gly Lys Lys Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

Thr Leu Val Thr Val Ser Ser
 115

<210> 92

<211> 119

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 92

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

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

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
 50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
 85 90 95

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

JPOXMLDOC01-seqI

Thr Leu Val Thr Val Ser Ser
115

<210> 93
<211> 119
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<400> 93

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

Thr Leu Thr Leu Thr Cys Lys Val Ser Gly Ile Asp Leu Ser His Asp
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 94
<211> 119
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<400> 94

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

Thr Leu Thr Leu Thr Cys Lys Val Ser Gly Ile Asp Leu Ser His Glu
20 25 30

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

JPOXMLDOC01-seq1

Ser Ile Ile Ser Tyr Ala Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 95
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<220>
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<400> 95

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

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

Asp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ile Ile Ser Tyr Ala Gly Ser Lys Tyr Tyr Ala Ser Trp Ala Lys
50 55 60

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

Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

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

Thr Leu Val Thr Val Ser Ser
115

<210> 96
<211> 110
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JPOXMLDOC01-seqI

<220>

<223> An artificial ly synthesized sequence

<400> 96

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

Glu Arg Ala Thr Leu Ser Cys Thr Ser Ser Gln Ser Val Tyr His Ala
20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

Gly Arg Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 97

<211> 110

<212> PRT

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<223> An artificial ly synthesized sequence

<400> 97

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

Glu Arg Ala Thr Leu Ser Cys Thr Thr Ser Gln Ser Val Tyr His Glu
20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
85 90 95

JPOXMLDOC01-seq1

Gly Arg Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 98
 <211> 110
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 98

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

Glu Arg Ala Thr Leu Ser Cys Thr Ser Ser Gln Ser Val Phe His Glu
 20 25 30

Asn Trp Leu Ser Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
 35 40 45

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

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

Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys Ala Gly Gly Tyr Gly Gly
 85 90 95

Gly Arg Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 99
 <211> 110
 <212> PRT
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<220>
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<400> 99

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

Glu Arg Ala Thr Leu Ser Cys Thr Thr Ser Gln Ser Val Tyr His Glu
 20 25 30

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

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

JPOXMLDOC01-seq1

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

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

Gly Arg Tyr Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 100
 <211> 357
 <212> DNA
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<220>
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 acctgcacag tgagtgggat cgacctgagc cacgacgaca tctcctgggt gcggcaggca 120
 cccggaagg gcctggaatg ggtcggcatc attagctacg ccgggagcac atactatgcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcct 300
 gcttactctc acggagggga tctgtgggga caggaaccc tggtagacagt ctctagt 357

<210> 101
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 101
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 acctgcacag tgagtgggat cgacctgagc cacgacgaca tctcctgggt gcggcaggca 120
 cccggaagg gcctggaatg ggtcggcatc attagctacg ccgggagcat gtactatgcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcct 300
 gcttactctc acggagggga taagtgggga caggaaccc tggtagacagt ctctagt 357

<210> 102
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 <212> DNA
 <213> Artificial sequence

<220>
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<400> 102
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 acctgcacag tgagtgggat cgacctgagc cacaccgaca tctcctgggt gcggcaggca 120

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cccggaaagg gcctggaatg ggtcggcatc attagctacg ccggaagac atactatgcc 180
 agctgggcta aaaaaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcct 300
 gcttactctc acggagggga tctgtgggga caggaaccc tggtgacagt ctctagt 357

<210> 103
 <211> 357
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<220>
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 cccggaaagg gcctggaatg ggtcggcatc attagctacg ccggaagaa atactatgcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcct 300
 gcttactctc acggagggga tctgtgggga caggaaccc tggtgacagt ctctagt 357

<210> 104
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
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<400> 104
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 cccggaaagg gcctggaatg ggtcggcatc attagctacg ccgggagcaa atacaaggcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggacc cgtggataca gcaacttact attgtgccag gggcgtcct 300
 gcttactctc acggagggga tctgtgggga caggaaccc tggtgacagt ctctagt 357

<210> 105
 <211> 357
 <212> DNA
 <213> Artificial sequence

<220>
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<400> 105
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 cccggaaagg gcctggaatg ggtcggcatc attagctacg ccggaagaa atactatgcc 180

JPOXMLD0C01-seq1

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 actatgacca atatggaccc cgtggataca gcaacttact attgtgccag gggcgtccct 300
 gcttactctc acggagggga tctgtgggga caggaaccc tggtgacagt ctctagt 357

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 cccgggaagg gactggaatg ggtctctatc attagttacg ccggcagcac ctactatgcc 180
 tcttgggcta aaggcaggct gaccatttct aaggacacaa gtaaaaacca ggtggtcctg 240
 accatgacaa atatggaccc cgtggatact gcaacctact attgcgcccg gggcgtccct 300
 gcttatagcc acggcggcga tctgtgggga caggggacac tggtgactgt cagctcc 357

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 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240
 actatgacca atatggaccc cgtggataca gcaacttact attgtgccag gggcgtccct 300
 gcttactctc acggagggga tctgtgggga caggaaccc tggtgacagt ctctagt 357

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 cccggaaagg gcctggaatg ggtctccatc attagctacg ccgggagcac atactatgcc 180
 agctgggcta aaggaagact gactatctcc aaggacacct ctaaaaacca ggtggtcctg 240

JPOXMLD0C01-seq1

actatgacca atatggaccc cgtggataca gcaacttact attgtgccag gggcgtccct 300
gcttactctc acggagggga tctgtgggga cagggaaacc tggtgacagt ctctagt 357

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cccgggaagg gactggaatg ggtctctatc attagttacg ccggcagcaa gtactatgcc 180
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accatgacaa atatggaccc cgtggatact gcaacctact attgcgcccg gggcgtccct 300
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aagccagggc agccccctaa actgctgac tattgggcat caaactggc ctacggcgtc 180
ccctccagat tctccgatc tggcagtggg actgacttta ccctgacat cagcagcctc 240
cagcccagg atgccgctac ctactattgt gctggcgggt acggaggcgg gcggtatgca 300
tttgacagg gcacaaagg ggaatcaaa 330

<210> 111
<211> 330
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<400> 111
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aagccagggc agccccctaa actgctgac tattgggcat caaactggc ctacggcgtc 180
ccctccagat tctccgatc tggcagtggg actgacttta ccctgacat cagcagcctc 240
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 aagccagggc agccccctaa actgctgac tattgggcat caaactggc ctggggcgctc 180
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<210> 113
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 ccctccagat tctccgcat tggcagtggg actgacttta ccctgacct cagcagcctc 240
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<220>
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<400> 114
 His Asp Asp Ile Ser
 1 5

<210> 115
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<400> 115

His Glu Asp Ile Ser
1 5

<210> 116

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 116

Ile Ile Ser Tyr Ala Gly Ser Met Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 117

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 117

Ile Ile Ser Tyr Ala Gly Lys Thr Tyr Tyr Ala Ser Trp Ala Lys Lys
1 5 10 15

<210> 118

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 118

Ile Ile Ser Tyr Ala Gly Lys Lys Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 119

<211> 16

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<213> Artificial sequence

<220>

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<400> 119

Ile Ile Ser Tyr Ala Gly Ser Lys Tyr Lys Ala Ser Trp Ala Lys Gly
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<210> 120

<211> 16

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<220>

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<400> 120

Ile Ile Ser Tyr Ala Gly Ser Lys Tyr Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

<210> 121

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 121

Gly Val Pro Ala Tyr Ser His Gly Gly Asp Lys
1 5 10

<210> 122

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 122

Thr Ser Ser Gln Ser Val Tyr His Ala Asn Trp Leu Ser
1 5 10

<210> 123

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 123

Thr Thr Ser Gln Ser Val Tyr His Glu Asn Trp Leu Ser
1 5 10

<210> 124

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> An artificial ly synthesized sequence

<400> 124

Thr Ser Ser Gln Ser Val Phe His Glu Asn Trp Leu Ser
1 5 10

<210> 125

<211> 7

<212> PRT
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<220>
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<400> 125

Trp Ala Ser Thr Leu Ala Trp
 1 5

<210> 126
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 <223> Xaa is Ser or His

<220>
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 <222> (2)..(2)
 <223> Xaa is Tyr, Thr, Asp or Glu

<400> 126

Xaa Xaa Asp Ile Ser
 1 5

<210> 127
 <211> 16
 <212> PRT
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<220>
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<220>
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 <222> (4)..(4)
 <223> Xaa is Tyr or His

<220>
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 <222> (7)..(7)
 <223> Xaa is Ser or Lys

<220>
 <221> misc_feature
 <222> (8)..(8)
 <223> Xaa is Thr, Met or Lys

<220>
 <221> misc_feature
 <222> (10)..(10)
 <223> Xaa is Tyr or Lys

<220>
 <221> misc_feature

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<222> (11)..(11)
 <223> Xaa is Ala, Met or Glu

<220>
 <221> mi sc_feature
 <222> (12)..(12)
 <223> Xaa is Ser or Glu

<220>
 <221> mi sc_feature
 <222> (16)..(16)
 <223> Xaa is Gly or Lys

<400> 127

I l e I l e Ser Xaa Al a Gly Xaa Xaa Tyr Xaa Xaa Xaa Trp Al a Lys Xaa
 1 5 10 15

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<220>
 <221> mi sc_feature
 <222> (5)..(5)
 <223> Xaa is Tyr or Hi s

<220>
 <221> mi sc_feature
 <222> (7)..(7)
 <223> Xaa is Thr or Hi s

<220>
 <221> mi sc_feature
 <222> (11)..(11)
 <223> Xaa is Leu or Lys

<400> 128

G l y Val Pro Al a Xaa Ser Xaa Gly Gly Asp Xaa
 1 5 10

<210> 129
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 <223> Xaa is Gl n or Thr

<220>
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 <222> (2)..(2)
 <223> Xaa is Ser or Thr

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<222> (5)..(5)
<223> Xaa i s Ser or Gl u

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<222> (7)..(7)
<223> Xaa i s Tyr or Phe

<220>
<221> mi sc_feature
<222> (8)..(8)
<223> Xaa i s Asp or Hi s

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<221> mi sc_feature
<222> (9)..(9)
<223> Xaa i s Asn, Asp, Al a or Gl u

<400> 129

Xaa Xaa Ser Gl n Xaa Val Xaa Xaa Xaa Asn Trp Leu Ser
1 5 10

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<222> (3)..(3)
<223> Xaa i s Ser or Gl u

<220>
<221> mi sc_feature
<222> (7)..(7)
<223> Xaa i s Ser, Tyr, Phe or Trp

<400> 130

Trp Al a Xaa Thr Leu Al a Xaa
1 5

<210> 131
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<223> Xaa i s Leu or Arg

<400> 131

Al a Gly Gly Tyr Gly Gly Gly Xaa Tyr Al a

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<400> 132

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

Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser
 20 25 30

<210> 133
 <211> 30
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<400> 133

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

Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Ile Asp Leu Ser
 20 25 30

<210> 134
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<220>
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<400> 134

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

Thr Leu Thr Leu Thr Cys Lys Val Ser Gly Ile Asp Leu Ser
 20 25 30

<210> 135
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<400> 135

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Gly

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

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<400> 137

Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val Val Leu Thr
 1 5 10 15

Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
 20 25 30

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<400> 138

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 1 5 10

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<400> 139

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

Glu Arg Ala Thr Leu Ser Cys
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<400> 140

Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
 1 5 10 15

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<400> 141

Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
 1 5 10 15

<210> 142
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 <212> PRT
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<400> 142

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Ala Ala Thr Tyr Tyr Cys
 20 25 30

<210> 143
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<400> 143

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
 1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys
 20 25 30

