(11) Application No. AU 2016262766 B2

(12) STANDARD PATENT(19) AUSTRALIAN PATENT OFFICE

WO 2008/150494 A1

(54)	Title FcyRIIb-specific Fc antibody			
(51)	A61K 39/395 (2006.01) A A61P 1/04 (2006.01) A A61P 3/10 (2006.01) A A61P 5/00 (2006.01) A A61P 7/06 (2006.01) A A61P 7/06 (2006.01) A A61P 11/02 (2006.01) A	61P 13/12 (2006.01) 61P 17/00 (2006.01) 61P 17/04 (2006.01) 61P 17/06 (2006.01) 61P 19/02 (2006.01) 61P 25/00 (2006.01) 61P 31/04 (2006.01) 61P 35/00 (2006.01) 607K 16/28 (2006.01)		
(21)	Application No: 2016262766	(22)	Date of Filing:	2016.11.25
(43) (43) (44)	Publication Journal Date: 2016	.12.15 .12.15 .10.04		
(62)	Divisional of: 2012222252			
(71)	Applicant(s) Chugai Seiyaku Kabushiki Kaisha			
(72)	Inventor(s) MIMOTO, Futa;KURAMOCHI, Taichi;IGAWA, Tomoyuki;KATADA, Hitoshi;KADONO, Shojiro			
(74)	Agent / Attorney Spruson & Ferguson, GPO Box 3898, Sydney, NSW, 2001, AU			
(56)	Related Art VERI, MC. et al., Immunology, 2007, vol. 121, pages 392-404 WO 2005/115452 A2 CHU, S. Y. et al., Molecular Immunology, 2008, vol. 45, pages 3926-3933			

FcyRIIb-SPECIFIC Fc ANTIBODY

ABSTRACT

An objective of the present invention is to provide a polypeptide containing an Fc region having maintained or decreased binding activities towards both allotypes of Fc γ RIIa, types H and R, and having enhanced Fc γ RIIb-binding activity in comparison with a parent polypeptide; a pharmaceutical composition containing the polypeptide; an agent for treating or preventing immunological inflammatory diseases that includes the pharmaceutical composition; a production method thereof; and a method for maintaining or decreasing binding activities towards both allotypes of Fc γ RIIa and enhancing the Fc γ RIIb-binding activity. Specifically, it is found that a polypeptide containing an antibody Fc region that has an alteration of substituting Pro at position 238 (EU numbering) with Asp or Leu at position 328 (EU numbering) with Glu enhances Fc γ RIIa, types H and R. It is also found that a polypeptide containing an antibody Fc region that contains an alteration of substituting Pro at position 238 (EU numbering) with Asp

5 and several other alterations, enhances FcγRIIb-binding activity, and maintains or decreases binding activities towards both allotypes of FcγRIIa, types H and R.

DESCRIPTION FcyRIIb-SPECIFIC Fc ANTIBODY

Cross-Reference to Related Applications

The present application is a divisional of Australian Patent Application No. 2012222252 (national phase of PCT/JP2012/054624) claiming priority to JP 2011-219835 and JP 2011-040923. The entire contents of each of the afore-mentioned applications is hereby incorporated by reference.

Technical Field

The present invention relates to polypeptides comprising an IgG Fc region that have maintained or decreased binding activities towards both allotypes of FcyRIIa, H type and R type, in which the amino acid at position 131 (EU numbering) in FcyRIIa is His (type H) or Arg (type R), and having enhanced FcyRIIb-binding activity in comparison with a parent polypeptide by introducing amino acid substitutions into the IgG Fc region; pharmaceutical compositions comprising the polypeptide; therapeutic agents or preventive agents comprising the polypeptide for immunological inflammatory diseases; and methods for producing them. Furthermore, the present invention relates to methods for maintaining or decreasing binding activities towards both allotypes of FcyRIIa, H type and R type, in which the amino acid at position 131 (EU numbering) in FcyRIIa is His (type H) or Arg (type R), and enhancing FcyRIIb-binding activity in comparison with a parent polypeptide; and methods for suppressing antibody production compared with the parent polypeptide in in vivo administration. The present invention also relates to methods for producing a polypeptide having maintained or decreased binding activities towards both allotypes of FcyRIIa, H type and R type, in which the amino acid at position 131 (EU numbering) in FcyRIIa is His (type H) or Arg (type R), and having enhanced FcyRIIb-binding activity in comparison with a parent polypeptide; and methods for producing a polypeptide that suppresses antibody production compared with a parent polypeptide in in vivo administration.

Background Art

Antibodies are drawing attention as pharmaceuticals since they are highly stable in blood and have few side effects (Non-patent Documents 1 and 2). Almost all antibody

pharmaceuticals 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) (Non-patent Document 3). For an antibody to exhibit ADCC activity, the antibody Fc region must bind to an Fc γ receptor (hereinafter denoted as Fc γ R) which is an antibody-binding receptor present on the surface of effector cells such as killer cells, natural killer cells, and activated macrophages.

In humans, the FcγRIa (CD64A), FcγRIIa (CD32A), FcγRIIb (CD32B), FcγRIIIa (CD16A), and FcγRIIIb (CD16B) isoforms have been reported as the FcγR protein family, and the respective allotypes have also been reported (Non-patent Document 7). FcγRIa, FcγRIIa, and

Fc γ RIIIa are called activating Fc γ R since they have immunologically active functions, and Fc γ RIIb is called inhibitory Fc γ R since it has immunosuppressive functions (Non-patent Document 8).

In the binding between the Fc region and Fc γ 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 (Non-patent Documents 4, 5, and 6). Various variants having Fc γ 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 γ R have been obtained (Patent Documents 1, 2, 3, and 4).

When activating Fc γ R is cross-linked with an immune complex, it phosphorylates immunoreceptor tyrosine-based activating motifs (ITAMs) contained in the intracellular domain or FcR common γ -chain (an interaction partner), activates a signal transducer SYK, and triggers inflammatory immune response by initiating an activation signal cascade (Non-patent Document 9).

FcγRIIb is the only FcγR expressed on B cells (Non-patent Document 10). Interaction of the antibody Fc region with FcγRIIb has been reported to suppress the primary immune response of B cells (Non-patent Document 11). Furthermore, it is reported that when FcγRIIb on B cells and a B cell receptor (BCR) are cross-linked *via* an immune complex in blood, B cell activation is suppressed, and antibody production by B cells is suppressed (Non-patent

0 Document 12). In this immunosuppressive signal transduction mediated by BCR and FcγRIIb, the immunoreceptor tyrosine-based inhibitory motif (ITIM) contained in the intracellular domain of FcγRIIb is necessary (Non-patent Documents 13 and 14). When ITIM is phosphorylated upon signaling, SH2-containing inositol polyphosphate 5-phosphatase (SHIP) is recruited, transduction of other activating FcγR signal cascades is inhibited, and inflammatory immune

25 response is suppressed (Non-patent Document 15). Furthermore, aggregation of FcγRIIb 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 (Non-patent Document 16).

Furthermore, FcγRIIb is also expressed on dendritic cells, macrophages, activated
 neutrophils, mast cells, and basophils. FcγRIIb inhibits the functions of activating FcγR such as phagocytosis and release of inflammatory cytokines in these cells, and suppresses inflammatory immune responses (Non-patent Document 8).

The importance of immunosuppressive functions of FcyRIIb has been elucidated so far through studies using FcyRIIb knockout mice. There are reports that in FcyRIIb knockout mice, humoral immunity is not appropriately regulated (Non-Patent Document 17), sensitivity towards

35 humoral immunity is not appropriately regulated (Non-Patent Document 17), sensitivity towards collagen-induced arthritis (CIA) is increased (Non-patent Document 18), lupus-like symptoms

35

are presented, and Goodpasture's syndrome-like symptoms are presented (Non-patent Document 19).

Furthermore, regulatory inadequacy of $Fc\gamma RIIb$ has been reported to be related to human autoimmnue 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) (Non-patent Documents 20, 21, 22, 23, and 24), and decrease of $Fc\gamma RIIb$ expression on the surface of B cells in SLE patients (Non-patent Document 25 and 26) have been reported.

From mouse models and clinical findings as such, FcγRIIb is considered to play the role of controlling autoimmune diseases and inflammatory diseases mainly through involvement with B cells, and it is a promising target molecule for controlling autoimmune diseases and inflammatory diseases.

IgG1, mainly used as a commercially available antibody pharmaceutical, is known to bind not only to Fc γ RIIb, but also strongly to activating Fc γ R (Non-patent Document 27). It may be possible to develop antibody pharmaceuticals having greater immunosuppressive properties compared with those of IgG1, by utilizing an Fc region with enhanced Fc γ RIIb binding, or improved Fc γ RIIb-binding selectivity compared with activating Fc γ 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 γ RIIb binding may inhibit B cell activation (Non-patent Document 28).

- It has been reported that crosslinking FcγRIIb 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 (Non-patent Document 29). Besides IgE, it has been reported that when FcγRIIb and CD79b forming a B-cell receptor
- 25 complex are cross-linked by an antibody, B cell proliferation is suppressed *in vitro*, and symptoms are alleviated in the collagen arthritis model (Non-patent Document 30).

Besides B cells, it has been reported that crosslinking of FccRI and FcγRIIb on mast cells using molecules, in which the Fc portion of an IgG with enhanced FcγRIIb binding is fused to the Fc portion of IgE that binds to an IgE receptor FccRI, causes FcγRIIb phosphorylation of

30 FcγRIIb, thereby suppressing FcεRI-dependent calcium influx. This suggests that inhibition of degranulation *via* FcγRIIb stimulation is possible by enhancing FcγRIIb binding (Non-patent Document 31).

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 autoimmune diseases.

Furthermore, mutants with enhanced FcyRIIb 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, FcyRIIb has been found to play an important role in the agonistic activity of agonist antibodies against the anti-TNF receptor family. Specifically, it has been suggested that interaction with FcyRIIb is required for the agonistic activity of antibodies against CD40, DR4, DR5, CD30, and CD137, which are included in the TNF receptor family (Non-patent Documents 32, 33, 34, 35, 36, and 37). Non-patent Document 32 shows that the use of antibodies with enhanced FcyRIIb binding enhances the anti-tumor effect of anti-CD40 antibodies. Accordingly, antibodies with enhanced FcyRIIb are expected to have an effect of enhancing agonistic activity of agonist antibodies including antibodies against the anti-TNF receptor family.

Antibodies having an Fc with improved FcyRIIb-binding activity have been reported (Non-patent Document 28). In this Document, FcyRIIb-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 FcyRIIb, and maintains the same level of binding to FcyRIa and FcyRIIa type H as that of a naturally-occurring IgG1. However, another report shows that this alteration enhances the binding to type-R FcyRIIa several hundred times to the same level of FcyRIIb binding, which means the FcyRIIb-binding selectivity is not improved in comparison with type-R FcyRIIa (Patent Document 5).