<210> 144
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<400> 144

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 145

<211> 121

<212> PRT

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<400> 145

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

Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Arg Tyr Tyr
20 25 30

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

Ile Ile Tyr Thr Gly Gly Asn Thr Asn Tyr Ala Ser Trp Ala Lys Gly
50 55 60

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

Gly Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Gly Phe Leu
85 90 95

Asp Tyr Ser His Tyr Thr Thr Gly Gly Tyr Tyr Leu Asp Leu Trp Gly
100 105 110

Pro Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 146

<211> 119

<212> PRT

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<400> 146

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

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

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

Ala Cys Ile Tyr Ala Gly Ile Ser Gly Ser Thr Tyr Tyr Ala Ser Trp
 50 55 60

Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Ser Thr Thr Val Thr
 65 70 75 80

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

Ala Arg Asp Pro Tyr His Phe Asp Tyr Gly Ser Leu Trp Gly Pro Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

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<400> 147

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

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Arg Tyr Trp
 20 25 30

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

Ile Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
 50 55 60

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

Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Asp Ser
 85 90 95

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

Thr Val Ser Ser
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<400> 148

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

Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Ser Tyr Ile
 20 25 30

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

Phe Ile Tyr Val Ser Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
 50 55 60

Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu Arg Ile Thr
 65 70 75 80

Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Val Arg Thr Trp
 85 90 95

Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
 100 105

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 <211> 115
 <212> PRT
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<400> 149

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

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

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

Ile Ile Tyr Gly Val Gly Ser Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
 50 55 60

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

Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Asp Asp

Tyr Gly Trp Gly Tyr Thr Asn Leu Trp Gly Pro Gly Thr Leu Val Thr
 100 105 110

Val Ser Ser
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<400> 150

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

Leu Thr Leu Thr Cys Thr Val Ser Gly Ile Asp Leu Ser Ser Ser Ser
 20 25 30

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

Phe Ile Ser Lys Ser Gly Tyr Thr Tyr Tyr Ala Ser Trp Ala Lys Gly
 50 55 60

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

Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Gly Gly
 85 90 95

Tyr Ser Gly Asp Trp Asp Tyr Phe Thr Leu Trp Gly Pro Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 151
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<220>
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<400> 151

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

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

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

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

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Glu Phe Ser Cys Gly
85 90 95

Ser Ala Asp Cys Thr Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 152
<211> 112
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<400> 152

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

Gly Thr Val Thr Ile Asn Cys Gln Ala Ser Gln Ser Val Tyr Gly Gly
20 25 30

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

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

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

Gln Cys Asp Asp Ala Ala Ala Tyr Tyr Cys Ala Gly Tyr Arg Thr Tyr
85 90 95

Ser Asp Asp Asp Asn Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 153
<211> 112
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<400> 153

Gln Val Leu Thr Gln Thr Pro Ala Ser Val Ser Ala Ala Val Gly Gly
 1 5 10 15
 Thr Val Thr Ile Asn Cys Gln Ser Ser Gln Ser Val Ala Gly Asn Asp
 20 25 30
 Asn Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
 35 40 45
 Ile Tyr Tyr Ala Ser Asn Leu Ala Ser Gly Val Ser Ser Arg Phe Lys
 50 55 60
 Gly Ser Gly Ser Gly Thr Arg Phe Thr Leu Thr Ile Ser Asp Val Gln
 65 70 75 80
 Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Asn Tyr Asp Cys Ser
 85 90 95
 Ser Ala Asp Cys Asp Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 154

<211> 109

<212> PRT

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<400> 154

Gln Val Leu Thr Gln Thr Pro Ser Ser Thr Ser Ala Ala Val Gly Gly
 1 5 10 15
 Thr Val Thr Ile Asn Cys Gln Ser Ser Gln Ser Val Tyr Asp Asn Asn
 20 25 30
 Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Arg Leu
 35 40 45
 Ile Tyr Gly Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Lys
 50 55 60
 Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Asp Leu Glu
 65 70 75 80
 Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Gly Tyr Ser Gly Asn
 85 90 95
 Ile Tyr Pro Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

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<210> 155
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<400> 155

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

Thr Val Thr Ile Asn Cys Gln Ser Ser Gln Ser Val Tyr Asn Asn Asn
 20 25 30

Tyr Leu Ala Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu
 35 40 45

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

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

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Ser Tyr Tyr Ser Ser
 85 90 95

Gly Trp Tyr Arg Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 156
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<400> 156

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

Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser Glu Ser Ile Gly Asn
 20 25 30

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

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

Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu Thr Ile Ser Asp Leu Glu
 65 70 75 80

JPOXMLDOC01-seqI

Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gly Tyr Phe Trp Ser Ser
85 90 95

Ser Thr Ile Tyr Ala Phe Trp Ala Phe Gly Gly Gly Thr Lys Val Glu
100 105 110

Ile Lys

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<400> 157

Arg Tyr Tyr Val Ser
1 5

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Ser Tyr Tyr Tyr Met Cys
1 5

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Arg Tyr Trp Met Ser
1 5

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Ser Tyr Ile Met Gly
1 5

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Ser Tyr Ala Met Ser
1 5

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Ser Ser Ser Met Ile
1 5

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<400> 163

Ile Ile Tyr Thr Gly Gly Asn Thr Asn Tyr Ala Ser Trp Ala Lys Gly
1 5 10 15

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<400> 164

Cys Ile Tyr Ala Gly Ile Ser Gly Ser Thr Tyr Tyr Ala Ser Trp Ala
1 5 10 15

Lys Gly

<210> 165
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<400> 165

I l e I l e S e r S e r G l y G l y T h r T h r T y r T y r A l a S e r T r p A l a L y s G l y
1 5 10 15

<210> 166

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<223> A n a r t i f i c i a l l y s y n t h e s i z e d s e q u e n c e

<400> 166

P h e I l e T y r V a l S e r G l y S e r T h r T y r T y r A l a S e r T r p A l a L y s G l y
1 5 10 15

<210> 167

<211> 16

<212> PRT

<213> A r t i f i c i a l s e q u e n c e

<220>

<223> A n a r t i f i c i a l l y s y n t h e s i z e d s e q u e n c e

<400> 167

I l e I l e T y r G l y V a l G l y S e r T h r T y r T y r A l a S e r T r p A l a L y s G l y
1 5 10 15

<210> 168

<211> 16

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<220>

<223> A n a r t i f i c i a l l y s y n t h e s i z e d s e q u e n c e

<400> 168

P h e I l e S e r L y s S e r G l y T y r T h r T y r T y r A l a S e r T r p A l a L y s G l y
1 5 10 15

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<211> 16

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<220>

<223> A n a r t i f i c i a l l y s y n t h e s i z e d s e q u e n c e

<400> 169

P h e L e u A s p T y r S e r H i s T y r T h r T h r G l y G l y T y r T y r L e u A s p L e u
1 5 10 15

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<211> 10

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Asp Pro Tyr His Phe Asp Tyr Gly Ser Leu
1 5 10

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Asp Ser Arg Tyr Gly Ala Ala Arg Leu Asp Leu
1 5 10

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Thr Trp Asp Leu
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<400> 173

Asp Asp Tyr Gly Trp Gly Tyr Thr Asn Leu
1 5 10

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<220>
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<400> 174

Gly Gly Tyr Ser Gly Asp Trp Asp Tyr Phe Thr Leu
1 5 10

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Gln Ala Ser Gln Ser Val Tyr Asn Asn Lys Asn Leu Ala
1 5 10

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<400> 176

Gln Ala Ser Gln Ser Val Tyr Gly Gly Asn Glu Leu Ser
1 5 10

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<400> 177

Gln Ser Ser Gln Ser Val Ala Gly Asn Asp Asn Leu Ala
1 5 10

<210> 178

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<400> 178

Gln Ser Ser Gln Ser Val Tyr Asp Asn Asn Trp Leu Ala
1 5 10

<210> 179

<211> 13

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<400> 179

Gln Ser Ser Gln Ser Val Tyr Asn Asn Asn Tyr Leu Ala
1 5 10

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Gln Ala Ser Glu Ser Ile Gly Asn Ala Leu Ala
 1 5 10

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<400> 181

Tyr Ala Ser Thr Leu Pro Ser
 1 5

<210> 182
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<400> 182

Ser Ala Ser Lys Leu Ala Ser
 1 5

<210> 183
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<400> 183

Tyr Ala Ser Asn Leu Ala Ser
 1 5

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<400> 184

Gly Ala Ser Thr Leu Asp Ser
 1 5

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Asp Ala Ser Lys Leu Ala Ser
1 5

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<211> 7
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Gly Ala Phe Asn Leu Glu Ser
1 5

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Gln Gly Glu Phe Ser Cys Gly Ser Ala Asp Cys Thr Ala
1 5 10

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<400> 188

Ala Gly Tyr Arg Thr Tyr Ser Asp Asp Asp Asn Ala
1 5 10

<210> 189
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Leu Gly Asn Tyr Asp Cys Ser Ser Ala Asp Cys Asp Ala

1

5

10

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<400> 190

Gln Gly Gly Tyr Ser Gly Asn Ile Tyr Pro
 1 5 10

<210> 191
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<400> 191

Gln Gly Ser Tyr Tyr Ser Ser Gly Trp Tyr Arg Ala
 1 5 10

<210> 192
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<400> 192

Gln Gly Tyr Phe Trp Ser Ser Ser Thr Ile Tyr Ala Phe Trp Ala
 1 5 10 15

<210> 193
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<400> 193

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

JPOXMLDOC01-seq1

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Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Gl u Leu Arg Arg Gl y Pro Lys Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Asn His Tyr Thr
305 310 315 320

Gl n Lys Ser Leu Ser Leu Ser Pro

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 <212> DNA
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

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 tggagggtgg ataacgcct ccaatcgggt aactcccagg agagtgtcac agagcaggac 180
 agtaaggact gcacctacag tctcagtagt accctgacgc tgtccaaagc agactacgag 240
 aacacaaaag tctacgcctg cgaagtcacc catcagggcc tgtcctcgcc cgtcaciaaag 300
 tcctcaaca ggggagagtg ttga 324

<210> 195
 <211> 330
 <212> PRT
 <213> Homo sapiens

<400> 195
 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
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 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

JPOXMLDOC01-seq1

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 196
<211> 326
<212> PRT
<213> Homo sapiens

<400> 196

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
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Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
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Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

JPOXMLDOC01-seq1
60

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55

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gl n Thr
65 70 75 80

Tyr Thr Cys Asn Val Asp Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Thr Val Gl u Arg Lys Cys Cys Val Gl u Cys Pro Pro Cys Pro Al a Pro
100 105 110

Pro Val Al a Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys Val Val Val Asp
130 135 140

Val Ser Hi s Gl u Asp Pro Gl u Val Gl n Phe Asn Trp Tyr Val Asp Gly
145 150 155 160 165

Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u Gl u Gl n Phe Asn
165 170 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val Hi s Gl n Asp Trp
180 185 190

Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
195 200 205

Al a Pro Ile Gl u Lys Thr Ile Ser Lys Thr Lys Gly Gl n Pro Arg Gl u
210 215 220

Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u Met Thr Lys Asn
225 230 235 240

Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255

Al a Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn Asn Tyr Lys Thr
260 265 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn Val Phe Ser Cys
290 295 300

Ser Val Met Hi s Gl u Al a Leu Hi s Asn Hi s Tyr Thr Gl n Lys Ser Leu
305 310 315 320

Ser Leu Ser Pro Gly Lys

325

<210> 197
 <211> 377
 <212> PRT
 <213> Homo sapiens

<400> 197

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
 100 105 110

Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
 115 120 125

Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
 130 135 140

Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
 145 150 155 160

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 165 170 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 180 185 190

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
 195 200 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 210 215 220

Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
 225 230 235 240

JPOXMLDOC01-seq1

Gln Asp Trp Leu Asn 245 Gly Lys Glu Tyr Lys 250 Cys Lys Val Ser Asn 255 Lys

Ala Leu Pro Ala 260 Pro Ile Glu Lys Thr 265 Ile Ser Lys Thr Lys 270 Gly Gln

Pro Arg Glu 275 Pro Gln Val Tyr Thr 280 Leu Pro Pro Ser Arg 285 Glu Glu Met

Thr Lys 290 Asn Gln Val Ser Leu 295 Thr Cys Leu Val Lys 300 Gly Phe Tyr Pro

Ser 305 Asp Ile Ala Val Glu 310 Trp Glu Ser Ser Gly 315 Gln Pro Glu Asn 320 Asn

Tyr Asn Thr Thr Pro 325 Pro Met Leu Asp Ser 330 Asp Gly Ser Phe 335 Phe Leu

Tyr Ser Lys Leu 340 Thr Val Asp Lys Ser 345 Arg Trp Gln Gln Gly 350 Asn Ile

Phe Ser Cys 355 Ser Val Met His Glu 360 Ala Leu His Asn 365 Arg Phe Thr Gln

Lys Ser 370 Leu Ser Leu Ser Pro 375 Gly Lys

<210> 198
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 <212> PRT
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<400> 198

Ala Ser Thr Lys 5 Gly Pro Ser Val Phe Pro 10 Leu Ala Pro Cys Ser 15 Arg

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

Phe Pro Glu 35 Pro Val Thr Val Ser 40 Trp Asn Ser Gly 45 Ala Leu Thr Ser

Gly Val 50 His Thr Phe Pro Ala 55 Val Leu Gln Ser Ser 60 Gly Leu Tyr Ser

Leu Ser Ser Val Val 70 Thr Val Pro Ser Ser 75 Leu Gly Thr Lys 80 Thr

Tyr Thr Cys Asn 85 Val Asp His Lys Pro Ser 90 Asn Thr Lys Val 95 Asp Lys

JPOXMLDOC01-seq1

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
 100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 195 200 205

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

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
 290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 305 310 315 320

Leu Ser Leu Ser Leu Gly Lys
 325

<210> 199
 <211> 1125
 <212> DNA
 <213> Homo sapiens

<400> 199
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 cacagaggct ggctactact gcaggctctcc agcagagtct tcacggaagg agaacctctg 360
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 aaaaagtggg atttagaaat ctctttgat tctggtcatg agaagaaggt aatttccagc 1020
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<210> 200
 <211> 951
 <212> DNA
 <213> Homo sapiens

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 gtgctgaaac ttgagcccc gtggatcaac gtgctccagg aggactctgt gactctgaca 180
 tgccaggggg ctcgcagccc tgagagcgac tccattcagt ggttccacaa tgggaatctc 240
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 tacacgtgcc agactggcca gaccagctc agcgaccctg tgcatctgac tgtgctttcc 360
 gaatggctgg tgctccagac ccctcacctg gagttccagg agggagaaac catcatgctg 420
 aggtgccaca gctggaagga caagcctctg gtcaaggcca cattcttcca gaatggaaaa 480
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 agtggtgatt accactgcac aggaacata ggctacacgc tgttctcatc caagcctgtg 600
 accatcactg tccaagtgcc cagcatgggc agctcttcac caatgggggt cattgtggct 660
 gtggtcattg cgactgctgt agcagccatt gttgctgctg tagtggcctt gatctactgc 720

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 gaaacagctg acggcggcta catgactctg aaccccaggg cacctactga cgatgataaa 900
 aacatctacc tgactcttcc tcccaacgac catgtcaaca gtaataacta a 951

<210> 201
 <211> 954
 <212> DNA
 <213> Homo sapiens

<400> 201
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 aaaaacatct acctgactct tcttccaac gaccatgtca acagtaataa ctaa 954

<210> 202
 <211> 876
 <212> DNA
 <213> Homo sapiens

<400> 202
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 ttctccatcc cacaagcaaa ccacagtcac agtggtgatt accactgcac aggaaacata 600
 ggctacacgc tgtactcatc caagcctgtg accatcactg tccaagctcc cagctcttca 660
 ccgatgggga tcattgtggc tgtggtcact gggattgctg tagcggccat tgttgctgct 720
 gtagtggcct tgatctactg caggaaaaag cggatttcag ccaatcccac taatcctgat 780
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 gctctggaag agcctgatga ccagaaccgt atttag 876

<210> 203
 <211> 933
 <212> DNA
 <213> Homo sapiens

<400> 203
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 tgcaaggaaa tgggagagac cctccctgag aaaccagcca atcccactaa tcctgatgag 840
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 ctggaagagc ctgatgacca gaaccgtatt tag 933

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 <211> 765
 <212> DNA
 <213> Homo sapiens

<400> 204
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 gacagtgtga ctctgaagtg ccaggagacc tactcccctg aggacaattc cacacagtgg 180

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 cagctagaag tccatatcgg ctggctgttg ctccaggccc ctcggtgggt gttcaaggag 360
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 tcattctttc cacctgggta ccaagtctct ttctgcttgg tgatggtact cctttttgca 660
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 <212> DNA
 <213> Homo sapiens

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 tttcacaatg agagcctcat ctcaagccag gcctcgagct acttcattga cgctgccaca 240
 gtcgacgaca gtggagagta caggtgccag acaaacctct ccaccctcag tgacccggtg 300
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 tatttacaga atggcaaagg caggaagtat tttcatcata attctgactt ctacattcca 480
 aaagccacac tcaaagacag cggctcctac ttctgcaggg ggctttttgg gagtaaaaat 540
 gtgtcttcag agactgtgaa catcaccatc actcaagggt tggcagtgtc aaccatctca 600
 tcattctttc cacctgggta ccaagtctct ttctgcttgg tgatggtact cctttttgca 660
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 aaggaccata aatttaaag gagaaaggac cctcaagaca aatga 765

<210> 206
 <211> 702
 <212> DNA
 <213> Homo sapiens

<400> 206
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 gacagtgtga ctctgaagtg ccaggagacc tactcccctg aggacaattc cacacagtgg 180
 tttcacaatg agagcctcat ctcaagccag gcctcgagct acttcattga cgctgccaca 240

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 tcattctctc cacctgggta ccaagtctct ttctgcttgg tgatggtact cctttttgca 660
 gtggacacag gactatattt ctctgtgaag acaaacattt ga 702

<210> 207
 <211> 374
 <212> PRT
 <213> Homo sapiens

<400> 207

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 Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp Val Ser
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 Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu His Leu
 35 40 45
 Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr Gln
 50 55 60
 Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn Asp Ser
 65 70 75 80
 Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro Ile
 85 90 95
 Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser Ser Arg
 100 105 110
 Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp Lys
 115 120 125
 Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala Phe
 130 135 140
 Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn Ile
 145 150 155 160
 Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His Arg Tyr
 165 170 175

JPOXMLDOC01-seq1

Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro Ala Pro
 180 185 190

Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn Leu Val
 195 200 205

Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Glu Arg Pro Gly Leu Glu
 210 215 220

Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly Arg Asn
 225 230 235 240

Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp Ser Gly
 245 250 255

Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Gly Asn Val Leu Lys Arg
 260 270

Ser Pro Glu Leu Glu Leu Gln Val Leu Gly Leu Gln Leu Pro Thr Pro
 275 280 285

Val Trp Phe His Val Leu Phe Tyr Leu Ala Val Gly Ile Met Phe Leu
 290 295 300

Val Asn Thr Val Leu Trp Val Thr Ile Arg Lys Glu Leu Lys Arg Lys
 305 310 315 320

Lys Lys Trp Asp Leu Glu Ile Ser Leu Asp Ser Gly His Glu Lys Lys
 325 330 335

Val Ile Ser Ser Leu Gln Glu Asp Arg His Leu Glu Glu Glu Leu Lys
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Glu Pro Gln Gly Ala Thr
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I l e A s n V a l L e u G l n G l u A s p S e r V a l T h r L e u T h r C y s G l n G l y A l a
50 55 60

A r g S e r P r o G l u S e r A s p S e r I l e G l n T r p P h e H i s A s n G l y A s n L e u
65 70 75 80

I l e P r o T h r H i s T h r G l n P r o S e r T y r A r g P h e L y s A l a A s n A s n A s n
85 90 95

A s p S e r G l y G l u T y r T h r C y s G l n T h r G l y G l n T h r S e r L e u S e r A s p
100 105 110

P r o V a l H i s L e u T h r V a l L e u S e r G l u T r p L e u V a l L e u G l n T h r P r o
115 120 125

H i s L e u G l u P h e G l n G l u G l y G l u T h r I l e M e t L e u A r g C y s H i s S e r
130 135 140

T r p L y s A s p L y s P r o L e u V a l L y s V a l T h r P h e P h e G l n A s n G l y L y s
145 150 155 160

S e r G l n L y s P h e S e r H i s L e u A s p P r o T h r P h e S e r I l e P r o G l n A l a
165 170 175

A s n H i s S e r H i s S e r G l y A s p T y r H i s C y s T h r G l y A s n I l e G l y T y r
180 185 190

T h r L e u P h e S e r S e r L y s P r o V a l T h r I l e T h r V a l G l n V a l P r o S e r
195 200 205

M e t G l y S e r S e r S e r P r o M e t G l y V a l I l e V a l A l a V a l V a l I l e A l a
210 215 220

T h r A l a V a l A l a A l a I l e V a l A l a A l a V a l V a l A l a L e u I l e T y r C y s
225 230 235 240

A r g L y s L y s A r g I l e S e r A l a A s n S e r T h r A s p P r o V a l L y s A l a A l a
245 250 255

G l n P h e G l u P r o P r o G l y A r g G l n M e t I l e A l a I l e A r g L y s A r g G l n
260 265 270

L e u G l u G l u T h r A s n A s n A s p T y r G l u T h r A l a A s p G l y G l y T y r M e t
275 280 285

T h r L e u A s n P r o A r g A l a P r o T h r A s p A s p A s p L y s A s n I l e T y r L e u
290 295 300

T h r L e u P r o P r o A s n A s p H i s V a l A s n S e r A s n A s n
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Ser Gln Ala Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro
35 40 45

Trp Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Gln Gly
50 55 60

Ala Arg Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn
65 70 75 80

Leu Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn
85 90 95

Asn Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser
100 105 110

Asp Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr
115 120 125

Pro His Leu Glu Phe Gln Glu Gly Glu Thr Ile Met Leu Arg Cys His
130 135 140

Ser Trp Lys Asp Lys Pro Leu Val Lys Val Thr Phe Phe Gln Asn Gly
145 150 155 160 165

Lys Ser Gln Lys Phe Ser His Leu Asp Pro Thr Phe Ser Ile Pro Gln
165 170 175

Ala Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly
180 185 190

Tyr Thr Leu Phe Ser Ser Lys Pro Val Thr Ile Thr Val Gln Val Pro
195 200 205

Ser Met Gly Ser Ser Ser Pro Met Gly Ile Ile Val Ala Val Val Ile
210 215 220

Ala Thr Ala Val Ala Ala Ile Val Ala Ala Val Val Ala Leu Ile Tyr
225 230 235 240

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Cys Arg Lys Lys Arg Ile Ser Ala Asn Ser Thr Asp Pro Val Lys Ala
 245 250 255

Ala Gln Phe Glu Pro Pro Gly Arg Gln Met Ile Ala Ile Arg Lys Arg
 260 265 270

Gln Leu Glu Glu Thr Asn Asn Asp Tyr Glu Thr Ala Asp Gly Gly Tyr
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Ser Gln Ala Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro
 35 40 45