0

5

Even if FcyRIIb binding had been enhanced compared with that of IgG1, only the effect of enhancing FcyRIIa binding and not the enhancement of FcyRIIb binding is considered to have influence on cells such as platelets which express FcyRIIa but do not express FcyRIIb (Nonpatent Document 8). For example, the group of patients who were administered bevacizumab, an antibody against VEGF, is known to have an increased risk for thromboembolism (Non-patent

- 25 Document 38). 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 (Non-patent Document 39). In both cases of these antibodies, later studies using animal models and such have suggested that the administered antibodies aggregate platelets via FcyRIIa binding on the platelets, and form blood clots (Non-patent Documents 40 and 41). In
- 30 systemic lupus erythematosus which is an autoimmune disease, platelets are activated via an FcyRIIa-dependent mechanism, and platelet activation has been reported to correlate with the severity of symptoms (Non-patent Document 42). Even if FcyRIIb binding is enhanced, administering an antibody with enhanced FcyRIIa binding to such patients who already have a high risk for developing thromboembolism will increase the risk for developing
- 35 thromboembolism, thus is extremely dangerous.

Furthermore, antibodies with enhanced FcyRIIa binding have been reported to enhance

0

25

macrophage-mediated antibody dependent cellular phagocytosis (ADCP) (Non-patent Document 43). When antibody's antigens are phagocytized by macrophages, antibodies themselves are also phagocytized at the same time. In that case, peptide fragments derived from those antibodies are also presented as an antigen and the antigenicity may become higher, thereby increasing the risk of production of antibodies against antibodies (anti- antibodies). More specifically, enhancing $Fc\gamma$ RIIa binding will increase the risk of production of antibodies against the antibodies against the antibodies against the antibodies, and this will remarkably decrease their value as pharmaceuticals.

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, higher antigenicity, and increased risk of anti-antibody production.

From such a viewpoint, the aforementioned Fc with enhanced FcγRIIb binding shows remarkably enhanced type-R FcγRIIa binding compared with that of a naturally-occurring IgG1. Therefore, its value as a pharmaceutical for patients carrying type-R FcγRIIa is considerably reduced. Types H and R of FcγRIIa are observed in Caucasians and African-Americans with approximately the same frequency (Non-patent Documents 44 and 45). Therefore, when this Fc 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.

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 spontaneously (Non-patent Documents 46 and 47). 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. 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.

Therefore, when considering generation of pharmaceuticals that utilize the $Fc\gamma RIIb$ binding-mediated immunosuppressive action, there is a need for an Fc that not only has

30 enhanced FcγRIIb-binding activity, but also has binding to both FcγRIIa, 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.

Meanwhile, cases where amino acid alterations were introduced into the Fc region to increase the FcyRIIb-binding selectivity have been reported so far (Non-patent Document 48).

35 However, all variants said to have improved FcγRIIb selectivity as reported in this document showed decreased FcγRIIb binding compared with that of a naturally-occurring IgG1.

Therefore, it is considered to be difficult for these variants to actually induce an FcγRIIbmediated immunosuppressive reaction more strongly than IgG1.

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.

From these results, in producing antibody pharmaceuticals 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

- 5 the antibodies (Non-patent Document 49). Therefore, to produce an Fc region that selectively binds to FcγRIIb, the most difficult problem may be conferring to the antibody Fc region with the property of selectively improved FcγRIIb-binding activity, which involves distinguishing these homologous sequences, and decreasing or not increasing the binding activity towards each allotype of FcγRIIa, while increasing the binding activity towards FcγRIIb. So far, variants
- 0 having sufficient $Fc\gamma RIIb$ selectivity have not been obtained. Patent Document 5 reports variants with enhanced $Fc\gamma RIIb$ -binding activity; however, the degree of enhancement is low, and there is a demand for development of variants having properties similar to those described above.

Prior Art Documents

25 [Patent Documents]
[Patent Document 1] WO 2000/42072
[Patent Document 2] WO 2006/019447
[Patent Document 3] WO 2004/99249
[Patent Document 4] WO 2004/29207

30 [Patent Document 5] US2009/0136485

[Non-patent Documents]

[Non-patent Document 1] Nat Biotechnol, 23(9), 1073-1078, 2005 [Non-patent Document 2] Eur J Pharm Biopharm, 59(3), 389-96, 2005

35 [Non-patent Document 3] Chem Immunol, 65, 88-110, 1997
 [Non-patent Document 4] J Biol Chem, 276(19), 16478-16483, 2001

[Non-patent Document 5] Eur J Immunol, 23(5), 1098-1104, 1993 [Non-patent Document 6] Immunology, 86(2), 319-324, 1995 [Non-patent Document 7] Immunol Lett, 82(1-2), 57-65, 2002 [Non-patent Document 8] Nat Rev Immunol, 10(5), 328-343, 2010 [Non-patent Document 9] Nat Rev Immunol, 8(1), 34-47, 2008 [Non-patent Document 10] Eur J Immunol, 19(8), 1379-1385, 1989 [Non-patent Document 11] J Exp Med, 129(6), 1183-1201, 1969 [Non-patent Document 12] Immunol Lett, 88(2), 157-161, 2003 [Non-patent Document 13] Science, 256(5065), 1808-1812, 1992 [Non-patent Document 14] Nature, 368(6466), 70-73, 1994 [Non-patent Document 15] Science, 290(5489), 84-89, 2000 [Non-patent Document 16] J Immunol, 181(8), 5350-5359 2008 [Non-patent Document 17] J Immunol, 163(2), 618-622, 1999 [Non-patent Document 18] J Exp Med, 189(1), 187-194, 1999 5 [Non-patent Document 19] J Exp Med, 191(5), 899-906, 2000 [Non-patent Document 20] Hum Genet, 117(2-3), 220-227, 2005 [Non-patent Document 21] J Biol Chem, 282(3), 1738-1746, 2007 [Non-patent Document 22] Arthritis Rheum, 54(12), 3908-3917, 2006 [Non-patent Document 23] Nat Med, 11(10), 1056-1058, 2005 0 [Non-patent Document 24] J Immunol, 176(9), 5321-5328, 2006 [Non-patent Document 25] J Exp Med, 203(9), 2157-2164, 2006 [Non-patent Document 26] J Immunol, 178(5), 3272-3280, 2007 [Non-patent Document 27] Blood, 113(16), 3716-3725, 2009 [Non-patent Document 28] Mol Immunol, 45(15), 3926-3933, 2008 25 [Non-patent Document 29] J Allergy Clin Immunol, 2012 Jan 16. in press (PMID: 22257644) [Non-patent Document 30] Arthritis Rheum, 62(7), 1933-1943, 2010 [Non-patent Document 31] Immunol Lett, 2012 Jan 25. in press (PMID: 22305932) [Non-patent Document 32] Science, 333(6045), 1030-1034, 2011 [Non-patent Document 33] Cancer Cell, 19(1), 101-113, 2011 30 [Non-patent Document 34] J Clin Invest, 2012 Feb 13. pii: 61226. doi: 10.1172/JCI61226. in press (PMID: 22326955) [Non-patent Document 35] J Immunol, 171(2), 562-568, 2003 [Non-patent Document 36] Blood, 108(2), 705-710, 2006 [Non-patent Document 37] J Immunol, 166(8), 4891-4898, 2001 35 [Non-patent Document 38] J Natl Cancer Inst, 99(16), 1232-1239, 2007 [Non-patent Document 39] Arthritis Rheum, 48(3), 719-727, 2003

[Non-patent Document 40] J Thromb Haemost, 7(1), 171-181, 2008
[Non-patent Document 41] J Immunol, 185(3), 1577-1583, 2010
[Non-patent Document 42] Sci Transl Med, 2(47), 47-63, 2010
[Non-patent Document 43] Mol Cancer Ther, 7(8), 2517-2527, 2008
[Non-patent Document 44] J Clin Invest, 97(5), 1348-1354, 1996
[Non-patent Document 45] Arthritis Rheum, 41(7), 1181-1189, 1998
[Non-patent Document 46] J Clin Invest, 115(10), 2914-2923, 2005
[Non-patent Document 47] Proc Natl Acad Sci USA, 102(8), 2910-2915, 2005
[Non-patent Document 48] Mol Immunol, 40(9), 585-593, 2003
[Non-patent Document 49] J Exp Med, 172, 19-25, 1990

Summary of the Invention

In a first aspect, the invention provides a polypeptide variant comprising an antibody Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H), and enhanced $Fc\gamma RIIb$ -binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for $Fc\gamma RIIa$ (type H)] / [KD value of the polypeptide variant for $Fc\gamma RIIb$] is 4.2 or more, wherein the amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp.

In a second aspect, the invention provides a pharmaceutical composition comprising the polypeptide of the first aspect.

In a third aspect, the invention provides an agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of the first aspect or the pharmaceutical composition of the second aspect.

In a fourth aspect, the invention provides an agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of the first aspect or the pharmaceutical composition of the second aspect.

In a fifth aspect, the invention provides an agent for treating a disease, which comprises the polypeptide of the first aspect or the pharmaceutical composition of the second aspect, wherein the disease is a disease with deficiency of a biologically essential protein.

In a sixth aspect, the invention provides an antiviral agent comprising the polypeptide of the first aspect or the pharmaceutical composition of the second aspect.

In a seventh aspect, the invention provides use of a polypeptide according to the first aspect or the pharmaceutical composition of the second aspect in the manufacture of a medicament for treating or preventing an immunological inflammatory disease.

In an eighth aspect, the invention provides use of a polypeptide according to the first aspect in the manufacture of a medicament for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils.

The present invention was achieved in view of the above circumstances. An aspect of the present invention is to provide polypeptides comprising an IgG Fc region that have maintained or decreased binding activities towards both allotypes of FcyRIIa, H type and R

type, in which the amino acid at position 131 (EU numbering) in FcyRIIa is His (type H) or Arg (type R), and having enhanced FcyRIIb-binding activity in comparison with a parent polypeptide through introduction of amino acid substitutions into the IgG Fc region; pharmaceutical compositions comprising the polypeptide; therapeutic agents or preventive agents comprising the polypeptide for immunological inflammatory diseases; and methods for producing them. Furthermore, an aspect of the invention is to provide a method for maintaining or decreasing binding activities towards both allotypes of FcyRIIa, H type and R type, in which the amino acid at position 131 (EU numbering) in FcyRIIa is His (type H) or Arg (type R), and for enhancing FcyRIIb-binding activity in comparison with a parent polypeptide; and a method for suppressing antibody production in comparison with a parent polypeptide in *in vivo* administration. In addition, an aspect of the invention is to provide methods for producing a polypeptide having maintained or decreased binding activities towards both allotypes of FcyRIIa, H type and R type, in which the amino acid at position 131 (EU numbering) in FcyRIIa is His (type H) or Arg (type R), and having enhanced FcyRIIb-binding activity in comparison with a parent polypeptide; and methods for producing a polypeptide with suppressed antibody production in comparison with a parent polypeptide when administered in vivo. In one or more embodiments the invention aims to achieve one or more of the stated aspects.