Trp Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Gln Gly
 50 55 60

Ala Arg Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn
 65 70 75 80

Leu Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn
 85 90 95

Asn Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser
 100 105 110

Asp Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr
 115 120 125

Pro His Leu Glu Phe Gln Glu Gly Glu Thr Ile Met Leu Arg Cys His
 130 135 140

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

JPOXMLDOC01-seq1

Lys Ser Gln Lys Phe Ser Arg Leu Asp Pro Thr Phe Ser Ile Pro Gln
 165 170 175

Ala Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly
 180 185 190

Tyr Thr Leu Phe Ser Ser Lys Pro Val Thr Ile Thr Val Gln Val Pro
 195 200 205

Ser Met Gly Ser Ser Ser Pro Met Gly Ile
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Met Thr Met Glu Thr Gln Met Ser Gln Asn Val Cys Pro Arg Asn Leu
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Trp Leu Leu Gln Pro Leu Thr Val Leu Leu Leu Ala Ser Ala Asp
 20 25 30

Ser Gln Ala Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro
 35 40 45

Trp Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Gln Gly
 50 55 60

Ala Arg Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn
 65 70 75 80

Leu Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn
 85 90 95

Asn Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser
 100 105 110

Asp Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr
 115 120 125

Pro His Leu Glu Phe Gln Glu Gly Glu Thr Ile Met Leu Arg Cys His
 130 135 140

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

Lys Ser Gln Lys Phe Ser His Leu Asp Pro Thr Phe Ser Ile Pro Gln
 165 170 175

JPOXMLDOC01-seq1

Ala Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly
 180 185 190

Tyr Thr Leu Phe Ser Ser Lys Pro Val Thr Ile Thr Val Gln Val Pro
 195 200 205

Ser Met Gly Ser Ser Ser Pro Met Gly Ile
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 20 25 30

Ala Val Leu Phe Leu Ala Pro Val Ala Gly Thr Pro Ala Ala Pro Pro
 35 40 45

Lys Ala Val Leu Lys Leu Glu Pro Gln Trp Ile Asn Val Leu Gln Glu
 50 55 60

Asp Ser Val Thr Leu Thr Cys Arg Gly Thr His Ser Pro Glu Ser Asp
 65 70 75 80

Ser Ile Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
 85 90 95

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Thr
 100 105 110

Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp Pro Val His Leu Thr Val
 115 120 125

Leu Ser Glu Trp Leu Val Leu Gln Thr Pro His Leu Glu Phe Gln Glu
 130 135 140

Gly Glu Thr Ile Val Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu
 145 150 155 160

Val Lys Val Thr Phe Phe Gln Asn Gly Lys Ser Lys Lys Phe Ser Arg
 165 170 175

Ser Asp Pro Asn Phe Ser Ile Pro Gln Ala Asn His Ser His Ser Gly
 180 185 190

Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr Thr Leu Tyr Ser Ser Lys
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195

200

205

Pro Val Thr Ile Thr Val Gln Ala Pro Ser Ser Ser Pro Met Gly Ile
210 215 220

Ile Val Ala Val Val Thr Gly Ile Ala Val Ala Ala Ile Val Ala Ala
225 230 235 240

Val Val Ala Leu Ile Tyr Cys Arg Lys Lys Arg Ile Ser Ala Asn Pro
245 250 255

Thr Asn Pro Asp Glu Ala Asp Lys Val Gly Ala Glu Asn Thr Ile Thr
260 265 270

Tyr Ser Leu Leu Met His Pro Asp Ala Leu Glu Glu Pro Asp Asp Gln
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Asn Arg Ile
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20 25 30

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35 40 45

Lys Ala Val Leu Lys Leu Glu Pro Gln Trp Ile Asn Val Leu Gln Glu
50 55 60

Asp Ser Val Thr Leu Thr Cys Arg Gly Thr His Ser Pro Glu Ser Asp
65 70 75 80

Ser Ile Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
85 90 95

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Thr
100 105 110

Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp Pro Val His Leu Thr Val
115 120 125

Leu Ser Glu Trp Leu Val Leu Gln Thr Pro His Leu Glu Phe Gln Glu
130 135 140

JPOXMLDOC01-seq1

Gly 145 Glu Thr Ile Val Leu 150 Arg Cys His Ser Trp 155 Lys Asp Lys Pro Leu 160

Val Lys Val Thr Phe 165 Phe Gln Asn Gly Lys 170 Ser Lys Lys Phe Ser 175 Arg

Ser Asp Pro Asn 180 Phe Ser Ile Pro Gln 185 Ala Asn His Ser His Ser Gly

Asp Tyr His 195 Cys Thr Gly Asn 200 Ile Gly Tyr Thr Leu Tyr 205 Ser Ser Lys

Pro Val 210 Thr Ile Thr Val Gln 215 Ala Pro Ser Ser Ser 220 Pro Met Gly Ile

Ile 225 Val Ala Val Val Thr 230 Gly Ile Ala Val Ala 235 Ala Ile Val Ala 240

Val Val Ala Leu Ile 245 Tyr Cys Arg Lys Lys 250 Arg Ile Ser Ala Leu 255 Pro

Gly Tyr Pro Glu 260 Cys Arg Glu Met Gly 265 Glu Thr Leu Pro Glu 270 Lys Pro

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Asp Asp Gln Asn Arg Ile 310

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Lys Ala Val Leu Lys Leu Glu 55 Pro Gln Trp Ile Asn Val Leu Gln Glu 60

JPOXMLDOC01-seq1

Asp Ser Val Thr Leu Thr Cys Arg Gly Thr His Ser Pro Glu Ser Asp
65 70 75 80

Ser Ile Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
85 90 95

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Thr
100 105 110

Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp Pro Val His Leu Thr Val
115 120 125

Leu Ser Glu Trp Leu Val Leu Gln Thr Pro His Leu Glu Phe Gln Glu
130 135 140

Gly Glu Thr Ile Val Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu
145 150 155 160

Val Lys Val Thr Phe Phe Gln Asn Gly Lys Ser Lys Lys Phe Ser Arg
165 170 175

Ser Asp Pro Asn Phe Ser Ile Pro Gln Ala Asn His Ser His Ser Gly
180 185 190

Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr Thr Leu Tyr Ser Ser Lys
195 200 205

Pro Val Thr Ile Thr Val Gln Ala Pro
210 215

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20 25 30

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35 40 45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
50 55 60

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65 70 75 80

JPOXMLDOC01-seq1

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

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
 100 105 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
 115 120 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
 130 135 140

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
 145 150 155 160 165 170

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
 165 170 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
 180 185 190

Gly Leu Ser Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
 195 200 205

Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gly
 210 215 220

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 225 230 235 240

Lys Asp His Lys Phe Lys Trp Arg Lys Asp Pro Gln Asp Lys
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 20 25 30

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
 35 40 45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
 50 55 60

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
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JPOXMLDOC01-seq1

65 70 75 80

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

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
100 105 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
115 120 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
130 135 140

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
145 150 155 160

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Phe
165 170 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
180 185 190

Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
195 200 205

Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gly
210 215 220

Leu Tyr Phe Ser Val Lys Thr Asn Ile Arg Ser Ser Thr Arg Asp Trp
225 230 235 240

Lys Asp His Lys Phe Lys Trp Arg Lys Asp Pro Gln Asp Lys
245 250

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<213> Homo sapiens

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20 25 30

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
35 40 45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
50 55 60

JPOXMLDOC01-seqI

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65 70 75 80

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

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
100 105 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
115 120 125

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
130 135 140

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
145 150 155 160 165

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Phe
165 170 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
180 185 190

Gly Leu Ala Val Ser Thr Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
195 200 205

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20 25 30

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
35 40 45

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
50 55 60

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
65 70 75 80

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

JPOXMLDOC01-seq1

Ser Asp Pro Val 100 Gln Leu Glu Val 105 His Ile Gly Trp Leu 110 Leu Leu Gln

Ala Pro Arg 115 Trp Val Phe Lys Glu 120 Glu Asp Pro Ile His 125 Leu Arg Cys

His 130 Ser Trp Lys Asn Thr Ala 135 Leu His Lys Val Thr 140 Tyr Leu Gln Asn

Gly 145 Lys Gly Arg Lys Tyr 150 Phe His His Asn Ser 155 Asp Phe Tyr Ile Pro 160

Lys Ala Thr Leu Lys 165 Asp Ser Gly Ser Tyr 170 Phe Cys Arg Gly Leu 175 Val

Gly Ser Lys Asn 180 Val Ser Ser Glu Thr 185 Val Asn Ile Thr Ile Thr Gln

Gly Leu Ala 195 Val Ser Thr Ile Ser 200 Ser Phe Phe Pro 205 Pro Gly Tyr Gln

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Gly Ala Tyr 50 Ser Pro Glu Asp 55 Asn Ser Thr Gln Trp 60 Phe His Asn Glu

Ser Leu Ile 65 Ser Ser Gln 70 Ala Ser Ser Tyr Phe 75 Ile Asp Ala Ala Thr 80

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

Ser Asp Pro Val 100 Gln Leu Glu Val 105 His Ile Gly Trp Leu 110 Leu Leu Gln

Ala Pro Arg 115 Trp Val Phe Lys Glu 120 Glu Asp Pro Ile His 125 Leu Arg Cys

JPOXMLDOC01-seq1

Hi s Ser Trp Lys Asn Thr Ala Leu Hi s Lys Val Thr Tyr Leu Gl n Asn
 130 135 140

Gl y Lys Asp Arg Lys Tyr Phe Hi s Hi s Asn Ser Asp Phe Hi s Ile Pro
 145 150 155 160

Lys Ala Thr Leu Lys Asp Ser Gl y Ser Tyr Phe Cys Arg Gl y Leu Val
 165 170 175

Gl y Ser Lys Asn Val Ser Ser Gl u Thr Val Asn Ile Thr Ile Thr Gl n
 180 185 190

Gl y Leu Ala Val Ser Thr Ile Ser Ser Phe Ser Pro Pro Gl y Tyr Gl n
 195 200 205

Val Ser Phe Cys Leu Val Met Val Leu Leu Phe Ala Val Asp Thr Gl y
 210 215 220

Leu Tyr Phe Ser Val Lys Thr Asn Ile
 225 230

- <210> 220
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- <213> Macaca fasci cul ari s
- <400> 220

Met Ser Gl n Asn Val Cys Pro Gl y Asn Leu Trp Leu Leu Gl n Pro Leu
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Lys Ala Val Leu Lys Leu Gl u Pro Pro Trp Ile Asn Val Leu Arg Gl u
 35 40 45

Asp Ser Val Thr Leu Thr Cys Gl y Gl y Ala Hi s Ser Pro Asp Ser Asp
 50 55 60

Ser Thr Gl n Trp Phe Hi s Asn Gl y Asn Leu Ile Pro Thr Hi s Thr Gl n
 65 70 75 80

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gl y Gl u Tyr Arg
 85 90 95

Cys Gl n Thr Gl y Arg Thr Ser Leu Ser Asp Pro Val Hi s Leu Thr Val
 100 105 110

Leu Ser Gl u Trp Leu Ala Leu Gl n Thr Pro Hi s Leu Gl u Phe Arg Gl u
 115 120 125

Gl y Gl u Thr Ile Met Leu Arg Cys Hi s Ser Trp Lys Asp Lys Pro Leu

JPOXMLDOC01-seq1

130

135

140

I l e L y s V a l T h r P h e P h e G l n A s n G l y I l e A l a L y s L y s P h e S e r H i s
145 150 160

M e t A s p P r o A s n P h e S e r I l e P r o A r g A l a A s n H i s S e r H i s S e r G l y
165 170 175

A s p T y r H i s C y s T h r G l y A s n I l e G l y T y r T h r P r o T y r S e r S e r L y s
180 185 190

P r o V a l T h r I l e T h r V a l G l n V a l P r o S e r V a l G l y S e r S e r S e r P r o
195 200 205

M e t G l y I l e
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T h r V a l L e u L e u L e u L e u A l a S e r A l a A s p S e r G l n T h r A l a P r o P r o
20 25 30

L y s A l a V a l L e u L y s L e u G l u P r o P r o T r p I l e A s n V a l L e u A r g G l u
35 40 45

A s p S e r V a l T h r L e u T h r C y s G l y G l y A l a H i s S e r P r o A s p S e r A s p
50 55 60