comparison with a parent polypeptide. As a result, the present inventors discovered that a polypeptide comprising an antibody Fc region that comprises an alteration produced by substituting Pro at position 238 (EU numbering) with Asp or Leu at position 328 (EU numbering) with Glu enhances $Fc\gamma RIIb$ -binding activity, and decreases Fc region-mediated binding activity towards both allotypes of $Fc\gamma RIIa$, types H and R. Furthermore, the present inventors discovered that a polypeptide comprising an antibody Fc region that comprises an alteration of substituting Pro at position 238 (EU numbering) with Asp and several other alterations that enhance $Fc\gamma RIIb$ -binding activity, and maintains or decreases Fc region-mediated binding activities towards both allotypes of $Fc\gamma RIIa$, types H and R.

More specifically, the present invention relates to the following:

[1] a polypeptide variant comprising an antibody Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H), and enhanced $Fc\gamma RIIb$ -binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for $Fc\gamma RIIa$ (type R)]

- 5 / [KD value of the polypeptide variant for FcγRIIb] is 1.2 or more;
 [2] the polypeptide of [1], wherein the value of [KD value of the polypeptide variant for FcγRIIa (type H)] / [KD value of the polypeptide variant for FcγRIIb] is 4.2 or more;
 [3] the polypeptide of [1] or [2], wherein the value of [KD value of the parent polypeptide for FcγRIIb] / [KD value of the polypeptide variant for FcγRIIb] is 1.6 or more;
- [4] the polypeptide of any one of [1] to [3], wherein the value of [KD value of the stronger of the binding activities of the polypeptide variant towards FcγRIIa (type R) and FcγRIIa (type H)] / [KD value of the stronger of the binding activities of the parent polypeptide towards FcγRIIa (type R) and FcγRIIa (type H)] is 0.7 or more;

[5] the polypeptide of any one of [1] to [4], which has maintained or decreased FcγRIIIa-binding activity compared with that of a parent polypeptide;

[6] the polypeptide of any one of [1] to [5], which has maintained or decreased $Fc\gamma RIa$ -binding activity compared with that of a parent polypeptide;

[7] the polypeptide of any one of [1] to [6], wherein an amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU

30 numbering) with Glu;

25

[8] the polypeptide of any one of [1] to [7], wherein an amino acid alteration is at least one substitution selected from the group consisting of:

substitution of Pro at position 238 (EU numbering) with Asp;

substitution of Gly at position 237 (EU numbering) with Trp;

35 substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val;

substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn; substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu; substitution of Lys at position 326 (EU numbering) with Gln; substitution of Lys at position 326 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala; substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; 5 substitution of Gly at position 237 (EU numbering) with Leu; substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; 0 substitution of Glu at position 233 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser; 25 substitution of Lys at position 326 (EU numbering) with Thr; substitution of Val at position 323 (EU numbering) with Ile; substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Met; substitution of Tyr at position 296 (EU numbering) with Asp; 30 substitution of Lys at position 326 (EU numbering) with Ala; substitution of Lys at position 326 (EU numbering) with Asn; and

substitution of Ala at position 320 (EU numbering) with Met; [9] the polypeptide of any one of [1] to [8], wherein the polypeptide comprising the antibody Fc region is an IgG antibody;

35 [10] the polypeptide of any one of [1] to [8], wherein the polypeptide comprising the antibody Fc region is an Fc fusion protein molecule;

[11] a method for maintaining or decreasing binding activities towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H) and enhancing $Fc\gamma RIIb$ -binding activity of a polypeptide in comparison with a parent polypeptide, which comprises adding at least one amino acid alteration in the Fc region of the polypeptide comprising the antibody Fc region, wherein the amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;

[12] a method for suppressing production of an antibody against a polypeptide comprising antibody Fc region in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration to the Fc region of the

polypeptide, wherein the amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;
 [13] the method of [11] or [12], wherein the amino acid alteration is at least one substitution selected from the group consisting of:

substitution of Pro at position 238 (EU numbering) with Asp;

- 5 substitution of Gly at position 237 (EU numbering) with Trp; substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn;
- substitution of Pro at position 271 (EU numbering) with Gly;
 substitution of Lys at position 326 (EU numbering) with Leu;
 substitution of Lys at position 326 (EU numbering) with Gln;
 substitution of Lys at position 326 (EU numbering) with Glu;
 substitution of Lys at position 326 (EU numbering) with Met;
- 25 substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala;
- 30 substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; substitution of Gly at position 237 (EU numbering) with Leu; substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr;
- 35 substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg;

substitution of Glu at position 233 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser; substitution of Lys at position 326 (EU numbering) with Thr; substitution of Val at position 323 (EU numbering) with Ile; substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Met; substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Ala at position 326 (EU numbering) with Met; [14] the method of any one of [11] to [13], wherein the polypeptide comprising the antibody Fc

5 region is an IgG antibody;

[15] the method of any one of [11] to [13], wherein the polypeptide comprising the antibody Fc region is an Fc fusion protein molecule;

[16] a method for producing a polypeptide having maintained or decreased binding activities towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H) and having enhanced $Fc\gamma RIIb$ -binding activity in

0 comparison with a parent polypeptide, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an antibody Fc region, wherein the amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;