S e r T h r G l n T r p P h e H i s A s n G l y A s n L e u I l e P r o T h r H i s T h r G l n
65 70 75 80

P r o S e r T y r A r g P h e L y s A l a A s n A s n A s n A s p S e r G l y G l u T y r A r g
85 90 95

C y s G l n T h r G l y A r g T h r S e r L e u S e r A s p P r o V a l H i s L e u T h r V a l
100 105 110

L e u S e r G l u T r p L e u A l a L e u G l n T h r T h r H i s L e u G l u P h e A r g G l u
115 120 125

G l y G l u T h r I l e M e t L e u A r g C y s H i s S e r T r p L y s A s p L y s P r o L e u
130 135 140

I l e L y s V a l A l a P h e P h e G l n A s n G l y L y s S e r L y s A s n P h e S e r H i s
145 150 155 160

JPOXMLDOC01-seq1

Met Asn Pro Asn Phe Ser Ile Pro Gln Ala Asn His Ser His Ser Gly
 165 170 175

Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr Thr Pro Tyr Ser Ser Lys
 180 185 190

Pro Val Thr Ile Thr Val Gln Val Pro Ser Val Gly Ser Ser Ser Pro
 195 200 205

Met Gly Ile
 210

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Met Ser Gln Asn Val Cys Pro Gly Asn Leu Trp Leu Leu Gln Pro Leu
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Thr Val Leu Leu Leu Ala Ser Ala Asp Ser Gln Thr Ala Pro Pro
 20 25 30

Lys Ala Val Leu Lys Leu Glu Pro Pro Trp Ile Asn Val Leu Arg Glu
 35 40 45

Asp Ser Val Thr Leu Thr Cys Gly Gly Ala His Ser Pro Asp Ser Asp
 50 55 60

Ser Thr Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
 65 70 75 80

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Arg
 85 90 95

Cys Gln Thr Gly Arg Thr Ser Leu Ser Asp Pro Val His Leu Thr Val
 100 105 110

Leu Ser Glu Trp Leu Ala Leu Gln Thr Thr His Leu Glu Phe Arg Glu
 115 120 125

Gly Glu Thr Ile Met Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu
 130 135 140

Ile Lys Val Ala Phe Phe Gln Asn Gly Ile Ser Lys Lys Phe Ser Pro
 145 150 155 160

Met Asn Pro Asn Phe Ser Ile Pro Arg Ala Asn His Ser His Ser Gly
 165 170 175

JPOXMLDOC01-seq1

Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr Thr Pro Tyr Ser Ser Lys
 180 185 190

Pro Val Thr Ile Thr Val Gln Val Pro Ser Val Gly Ser Ser Ser Pro
 195 200 205

Met Gly Ile
 210

<210> 223
 <211> 217
 <212> PRT
 <213> Macaca fascicularis
 <400> 223

Met Gly Ile Leu Ser Phe Leu Pro Val Leu Ala Thr Glu Ser Asp Trp
 1 5 10 15

Ala Asp Cys Lys Ser Ser Gln Pro Trp Gly His Met Leu Leu Trp Thr
 20 25 30

Ala Val Leu Phe Leu Ala Pro Val Ala Gly Thr Pro Ala Ala Pro Pro
 35 40 45

Lys Ala Val Leu Lys Leu Glu Pro Pro Trp Ile Asn Val Leu Arg Glu
 50 55 60

Asp Ser Val Thr Leu Thr Cys Gly Gly Ala His Ser Pro Asp Ser Asp
 65 70 75 80

Ser Thr Gln Trp Phe His Asn Gly Asn Leu Ile Pro Thr His Thr Gln
 85 90 95

Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser Gly Glu Tyr Arg
 100 105 110

Cys Gln Thr Gly Arg Thr Ser Leu Ser Asp Pro Val His Leu Thr Val
 115 120 125

Leu Ser Glu Trp Leu Ala Leu Gln Thr Pro His Leu Glu Phe Arg Glu
 130 135 140

Gly Glu Thr Ile Met Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu
 145 150 155 160

Ile Lys Val Thr Phe Phe Gln Asn Gly Ile Ser Lys Lys Phe Ser His
 165 170 175

Met Asn Pro Asn Phe Ser Ile Pro Gln Ala Asn His Ser His Ser Gly
 180 185 190

JPOXMLDOC01-seq1

Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr Thr Pro Tyr Ser Ser Lys
 195 200 205

Pro Val Thr Ile Thr Val Gln Val Pro
 210 215

<210> 224
 <211> 208
 <212> PRT
 <213> Macaca fascicul aris

<400> 224

Met Trp Gln Leu Leu Leu Pro Thr Ala Leu Leu Leu Leu Val Ser Ala
 1 5 10 15

Gly Met Arg Ala Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
 20 25 30

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
 35 40 45

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

Ser Leu Ile Ser Ser Gln Thr Ser Ser Tyr Phe Ile Ala Ala Ala Arg
 65 70 75 80

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

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
 100 105 110

Ala Pro Arg Trp Val Phe Lys Glu Glu Glu Ser Ile His Leu Arg Cys
 115 120 125

His Ser Trp Lys Asn Thr Leu Leu His Lys Val Thr Tyr Leu Gln Asn
 130 135 140

Gly Lys Gly Arg Lys Tyr Phe His Gln Asn Ser Asp Phe Tyr Ile Pro
 145 150 155 160

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Ile
 165 170 175

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
 180 185 190

Asp Leu Ala Val Ser Ser Ile Ser Ser Phe Phe Pro Pro Gly Tyr Gln
 195 200 205

<210> 225

JPOXMLDOC01-seq1

<211> 115
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 <213> Artificial sequence

<220>
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<400> 225

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

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

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

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

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

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

Thr Arg Phe Tyr Ser Tyr Thr Tyr Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110

Val Ser Ser
 115

<210> 226
 <211> 219
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 226

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

Glu Pro Ala Ser Ile Ser Cys Gln Ala Ser Glu Ser Leu Val His Ser
 20 25 30

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

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

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

JPOXMLDOC01-seq1

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Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Ser	Gln	Asn
				85					90					95	
Thr	His	Val	Pro	Pro	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Glu
			100					105					110		
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
		115					120					125			
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
	130					135					140				
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
145					150					155					160
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
				165					170					175	
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu
			180					185					190		
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
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Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					
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<213>		Artificial				sequence									
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Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
			20					25					30		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser
		35					40					45			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
	50					55					60				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr
65					70					75					80

JPOXMLDOC01-seq1

Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 95
 Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro Pro Cys 110
 Pro Ala Pro 115 Glu Leu Leu Gly Gly 120 Pro Ser Val Phe Leu Phe Pro Pro 125
 Lys Pro 130 Lys Asp Thr Leu Met 135 Ile Ser Arg Thr Pro 140 Glu Val Thr Cys
 Val Val Val Asp Val 150 Ser His Glu Asp Pro 155 Glu Val Lys Phe Asn Trp 160
 Tyr Val Asp Gly Val 165 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 175
 Glu Gln Tyr Asn 180 Ser Thr Tyr Arg Val 185 Val Ser Val Leu Thr Val Leu 190
 His Gln Asp 195 Trp Leu Asn Gly Lys 200 Glu Tyr Lys Cys Lys Val Ser Asn 205
 Lys Ala 210 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 220
 Gln Pro Arg Glu Pro 230 Gln Val Tyr Thr Leu Pro 235 Pro Ser Arg Asp Glu 240
 Leu Thr Lys Asn 245 Gln Val Ser Leu Thr Cys 250 Leu Val Lys Gly Phe Tyr 255
 Pro Ser Asp 260 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn 270
 Asn Tyr Lys 275 Thr Thr Pro Pro Val 280 Leu Asp Ser Asp Gly Ser Phe Phe 285
 Leu Tyr Ser 290 Lys Leu Thr Val 295 Asp Lys Ser Arg Trp Gln Gln Gly Asn 300
 Val Phe Ser Cys Ser 310 Val Met His Glu Ala Leu 315 His Asn His Tyr Thr 320
 Gln Lys Ser Leu Ser 325 Leu Ser Pro

<210> 228
 <211> 328
 <212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 228

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr

JPOXMLDOC01-seq1

245

250

255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Glu Ser Leu Ser Leu Ser Pro
325

<210> 229

<211> 328

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 229

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

JPOXMLDOC01-seq1

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Met Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 230
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 230

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 Page 123

JPOXMLDOC01-seq1

35

40

45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Met Val Leu Asp Arg Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

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

305

310

315

320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 231
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 231

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

JPOXMLDOC01-seq1

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 232
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 232

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

JPOXMLDOC01-seq1

100

105

110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Asp Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 233
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 233

JPOXMLDOC01-seq1

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

JPOXMLDOC01-seq1

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Al a Leu His Asn His Tyr Thr
 305 310 315 320

Gl n Lys Ser Leu Ser Leu Ser Pro
 325

<210> 234
 <211> 328
 <212> PRT
 <213> Arti ficial sequence

<220>
 <223> An arti ficial l y synthesi zed sequence

<400> 234

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Asp Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Al a Lys Thr Lys Pro Arg Gl u
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JPOXMLDOC01-seq1

165

170

175

Gl u Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

Hi s Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met Hi s Gl u Ala Leu Hi s Asn Hi s Tyr Thr
305 310 315 320

Gl n Lys Ser Leu Ser Leu Ser Pro
325

<210> 235
<211> 328
<212> PRT
<213> Arti fici al sequence

<220>
<223> An arti fici al l y synthesi zed sequence

<400> 235

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val Hi s Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

JPOXMLDOC01-seq1

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Gl u Leu Leu Thr Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser Asp Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175
 Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
 225 230 235 240
 Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gl n Lys Ser Leu Ser Leu Ser Pro
 325

JPOXMLDOC01-seq1

<210> 236
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 236

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

JPOXMLDOC01-seq1

225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Met Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 237
<211> 328
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<400> 237

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Met Val Leu Arg Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
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<210> 238
 <211> 328
 <212> PRT
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<220>
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<400> 238

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 Page 134

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn

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300

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295

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 239

<211> 328

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 239

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

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His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
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<210> 240
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
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85

90

95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 241
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 <212> PRT
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JPOXMLDOC01-seq1

<220>

<223> An artificially synthesized sequence

<400> 241

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Thr Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

JPOXMLDOC01-seq1

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 242
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 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence
 <400> 242

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Asp Glu Asp Pro Glu Val Lys Phe Asn Trp
 Page 140

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145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 243
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 243

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

JPOXMLDOC01-seq1

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Thr Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

JPOXMLDOC01-seq1

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 244
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<220>
<223> An artificially synthesized sequence

<400> 244

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Trp Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Thr Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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210

215

220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 245
<211> 328
<212> PRT
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<220>
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<400> 245

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

JPOXMLDOC01-seq1

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 246
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 <212> PRT
 <213> Artificial sequence

<220>
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<400> 246

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 Page 145

JPOXMLDOC01-seq1

275

280

285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gl y Asn
 290 295 300

Val Phe Ser Cys Ser Val Met Hi s Gl u Al a Leu Hi s Al a Hi s Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 247
 <211> 328
 <212> PRT
 <213> Arti ficial sequence

<220>
 <223> An arti ficial ly synthesi zed sequence

<400> 247

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Leu Trp Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Asp Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u
 165 170 175

JPOXMLDOC01-seq1

Glu Leu Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Thr Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 248
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 248

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
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65 70 75 80

Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser 90 Asn Thr Lys Val Asp 95 Lys

Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro 110 Pro Cys

Pro Ala Pro 115 Glu Leu Leu Asn Gly 120 Pro Ser Val Phe Leu 125 Phe Pro Pro

Lys Pro 130 Lys Asp Thr Leu Met 135 Ile Ser Arg Thr Pro 140 Glu Val Thr Cys

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

Tyr Val Asp Gly Val 165 Glu Val His Asn Ala 170 Lys Thr Lys Pro Arg 175 Glu

Glu Gln Tyr Asn 180 Ser Thr Tyr Arg Val 185 Val Ser Val Leu Thr 190 Val Leu

His Arg Asp 195 Trp Leu Asn Gly Lys 200 Glu Tyr Lys Cys Lys 205 Val Ser Asn

Lys Ala 210 Leu Pro Lys Pro Ile 215 Glu Lys Thr Ile Ser 220 Lys Ala Lys Gly

Gln Pro Arg Glu Pro Gln 230 Val Tyr Thr Leu Pro 235 Pro Ser Arg Glu Glu 240

Met Thr Lys Asn 245 Gln Val Ser Leu Thr Cys 250 Leu Val Lys Gly Phe Tyr 255

Pro Ser Asp Ile 260 Ala Val Glu Trp Glu 265 Ser Asn Gly Gln Pro Glu Asn 270

Asn Tyr Lys 275 Thr Thr Pro Pro Val 280 Leu Asp Ser Asp Gly 285 Ser Phe Phe

Leu Tyr 290 Ser Lys Leu Thr Val 295 Arg Lys Ser Arg Trp Gln Gln Gly Asn 300

Val 305 Phe Ser Cys Ser Val 310 Met His Glu Ala Leu 315 His Asn His Tyr Thr 320

Gln Lys Ser Leu Ser 325 Leu Ser Pro

<210> 249

JPOXMLDOC01-seq1

<211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 249

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

JPOXMLDOC01-seq1

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 250
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 250

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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130

135

140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Arg Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 251
<211> 328
<212> PRT
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<220>
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<400> 251

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

JPOXMLDOC01-seq1

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Asn Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser Asp Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Arg Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Arg Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

JPOXMLDOC01-seq1

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 252
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 252

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

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

JPOXMLDOC01-seq1

195

200

205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 253
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 253

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

JPOXMLDOC01-seq1

Lys Val Glu Pro₁₀₀ Lys Ser Cys Asp Lys₁₀₅ Thr His Thr Cys Pro₁₁₀ Pro Cys

Pro Ala Pro₁₁₅ Glu Leu Leu Gly Gly₁₂₀ Asp Ser Val Phe Leu₁₂₅ Phe Pro Pro

Lys Pro₁₃₀ Lys Asp Val Leu Met₁₃₅ Ile Ser Arg Thr Pro₁₄₀ Glu Val Thr Cys

Val Val Val Asp Val Ser₁₅₀ His Glu Asp Pro Glu₁₅₅ Val Lys Phe Asn Trp₁₆₀

Tyr Val Asp Gly Val₁₆₅ Glu Val His Asn Ala₁₇₀ Lys Thr Lys Pro Arg₁₇₅ Glu

Glu Gln Tyr Asn₁₈₀ Ser Thr Tyr Arg Val₁₈₅ Val Ser Val Leu Pro₁₉₀ Val Leu

His Gln Asp₁₉₅ Trp Leu Asn Gly Lys₂₀₀ Glu Tyr Lys Cys Lys₂₀₅ Val Ser Asn

Lys Ala₂₁₀ Leu Pro Ala Pro Ile₂₁₅ Glu Lys Thr Ile Ser₂₂₀ Lys Ala Lys Gly

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro₂₃₅ Pro Ser Arg Glu Glu₂₄₀

Met Thr Lys Asn Gln₂₄₅ Val Ser Leu Thr Cys₂₅₀ Leu Val Lys Gly Phe Tyr₂₅₅

Pro Ser Asp Ile₂₆₀ Ala Val Glu Trp Glu₂₆₅ Ser Asn Gly Gln Pro₂₇₀ Glu Asn

Asn Tyr Lys₂₇₅ Thr Thr Pro Pro Val₂₈₀ Leu Asp Ser Asp Gly₂₈₅ Ser Phe Phe

Leu Tyr Ser Lys Leu Thr Val₂₉₅ Asp Lys Ser Arg Trp Gln Gln Gly Asn

Val Phe Ser Cys Ser Val₃₁₀ Met His Glu Ala Leu₃₁₅ His Asn His Tyr Thr₃₂₀

Gln Lys Ser Leu Ser₃₂₅ Leu Ser Pro

<210> 254
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
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JPOXMLDOC01-seq1

<400> 254

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

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

JPOXMLDOC01-seq1
265

260

270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 255
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 255

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

JPOXMLDOC01-seq1

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 256
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 256

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

JPOXMLDOC01-seq1

50

55

60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Gl u Leu Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Asn His Tyr Thr
305 310 315 320

Gl n Lys Ser Leu Ser Leu Ser Pro

<210> 257
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 257

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

JPOXMLDOC01-seq1

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 258
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 258

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
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115

120

125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 259
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 259

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

JPOXMLDOC01-seq1

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gl n Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gl n Pro Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

JPOXMLDOC01-seq1

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gl y Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gl n Lys Ser Leu Ser Leu Ser Pro
 325

<210> 260
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence
 <400> 260

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ser His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
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JPOXMLDOC01-seq1
185

180

190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 261
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 261

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

JPOXMLDOC01-seq1

Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 95
 Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro Pro Cys 110
 Pro Ala Pro 115 Glu Tyr Leu Gly Gly 120 Asp Ser Val Phe Leu Phe Pro Pro 125
 Lys Pro 130 Lys Asp Val Leu Met 135 Ile Ser Arg Thr Pro 140 Glu Val Thr Cys
 Val Val Ile Asp Val Ala His Glu Asp Pro Glu 155 Val Lys Phe Asn Trp 160
 Tyr Val Asp Gly Val 165 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 175
 Glu Gln Tyr Asn 180 Ser Thr Tyr Arg Val 185 Val Ser Val Leu Pro Val Leu 190
 His Gln Asp 195 Trp Leu Asn Gly Lys 200 Glu Tyr Lys Cys Lys Val Ser Asn 205
 Lys Ala 210 Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 220
 Gln Pro Arg Glu Pro Gln 230 Val Tyr Thr Leu Pro 235 Pro Ser Arg Glu Glu 240
 Met Thr Lys Asn 245 Gln Val Ser Leu Thr Cys 250 Leu Val Lys Gly Phe Tyr 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu 265 Ser Asn Gly Gln Pro Glu Asn 270
 Asn Tyr Lys 275 Thr Thr Pro Pro Val 280 Leu Asp Ser Asp Gly Ser Phe Phe 285
 Leu Tyr 290 Ser Lys Leu Thr Val 295 Asp Lys Ser Arg Trp Gln Gln Gly Asn 300
 Val Phe Ser Cys Ser Val 310 Met His Glu Ala Leu 315 His Asn His Tyr Thr 320
 Gln Lys Ser Leu Ser 325 Leu Ser Pro

<210> 262
 <211> 328
 <212> PRT

JPOXMLDOC01-seq1

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 262

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
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245

250

255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

<210> 263
<211> 328
<212> PRT
<213> Arti ficial sequence

<220>
<223> An arti ficial ly synthesi zed sequence

<400> 263

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

JPOXMLDOC01-seq1

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

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<400> 264

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
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35

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45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

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

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

JPOXMLDOC01-seq1

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
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<400> 266

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

JPOXMLDOC01-seq1

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Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
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JPOXMLDOC01-seq1

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

JPOXMLDOC01-seq1

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met Hi s Gl u Al a Leu Hi s Asn Hi s Tyr Thr
 305 310 315 320

Gl n Lys Ser Leu Ser Leu Ser Pro
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Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Il e Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Il e Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u

JPOXMLDOC01-seq1

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Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

JPOXMLDOC01-seq1

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Gl u Tyr Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175
 Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
 225 230 235 240
 Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
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 Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gl n Lys Ser Leu Ser Leu Ser Pro
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JPOXMLDOC01-seq1

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

JPOXMLDOC01-seq1

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
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<400> 272

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 Page 181

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Arg Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn

JPOXMLDOC01-seq1
300

290

295

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

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<213> Artificial sequence

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<223> An artificially synthesized sequence

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

JPOXMLDOC01-seq1

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

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 <211> 328
 <212> PRT
 <213> Artificial sequence

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 <223> An artificially synthesized sequence
 <400> 274

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
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85

90

95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

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JPOXMLDOC01-seq1

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<400> 275

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

JPOXMLDOC01-seq1

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
 325

<210> 276
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 276

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
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145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro
325

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<400> 277

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

JPOXMLDOC01-seq1

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320

JPOXMLDOC01-seq1

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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JPOXMLDOC01-seq1

210

215

220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

JPOXMLDOC01-seq1

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

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<400> 280

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 Page 192

JPOXMLDOC01-seq1

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Ser	Thr	Ser	Gly 20	Gly	Thr	Ala	Ala	Leu 25	Gly	Cys	Leu	Val	Lys 30	Asp	Tyr
Phe	Pro	Glu 35	Pro	Val	Thr	Val	Ser 40	Trp	Asn	Ser	Gly	Ala 45	Leu	Thr	Ser
Gly	Val 50	His	Thr	Phe	Pro	Ala 55	Val	Leu	Gln	Ser	Ser 60	Gly	Leu	Tyr	Ser
Leu 65	Ser	Ser	Val	Val	Thr 70	Val	Pro	Ser	Ser 75	Ser	Leu	Gly	Thr	Gln	Thr 80
Tyr	Ile	Cys	Asn 85	Val	Asn	His	Lys	Pro	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Lys	Val	Glu	Pro 100	Lys	Ser	Cys	Asp	Lys 105	Thr	His	Thr	Cys	Pro 110	Pro	Cys
Pro	Ala	Pro 115	Glu	Leu	Leu	Gly	Gly 120	Asp	Ser	Val	Phe	Leu 125	Phe	Pro	Pro
Lys	Pro 130	Lys	Asp	Val	Leu	Met 135	Ile	Ser	Arg	Thr	Pro 140	Glu	Val	Thr	Cys
Val 145	Val	Val	Asp	Val	Ser 150	His	Glu	Asp	Pro	Glu 155	Val	Lys	Phe	Asn	Trp 160
Tyr	Val	Asp	Gly	Val 165	Glu	Val	His	Asn	Ala 170	Lys	Thr	Lys	Pro	Arg 175	Glu
Glu	Gln	Tyr	Asn 180	Ser	Thr	Tyr	Arg	Val 185	Val	Ser	Val	Leu	Pro 190	Val	Leu
His	Gln	Asp 195	Trp	Leu	Asn	Gly	Lys 200	Glu	Tyr	Lys	Cys	Lys 205	Val	Ser	Asn
Lys	Ala 210	Leu	Pro	Lys	Pro	Ile 215	Glu	Lys	Thr	Ile	Ser 220	Lys	Ala	Lys	Gly
Gln 225	Pro	Arg	Glu	Pro	Gln 230	Val	Tyr	Thr	Leu	Pro 235	Pro	Ser	Arg	Glu	Glu 240
Met	Thr	Lys	Asn 245	Gln	Val	Ser	Leu	Thr	Cys 250	Leu	Val	Lys	Gly	Phe 255	Tyr
Pro	Ser	Asp	Ile 260	Ala	Val	Glu	Trp	Glu 265	Ser	Asn	Gly	Gln	Pro 270	Glu	Asn
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe

JPOXMLDOC01-seq1

275

280

285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gl y Asn
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Val Phe Ser Cys Ser Val Met Hi s Gl u Al a Leu Hi s Al a Hi s Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
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Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
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Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ser Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u
 165 170 175

JPOXMLDOC01-seq1

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

Hi s Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
 225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met Hi s Gl u Ala Leu Hi s Ala Hi s Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