[17] a method for producing a polypeptide with suppressed production of an antibody against the polypeptide in comparison with a parent polypeptide when administered *in vivo*, wherein the method comprises adding at least one amino acid alteration in the Fc region of a polypeptide comprising an antibody Fc region, wherein the amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;

[18] the method of [16] or [17], wherein the amino acid alteration is at least one substitution selected from the group consisting of:
 substitution of Pro at position 238 (EU numbering) with Asp;
 substitution of Gly at position 237 (EU numbering) with Trp;

substitution of Gly at position 237 (EU numbering) with Phe;

35 substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln;

- substitution of His at position 268 (EU numbering) with Asn; substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu; substitution of Lys at position 326 (EU numbering) with Gln; substitution of Lys at position 326 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala; substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; substitution of Gly at position 237 (EU numbering) with Leu; 5 substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; substitution of Glu at position 233 (EU numbering) with Asp; 0 substitution of His at position 268 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser; substitution of Lys at position 326 (EU numbering) with Thr; 25 substitution of Val at position 323 (EU numbering) with Ile; substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Met; substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ala;
- 30 substitution of Lys at position 326 (EU numbering) with Asn; and substitution of Ala at position 330 (EU numbering) with Met;
 [19] the method of any one of [16] to [18], wherein the polypeptide comprising the antibody Fc region is an IgG antibody;

[20] the method of any one of [16] to [18], wherein the polypeptide comprising the antibody Fc

35 region is an Fc fusion protein molecule;

[21] a polypeptide produced by the method of any one of [16] to [20];

[22] a pharmaceutical composition comprising the polypeptide of any one of [1] to [10] and [21];

[23] an agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of any one of [1] to [10] and [21];

[24] an agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of any 5 one of [1] to [10] and [21];

[25] the therapeutic agent or preventive agent of [24], wherein the immunological inflammatory disease is an autoimmune disease and is a disease which may be caused by production of an antibody against an autoantigen;

[26] an agent for treating a disease, which comprises the polypeptide of any one of [1] to [10] and [21], wherein the disease is a disease with deficiency of a biologically essential protein; and

[27] an antiviral agent comprising the polypeptide of any one of [1] to [10] and [21].

The present invention also relates to the following:

[A1] A polypeptide variant comprising an antibody Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards Fc γ RIIa (type R) and Fc γ RIIa (type H), and enhanced Fc γ RIIb-binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for Fc γ RIIa (type H)] / [KD value of the polypeptide variant for Fc γ RIIb] is 4.2 or more; [A2] the polypeptide of [A1], wherein the value of [KD value of the parent polypeptide for Fc γ RIIb] / [KD value of the polypeptide variant for Fc γ RIIb] is 1.6 or more;

[A3] the polypeptide of [A1] or [A2], wherein the value of [KD value of the stronger of the binding activities of the polypeptide variant towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H)] / [KD value of the stronger of the binding activities of the parent polypeptide towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H)] is 0.7 or more;

[A4] the polypeptide of any one of [A1] to [A3], which has maintained or decreased FcγRIIIa-binding activity compared with that of a parent polypeptide;

[A5] the polypeptide of any one of [A1] to [A4], which has maintained or decreased FcγRIa-binding activity compared with that of a parent polypeptide;

[A6] the polypeptide of any one of [A1] to [A5], wherein an amino acid alteration is substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu;

[A7] the polypeptide of any one of [A1] to [A6], wherein an amino acid alteration is at least one substitution selected from the group consisting of:

substitution of Pro at position 238 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Trp; substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn; substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu; substitution of Lys at position 326 (EU numbering) with Gln; substitution of Lys at position 326 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala; substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; substitution of Gly at position 237 (EU numbering) with Leu; substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; substitution of Glu at position 233 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser; substitution of Lys at position 326 (EU numbering) with Thr; substitution of Val at position 323 (EU numbering) with Ile; substitution of Val at position 323 (EU numbering) with Leu;

substitution of Val at position 323 (EU numbering) with Met; substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ala; substitution of Lys at position 326 (EU numbering) with Asn; and substitution of Ala at position 330 (EU numbering) with Met.

[A8] the polypeptide of any one of [A1] to [A7], wherein the polypeptide comprising the antibody Fc region is an IgG antibody;

[A9] the polypeptide of any one of [A1] to [A7], wherein the polypeptide comprising the antibody Fc region is an Fc fusion protein molecule;

[A10] a pharmaceutical composition comprising the polypeptide of any one of [A1] to [A9];

[A11] an agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of any one of [A1] to [A9];

[A12] an agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of any one of [A1] to [A9];

[A13] the therapeutic agent or preventive agent of [A12], wherein the immunological inflammatory disease is an autoimmune disease and is a disease which may be caused by production of an antibody against an autoantigen;

[A14] an agent for treating a disease, which comprises the polypeptide of any one of [A1] to [A9], wherein the disease is a disease with deficiency of a biologically essential protein;

[A15] an antiviral agent comprising the polypeptide of any one of [A1] to [A9];

[A16] use of a polypeptide according to any one of [A1] to [A9] in the manufacture of a medicament for treating or preventing an immunological inflammatory disease; and [A17] use of a polypeptide according to any one of [A1] to [A9] in the manufacture of a medicament for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils.