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<400> 282

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr

JPOXMLDOC01-seq1

65 70 75 80
 Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser 90 Asn Thr Lys Val Asp 95 Lys
 Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro 110 Pro Cys
 Pro Ala Pro 115 Glu Leu Leu Gly Gly 120 Asp Ser Val Phe Leu 125 Phe Pro Pro
 Lys Pro 130 Lys Asp Val Leu Met 135 Ile Ser Arg Thr Pro Glu 140 Val Thr Cys
 Val Val Val Asp Val Ala 150 His Glu Asp Pro Glu 155 Val Lys Phe Asn Trp 160
 Tyr Val Asp Gly Val 165 Glu Val His Asn Ala 170 Lys Thr Lys Pro Arg 175 Glu
 Glu Gln Tyr Asn 180 Ser Thr Tyr Arg Val 185 Val Ser Val Leu Pro 190 Val Leu
 His Gln Asp 195 Trp Leu Asn Gly Lys 200 Glu Tyr Lys Cys Lys 205 Val Ser Asn
 Lys Ala 210 Leu Pro Lys Pro Ile 215 Glu Lys Thr Ile Ser 220 Lys Ala Lys Gly
 Gln Pro Arg Glu Pro Gln 230 Val Tyr Thr Leu Pro 235 Pro Ser Arg Glu Glu 240
 Met Thr Lys Asn 245 Gln Val Ser Leu Thr Cys 250 Leu Val Lys Gly Phe Tyr 255
 Pro Ser Asp Ile 260 Ala Val Glu Trp Glu 265 Ser Asn Gly Gln Pro 270 Glu Asn
 Asn Tyr Lys 275 Thr Thr Pro Pro Val 280 Leu Asp Ser Asp Gly 285 Ser Phe Phe
 Leu Tyr 290 Ser Lys Leu Thr Val 295 Asp Lys Ser Arg Trp Gln Gln Gly Asn
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 Arg Lys Glu Leu Ser 325 Leu Ser Pro

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JPOXMLDOC01-seq1

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<220>
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<400> 283

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

JPOXMLDOC01-seq1

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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JPOXMLDOC01-seq1

130

135

140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

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<400> 285

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

JPOXMLDOC01-seq1

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

JPOXMLDOC01-seq1

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 Page 201

JPOXMLDOC01-seq1

195

200

205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 287
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<400> 287

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

JPOXMLDOC01-seq1

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

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JPOXMLDOC01-seq1

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

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

JPOXMLDOC01-seq1
265

260

270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

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<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 289

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

JPOXMLDOC01-seq1

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 290
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<400> 290

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

JPOXMLDOC01-seq1
60

50

55

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Gl u Leu Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
130 135 140

Val Val Ile Asp Val Ser His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Arg Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro

<210> 291
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 291

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

JPOXMLDOC01-seq1

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 292
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 292

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro

JPOXMLDOC01-seq1

115

120

125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 293
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 <212> PRT
 <213> Artificial sequence

<220>
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<400> 293

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

JPOXMLDOC01-seq1

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gl n Pro Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

JPOXMLDOC01-seq1

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gl y Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 294
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 294

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
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JPOXMLDOC01-seq1

180

185

190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240 245

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 295
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 295

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

JPOXMLDOC01-seq1

Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 95
 Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro Pro Cys 110
 Pro Ala Pro 115 Glu Tyr Leu Gly Gly 120 Asp Ser Val Phe Leu Phe Pro Pro 125
 Lys Pro 130 Lys Asp Val Leu Met 135 Ile Ser Arg Thr Pro 140 Glu Val Thr Cys
 Val Val Val Asp Val 150 Ser His Glu Asp Pro 155 Glu Val Lys Phe Asn Trp 160
 Tyr Val Asp Gly Val 165 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 175
 Glu Gln Tyr Asn 180 Ser Thr Tyr Arg Val 185 Val Ser Val Leu Pro Val Leu 190
 His Arg Asp 195 Trp Leu Asn Gly Lys 200 Glu Tyr Lys Cys Lys Val Ser Asn 205
 Lys Ala 210 Leu Pro Lys Pro Ile 215 Glu Lys Thr Ile Ser Lys Ala Lys Gly 220
 Gln Pro Arg Glu Pro 230 Gln Val Tyr Thr Leu Pro 235 Pro Ser Arg Glu Glu 240
 Met Thr Lys Asn 245 Gln Val Ser Leu Thr Cys 250 Leu Val Lys Gly Phe Tyr 255
 Pro Ser Asp 260 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn 270
 Asn Tyr Lys 275 Thr Thr Pro Pro Val 280 Leu Asp Ser Asp Gly Ser Phe Phe 285
 Leu Tyr Ser Lys 290 Leu Thr Val 295 Lys Lys Ser Arg Trp Gln Gln Gly Asn 300
 Val Phe Ser Cys Ser 310 Val Met His Glu Ala Leu 315 His Ala His Tyr Thr 320
 Arg Lys Glu Leu Ser 325 Leu Ser Pro

<210> 296
 <211> 328
 <212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 296

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr

JPOXMLDOC01-seq1

245

250

255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 297
 <211> 328
 <212> PRT
 <213> Arti ficial sequence

<220>
 <223> An arti ficial ly synthesi zed sequence

<400> 297

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

JPOXMLDOC01-seq1

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 298
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 298

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
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JPOXMLDOC01-seq1

35

40

45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr

305

310

315

320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 299
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 299

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

JPOXMLDOC01-seq1

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 300
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 300

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

JPOXMLDOC01-seq1

100

105

110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 301
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 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 301

JPOXMLDOC01-seq1

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160 165

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

JPOXMLDOC01-seq1

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Al a Leu His Al a His Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 302
 <211> 328
 <212> PRT
 <213> Arti ficial sequence

<220>
 <223> An arti ficial ly synthesi zed sequence

<400> 302

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Ile Asp Val Al a His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Al a Lys Thr Lys Pro Arg Gl u
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JPOXMLDOC01-seq1

165

170

175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

Hi s Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Arg Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met Hi s Gl u Ala Leu Hi s Ala Hi s Tyr Thr
305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
325

<210> 303
<211> 328
<212> PRT
<213> Arti fici al sequence

<220>
<223> An arti fici al ly synthesi zed sequence

<400> 303

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val Hi s Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

JPOXMLDOC01-seq1

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Gl u Tyr Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140
 Val Val Ile Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175
 Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
 225 230 235 240
 Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Ala His Tyr Thr
 305 310 315 320
 Arg Lys Gl u Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
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Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

JPOXMLDOC01-seq1

225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320
 Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

JPOXMLDOC01-seq1

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 306

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
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Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 Page 228

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gl n Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn

JPOXMLDOC01-seq1
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Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

JPOXMLDOC01-seq1

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
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85

90

95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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- <212> PRT
- <213> Artificial sequence

JPOXMLDOC01-seq1

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

JPOXMLDOC01-seq1

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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 <212> PRT
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp

JPOXMLDOC01-seq1

145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

JPOXMLDOC01-seq1

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

JPOXMLDOC01-seq1

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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JPOXMLDOC01-seq1
220

210

215

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<213> Artificial sequence

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<400> 313

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

JPOXMLDOC01-seq1

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
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JPOXMLDOC01-seq1

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Gly	Val 50	His	Thr	Phe	Pro	Ala 55	Val	Leu	Gln	Ser	Ser 60	Gly	Leu	Tyr	Ser		
Leu 65	Ser	Ser	Val	Val	Thr 70	Val	Pro	Ser	Ser 75	Ser	Leu	Gly	Thr	Gln	Thr 80		
Tyr	Ile	Cys	Asn 85	Val	Asn	His	Lys	Pro	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys		
Lys	Val	Glu	Pro 100	Lys	Ser	Cys	Asp	Lys 105	Thr	His	Thr	Cys	Pro 110	Pro	Cys		
Pro	Ala	Pro 115	Glu	Leu	Leu	Gly	Gly 120	Asp	Ser	Val	Phe	Leu 125	Phe	Pro	Pro		
Lys	Pro 130	Lys	Asp	Val	Leu	Met 135	Ile	Ser	Arg	Thr	Pro 140	Glu	Val	Thr	Cys		
Val 145	Val	Val	Asp	Val	Ser 150	His	Glu	Asp	Pro	Glu 155	Val	Lys	Phe	Asn	Trp 160		
Tyr	Val	Asp	Gly	Val 165	Glu	Val	His	Asn	Ala 170	Lys	Thr	Lys	Pro	Arg 175	Glu		
Glu	Gln	Tyr	Asn 180	Ser	Thr	Tyr	Arg	Val 185	Val	Ser	Val	Leu	Pro 190	Val	Leu		
His	Arg	Asp 195	Trp	Leu	Asn	Gly	Lys 200	Glu	Tyr	Lys	Cys	Lys 205	Val	Ser	Asn		
Lys	Ala 210	Leu	Pro	Lys	Pro	Ile 215	Glu	Lys	Thr	Ile	Ser 220	Lys	Ala	Lys	Gly		
Gln 225	Arg	Arg	Glu	Pro	Gln 230	Val	Tyr	Thr	Leu	Pro 235	Pro	Ser	Arg	Glu	Glu 240		
Met	Thr	Lys	Asn	Gln 245	Val	Ser	Leu	Thr	Cys 250	Leu	Val	Lys	Gly	Phe 255	Tyr		
Pro	Ser	Asp	Ile 260	Ala	Val	Glu	Trp	Glu 265	Ser	Asn	Gly	Gln	Pro 270	Glu	Asn		
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe		

JPOXMLDOC01-seq1

275

280

285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gl y Asn
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Val Phe Ser Cys Ser Val Met Hi s Gl u Al a Leu Hi s Al a Hi s Thr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
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Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u
 165 170 175

JPOXMLDOC01-seq1

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

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<220>
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<400> 316

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
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65
Tyr Ile Cys Asn Val 70
85 Asn His Lys Pro Ser 75
90 Asn Thr Lys Val Asp Lys
95

Lys Val Glu Pro 100
Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser 325
Leu Ser Pro

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<400> 317

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

JPOXMLDOC01-seq1

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 318

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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JPOXMLDOC01-seq1

130

135

140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 319

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

JPOXMLDOC01-seq1

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

JPOXMLDOC01-seq1

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 320

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn

JPOXMLDOC01-seq1

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200

205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 321

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

JPOXMLDOC01-seq1

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140 145

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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JPOXMLDOC01-seq1

<400> 322

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

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

JPOXMLDOC01-seq1
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270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 323

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

JPOXMLDOC01-seq1

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

JPOXMLDOC01-seq1
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Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Gl u Leu Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
130 135 140

Val Val Ile Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Arg Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

JPOXMLDOC01-seq1

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 326

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
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115

120

125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 327

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

JPOXMLDOC01-seq1

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

JPOXMLDOC01-seq1

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gl y Asn
 290 295 300

Val Phe Ser Cys Ser Val Met His Gl u Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

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<220>
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<400> 328

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
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JPOXMLDOC01-seq1
185

180

190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240 245

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

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<220>
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

JPOXMLDOC01-seq1

Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 95
 Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro Pro Cys 110
 Pro Ala Pro 115 Glu Tyr Leu Gly Gly 120 Asp Ser Val Phe Leu Phe Pro Pro 125
 Lys Pro 130 Lys Asp Val Leu Met 135 Ile Ser Arg Thr Pro 140 Glu Val Thr Cys
 Val Val Ile Asp Val Ala His Glu Asp Pro Glu 155 Val Lys Phe Asn Trp 160
 Tyr Val Asp Gly Val 165 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 175
 Glu Gln Tyr Asn 180 Ser Thr Tyr Arg Val 185 Val Ser Val Leu Pro Val Leu 190
 His Arg Asp 195 Trp Leu Asn Gly Lys 200 Glu Tyr Lys Cys Lys Val Ser Asn 205
 Lys Ala 210 Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 220
 Gln Pro Arg Glu Pro Gln 230 Val Tyr Thr Leu Pro 235 Pro Ser Arg Glu Glu 240
 Met Thr Lys Asn 245 Gln Val Ser Leu Thr Cys 250 Leu Val Lys Gly Phe Tyr 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu 265 Ser Asn Gly Gln Pro Glu Asn 270
 Asn Tyr Lys 275 Thr Thr Pro Pro Val 280 Leu Asp Ser Asp Gly Ser Phe Phe 285
 Leu Tyr Ser Lys Leu Thr Val 295 Lys Lys Ser Arg Trp Gln Gln Gly Asn 300
 Val Phe Ser Cys Ser Val 310 Met His Glu Ala Leu 315 His Ala His Thr Thr 320
 Arg Lys Glu Leu Ser 325 Leu Ser Pro

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
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20 25 30Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
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245

250

255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

JPOXMLDOC01-seq1

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 332

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser

JPOXMLDOC01-seq1

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45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr

305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 333

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

JPOXMLDOC01-seq1

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 334

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
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100

105

110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 335

JPOXMLDOC01-seq1

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

JPOXMLDOC01-seq1

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu Hi s Gl u Al a Leu Hi s Al a Hi s Thr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 336
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 <212> PRT
 <213> Arti ficial sequence

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 <223> An arti ficial ly synthesi zed sequence

<400> 336

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Al a Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u
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165

170

175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

Hi s Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu Hi s Gl u Ala Leu Hi s Ala Hi s Thr Thr
305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
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<223> An arti fici al l y synthesi zed sequence

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Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val Hi s Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

JPOXMLDOC01-seq1

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Gl u Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140
 Val Val Ile Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175
 Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
 225 230 235 240
 Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Leu His Gl u Ala Leu His Ala His Thr Thr
 305 310 315 320
 Arg Lys Gl u Leu Ser Leu Ser Pro
 325

JPOXMLDOC01-seq1

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 <212> PRT
 <213> Artificial sequence

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<400> 338

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

JPOXMLDOC01-seq1

225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<210> 339
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 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence
 <400> 339

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

JPOXMLDOC01-seq1

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<210> 340
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 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 340

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 Page 275

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Arg Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn

JPOXMLDOC01-seq1
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295

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 341

<211> 328

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 341

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

JPOXMLDOC01-seq1

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 342
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 342

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
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85

90

95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 343
 <211> 328
 <212> PRT
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JPOXMLDOC01-seq1

<220>

<223> An artificially synthesized sequence

<400> 343

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

JPOXMLDOC01-seq1

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 344
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence
 <400> 344

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 Page 281

JPOXMLDOC01-seq1

145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 345
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 345

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

JPOXMLDOC01-seq1

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

JPOXMLDOC01-seq1

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 346
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 346

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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JPOXMLDOC01-seq1

210

215

220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 347
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 347

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

JPOXMLDOC01-seq1

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 348
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 348

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 Page 286

JPOXMLDOC01-seq1

1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
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JPOXMLDOC01-seq1

275

280

285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gl y Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu Hi s Gl u Al a Leu Hi s Al a Hi s Thr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 349

<211> 328

<212> PRT

<213> Arti ficial sequence

<220>

<223> An arti ficial ly synthesi zed sequence

<400> 349

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Al a Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u
 165 170 175

JPOXMLDOC01-seq1

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 350
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 350

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr

JPOXMLDOC01-seq1

65 70 75 80

Tyr Ile Cys Asn Val₈₅ Asn His Lys Pro Ser₉₀ Asn Thr Lys Val Asp₉₅ Lys

Lys Val Glu Pro₁₀₀ Lys Ser Cys Asp Lys₁₀₅ Thr His Thr Cys Pro₁₁₀ Pro Cys

Pro Ala Pro₁₁₅ Glu Leu Leu Gly Gly₁₂₀ Asp Ser Val Phe Leu₁₂₅ Phe Pro Pro

Lys Pro₁₃₀ Lys Asp Val Leu Met₁₃₅ Ile Ser Arg Thr Pro₁₄₀ Glu Val Thr Cys

Val Val Ile Asp Val Ala₁₅₀ His Glu Asp Pro Glu₁₅₅ Val Lys Phe Asn Trp₁₆₀

Tyr Val Asp Gly Val₁₆₅ Glu Val His Asn Ala₁₇₀ Lys Thr Lys Pro Arg₁₇₅ Glu

Glu Gln Tyr Asn₁₈₀ Ser Thr Tyr Arg Val₁₈₅ Val Ser Val Leu Pro₁₉₀ Val Leu

His Arg Asp₁₉₅ Trp Leu Asn Gly Lys₂₀₀ Glu Tyr Lys Cys Lys₂₀₅ Val Ser Asn

Lys Ala₂₁₀ Leu Pro Lys Pro Ile₂₁₅ Glu Lys Thr Ile Ser₂₂₀ Lys Ala Lys Gly

Gln Arg Arg Glu Pro Gln₂₃₀ Val Tyr Thr Leu Pro₂₃₅ Pro Ser Arg Glu Glu₂₄₀

Met Thr Lys Asn₂₄₅ Gln Val Ser Leu Thr Cys₂₅₀ Leu Val Lys Gly Phe Tyr₂₅₅

Pro Ser Asp Ile₂₆₀ Ala Val Glu Trp Glu₂₆₅ Ser Asn Gly Gln Pro₂₇₀ Glu Asn

Asn Tyr Lys₂₇₅ Thr Thr Pro Pro Val₂₈₀ Leu Asp Ser Asp Gly₂₈₅ Ser Phe Phe

Leu Tyr Ser Lys Leu Thr Val₂₉₅ Asp Lys Ser Arg Trp₃₀₀ Gln Gln Gly Asn

Val Phe Ser Cys Ser Val₃₁₀ Leu His Glu Ala₃₁₅ Leu His Ala His Thr Thr₃₂₀

Arg Lys Glu Leu Ser₃₂₅ Leu Ser Pro

<210> 351

JPOXMLDOC01-seq1

<211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 351

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

JPOXMLDOC01-seq1

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 352
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 352

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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JPOXMLDOC01-seq1

130

135

140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 353
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 353

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

JPOXMLDOC01-seq1

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Ile Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160 165
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

JPOXMLDOC01-seq1

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 354
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 354

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 Page 295

JPOXMLDOC01-seq1

195

200

205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 355
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 355

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

JPOXMLDOC01-seq1

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Thr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

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

JPOXMLDOC01-seq1
265

260

270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

JPOXMLDOC01-seq1

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser

JPOXMLDOC01-seq1
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55

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Gl u Leu Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gl n Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Gl u Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro

<210> 359
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<220>
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<400> 359

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

JPOXMLDOC01-seq1

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

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<400> 360

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
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115

120

125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 361

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

JPOXMLDOC01-seq1

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Gl n Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gl n Pro Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

JPOXMLDOC01-seq1

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gl y Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Gl u Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 362
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<400> 362

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Gl u Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu

JPOXMLDOC01-seq1

180

185

190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240 245

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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<400> 363

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

JPOXMLDOC01-seq1

Tyr Ile Cys Asn Val 85 Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 95

Lys Val Glu Pro 100 Lys Ser Cys Asp Lys 105 Thr His Thr Cys Pro Pro Cys 110

Pro Ala Pro Glu Leu Leu Gly Gly 120 Asp Ser Val Phe Leu Phe Pro Pro 115 125

Lys Pro Lys Asp Val Leu Met 135 Ile Ser Arg Thr Pro Glu Val Thr Cys 130 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp 145 150 155 160 165

Tyr Val Asp Gly Val 165 Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val 185 Val Ser Val Leu Pro Val Leu 180 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro 325

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<212> PRT

<213> Artificial sequence

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<223> An artificially synthesized sequence

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140Val Val Ile Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr

JPOXMLDOC01-seq1

245

250

255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

JPOXMLDOC01-seq1

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
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JPOXMLDOC01-seq1

35

40

45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr

305

310

315

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Arg Lys Glu Leu Ser Leu Ser Pro
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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

JPOXMLDOC01-seq1

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

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 <223> An artificially synthesized sequence

<400> 368

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys

JPOXMLDOC01-seq1

100

105

110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

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 <211> 328
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 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 369

JPOXMLDOC01-seq1

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160 165

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

JPOXMLDOC01-seq1

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu Hi s Gl u Al a Leu Hi s Al a Hi s Tyr Thr
 305 310 315 320

Arg Lys Gl u Leu Ser Leu Ser Pro
 325

<210> 370
 <211> 328
 <212> PRT
 <213> Arti fici al sequence

<220>
 <223> An arti fici al ly synthesi zed sequence

<400> 370

Al a Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Al a Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Al a Al a Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

Phe Pro Gl u Pro Val Thr Val Ser Trp Asn Ser Gly Al a Leu Thr Ser
 35 40 45

Gly Val Hi s Thr Phe Pro Al a Val Leu Gl n Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn Hi s Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr Hi s Thr Cys Pro Pro Cys
 100 105 110

Pro Al a Pro Gl u Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140

Val Val Val Asp Val Al a Hi s Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Gl u Val Hi s Asn Al a Lys Thr Lys Pro Arg Gl u
 Page 317

JPOXMLDOC01-seq1

165

170

175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

- <210> 371
- <211> 328
- <212> PRT
- <213> Artificial sequence

- <220>
- <223> An artificially synthesized sequence

<400> 371

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

JPOXMLDOC01-seq1

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Gl u Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Gl u Leu Leu Gly Gl y Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Gl u Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ala His Gl u Asp Pro Gl u Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Gl u Val His Asn Ala Lys Thr Lys Pro Arg Gl u
 165 170 175
 Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190
 His Arg Asp Trp Leu Asn Gly Lys Gl u Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Lys Pro Ile Gl u Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gl n Pro Arg Gl u Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Gl u Gl u
 225 230 235 240
 Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Gl u Trp Gl u Ser Asn Gly Gl n Pro Gl u Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gl n Gl n Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Leu His Gl u Ala Leu His Ala His Tyr Thr
 305 310 315 320
 Arg Lys Gl u Leu Ser Leu Ser Pro
 325

JPOXMLDOC01-seq1

<210> 372
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 372

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

JPOXMLDOC01-seq1

225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 373
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence
 <400> 373

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

JPOXMLDOC01-seq1

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 374
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 374

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 Page 322

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gl n Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gl n Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Gl u Gl n Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gl n Arg Arg Glu Pro Gl n Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gl n Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gl n Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gl n Gl n Gly Asn

JPOXMLDOC01-seq1
300

290

295

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 375

<211> 328

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 375

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

JPOXMLDOC01-seq1

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 376
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence
 <400> 376

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 Page 325

JPOXMLDOC01-seq1

85

90

95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 377
 <211> 328
 <212> PRT
 <213> Artificial sequence

JPOXMLDOC01-seq1

<220>

<223> An artificially synthesized sequence

<400> 377

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

JPOXMLDOC01-seq1

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325

<210> 378
 <211> 328
 <212> PRT
 <213> Artificial sequence

<220>
 <223> An artificially synthesized sequence

<400> 378

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp

JPOXMLDOC01-seq1

145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 379
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence

<400> 379

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

JPOXMLDOC01-seq1

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

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

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

JPOXMLDOC01-seq1

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 380
<211> 328
<212> PRT
<213> Artificial sequence

<220>
<223> An artificially synthesized sequence
<400> 380

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
Page 331

JPOXMLDOC01-seq1

210

215

220

Gln Arg Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
325

<210> 381

<211> 328

<212> PRT

<213> Artificial sequence

<220>

<223> An artificially synthesized sequence

<400> 381

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

JPOXMLDOC01-seq1

Pro Ala Pro Glu Tyr Leu Gly Gly Asp Ser Val Phe Leu Phe Pro Pro
 115 120 125

Lys Pro Lys Asp Val Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140

Val Val Ile Asp Val Ala His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Pro Val Leu
 180 185 190

His Arg Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205

Lys Ala Leu Pro Lys Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285

Leu Tyr Ser Lys Leu Thr Val Lys Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300

Val Phe Ser Cys Ser Val Leu His Glu Ala Leu His Ala His Tyr Thr
 305 310 315 320

Arg Lys Glu Leu Ser Leu Ser Pro
 325