The present invention also relates to methods for treating or preventing immunological inflammatory diseases, which comprise the step of administering to a subject a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention. Furthermore, the present invention relates to kits for use in the therapeutic methods or preventive methods of the present invention, which comprise a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention, or a polypeptide produced by the production

14b

invention. The present invention also relates to use of a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention in the production of therapeutic agents or preventive agents for immunological inflammatory diseases. In addition, the present invention relates to a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention for use in a therapeutic method or a preventive method of the present invention. The present invention also relates to methods for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprise the step of administering to a subject a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention. The present invention relates to kits for use in the inhibition method of the present invention, which comprises a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention, or a pharmaceutical composition of the present invention. The present invention relates to use of a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention in the production of agents that suppress activation of B cells, mast cells, dendritic cells, and/or basophils. The present invention relates to polypeptides of the present invention or polypeptides produced by the production methods of the present invention for use in the inhibitory methods of the present invention. The present invention relates to methods for treating diseases with deficiency of biologically essential proteins, which comprises the step of administering to a

14c

subject a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention. The present invention relates to kits for use in the therapeutic method of the present invention, which comprises a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention, or a pharmaceutical composition of the present invention. The present invention relates to use of a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention in the production of therapeutic agents for diseases with deficiency of biologically essential proteins. The present invention also relates to a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention for use in a therapeutic method of the present invention. The present invention relates to methods for inhibiting viruses, which comprises the step of administering to a subject a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention. The present invention relates to kits for use in the inhibition method of the present invention, which comprises a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention, or a pharmaceutical composition of the present invention. Furthermore, the present invention relates to use of a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention in the production of an antiviral agent. Furthermore, the present invention relates to a polypeptide of the present invention or a polypeptide produced by the production methods of the present invention for use in the inhibition method of the present invention.

Polypeptides comprising an Fc region having maintained or decreased binding activities towards both allotypes of Fc γ RIIa, types R and H, and having enhanced Fc γ RIIbbinding activity in comparison with a parent polypeptide are provided by the present invention. By using the polypeptides with enhanced binding selectivity for Fc γ RIIb than for both allotypes of Fc γ RIIa (types H and R), it is possible to transmit inhibitory signals of inflammatory immune response mediated by phosphorylation of ITIM of Fc γ RIIb in patients carrying either of the allotypes, type R and type H. Furthermore, by conferring an antibody Fc with the property of selective Fc γ RIIb binding, it may be possible to suppress anti-antibody production through the Fc γ RIIb-mediated immunosuppressive action.

Brief Description of the Drawings

Fig. 1 shows comparison of FcyRIa binding and FcyRIIb binding. Binding of the

antibody with substitution of Pro at position 238 (EU numbering) with Asp, and binding of the antibody with substitution of Leu at position 328 (EU numbering) with Glu have been labeled.

25

"Mutation A" refers to an alteration produced by substituting Pro at position 238 (EU numbering) with Asp and "mutation B" refers to an alteration produced by substituting Leu at position 328 (EU numbering) with Glu.

Fig. 2 shows comparison of FcyRIIa type H binding and FcyRIIb binding. Binding of the antibody with substitution of Pro at position 238 (EU numbering) with Asp, and binding of the antibody with substitution of Leu at position 328 (EU numbering) with Glu have been labeled. "Mutation A" refers to an alteration produced by substituting Pro at position 238 (EU numbering) with Asp, and "mutation B" refers to an alteration produced by substituting Leu at position 328 (EU numbering) with Glu.

Fig. 3 shows comparison of FcyRIIa type R binding and FcyRIIb binding. Binding of the antibody with substitution of Pro at position 238 (EU numbering) with Asp, and binding of the antibody with substitution of Leu at position 328 (EU numbering) with Glu have been labeled. "Mutation A" refers to an alteration produced by substituting Pro at position 238 (EU numbering) with Asp, and "mutation B" refers to an alteration produced by substituting Leu at

position 328 (EU numbering) with Glu.

Fig. 4 shows comparison of FcyRIIIa binding and FcyRIIb binding. Binding of the antibody with substitution of Pro at position 238 (EU numbering) with Asp, and binding of the antibody with substitution of Leu at position 328 (EU numbering) with Glu have been labeled. "Mutation A" refers to an alteration produced by substituting Pro at position 238 (EU

0 numbering) with Asp, and "mutation B" refers to an alteration produced by substituting Leu at position 328 (EU numbering) with Glu.

Fig. 5 shows the relationship between the amino acid residues constituting the Fc regions of IgG1, IgG2, IgG3, and IgG4, and EU numbering (herein, also referred to as EU INDEX).

Fig. 6 shows a graph in which the horizontal axis shows the relative value of $Fc\gamma RIIb$ binding activity of each PD variant, and the vertical axis shows the relative value of FcyRIIa type R-binding activity of each PD variant. The value for the amount of binding of each PD variant to each FcyR was divided by the value for the amount of binding of IL6R-F652, which is a control antibody prior to introduction of the alteration (altered Fc with substitution of Pro at

30 position 238 (EU numbering) with Asp), to each $Fc\gamma R$; and then the obtained value was multiplied by 100, and used as the relative binding activity value for each PD variant to each Fc γ R. The F652 plot in the figure shows the value for IL6R-F652.

Fig. 7 shows a graph in which the vertical axis shows the relative value of FcyRIIbbinding activity of variants produced by introducing each alteration into GpH7-B3 which does

35 not have the P238D alteration, and the horizontal axis shows the relative value of FcyRIIbbinding activity of variants produced by introducing each alteration into IL6R-F652 which has

0

the P238D alteration. The value for the amount of $Fc\gamma RIIb$ binding of each variant was divided by the value for the amount of $Fc\gamma RIIb$ binding of the pre-altered antibody; and then the obtained value was multiplied by 100, and used as the value of relative binding activity. Here, region A contains alterations that exhibit the effect of enhancing $Fc\gamma RIIb$ binding in both cases where an alteration is introduced into GpH7-B3 which does not have P238D and where an alteration is introduced into IL6R-F652 which has P238D. Region B contains alterations that exhibit the effect of enhancing $Fc\gamma RIIb$ binding when introduced into GpH7-B3 which does not have P238D, but do not exhibit the effect of enhancing $Fc\gamma RIIb$ binding when introduced into IL6R-F652 which has P238D.

Fig. 8 shows a crystal structure of the Fc(P238D) / $Fc\gamma RIIb$ extracellular region complex.

Fig. 9 shows an image of superimposing the crystal structure of the Fc(P238D) / Fc γ RIIb extracellular region complex and the model structure of the Fc(WT) / Fc γ RIIb extracellular region complex, with respect to the Fc γ RIIb extracellular region and the Fc CH2 domain A by the least squares fitting based on the C α atom pair distances.

Fig. 10 shows comparison of the detailed structure around P238D after superimposing the crystal structure of the Fc(P238D) / Fc γ RIIb extracellular region complex and the model structure of the Fc(WT) / Fc γ RIIb extracellular region complex with respect to the only Fc CH2 domain A or the only Fc CH2 domain B by the least squares fitting based on the C α atom pair distances.

Fig. 11 shows that a hydrogen bond can be found between the main chain of Gly at position 237 (EU numbering) in Fc CH2 domain A, and Tyr at position 160 in FcγRIIb in the crystal structure of the Fc(P238D) / FcγRIIb extracellular region complex.

Fig. 12 shows that an electrostatic interaction can be found between Asp at position 270
(EU numbering) in Fc CH2 domain B, and Arg at position 131 in FcγRIIb in the crystal structure of the Fc(P238D) / FcγRIIb extracellular region complex.

Fig. 13 shows a graph in which the horizontal axis shows the relative value of $Fc\gamma RIIb$ binding activity of each 2B variant, and the vertical axis shows the relative value of $Fc\gamma RIIa$ type R-binding activity of each 2B variant. The value for the amount of binding of each 2B variant to

30 each FcγR was divided by the value for the amount of binding of a control antibody prior to alteration (altered Fc with substitution of Pro at position 238 (EU numbering) with Asp) to each FcγR; and then the obtained value was multiplied by 100, and used as the value of relative binding activity of each 2B variant towards each FcγR.

Fig. 14 shows Glu at position 233 (EU numbering) in Fc Chain A and the surrounding
residues in the extracellular region of FcγRIIb in the crystal structure of the Fc(P238D) / FcγRIIb extracellular region complex.

Fig. 15 shows Ala at position 330 (EU numbering) in Fc Chain A and the surrounding residues in the extracellular region of $Fc\gamma RIIb$ in the crystal structure of the Fc(P238D) / Fc $\gamma RIIb$ extracellular region complex.

Fig. 16 shows the structures of Pro at position 271 (EU numbering) of Fc Chain B after superimposing the crystal structures of the Fc(P238D) / Fc γ RIIb extracellular region complex and the Fc(WT) / Fc γ RIIIa extracellular region complex by the least squares fitting based on the C α atom pair distances with respect to Fc Chain B.

Mode for Carrying Out the Invention

The present invention provides polypeptides comprising an IgG Fc region that have maintained or decreased Fc γ RIIa-binding, and having enhanced Fc γ RIIb-binding activity in comparison with a parent polypeptide by introducing amino acid substitution(s) into the IgG Fc region.

More specifically, the present invention provides a polypeptide comprising an antibody 5 Fc region that comprises a substitution of Pro at position 238 (EU numbering) with Asp or substitution of Leu at position 328 (EU numbering) with Glu, and a polypeptide comprising an antibody Fc region that comprises combination of a substitution of Pro at position 238 (EU numbering) with Asp and several specific amino acid substitutions. Furthermore, the present invention provides a method for maintaining or decreasing binding activity towards both

0 allotypes of Fc γ RIIa and enhancing the Fc γ RIIb-binding activity in comparison with a parent polypeptide. The present invention also provides a method for suppressing the antibody production in comparison with a parent polypeptide when the polypeptide is administered *in vivo*.

"Polypeptides of the present invention" generally refers to peptides or proteins
approximately ten amino acids or more in length. Furthermore, they are generally polypeptides derived from organisms, but are not particularly limited, and for example, they may be polypeptides comprising an artificially designed sequence. Furthermore, they may be any of naturally-occurring polypeptides, synthetic polypeptides, recombinant polypeptides, or such.

"Fcγ receptors" (herein, referred to as Fcγ receptors or FcγR) refers to receptors that 30 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 Fcγ receptor genes. In humans, this family includes FcγRI (CD64) including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32) including isoforms FcγRIIa (including allotypes H131 (type H) and R131 (type R)), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16) including isoforms

35 FcγRIIIa (including allotypes V158 and F158), and FcγRIIIb (including allotypes FcγRIIIb-NA1 and FcγRIIIb-NA2), and any human FcγRs, FcγR isoforms or allotypes yet to be discovered, but

is not limited thereto. The FcγR includes human, mouse, rat, rabbit, and monkey-derived FcγRs but is not limited thereto, and may be derived from any organism. Mouse FcγRs include FcγRI (CD64), FcγRII (CD32), FcγRIII (CD16), and FcγRIII-2 (CD16-2), and any mouse FcγRs, or FcγR isoforms or allotypes yet to be discovered, but are not limited thereto. Favorable examples of such Fcγ receptors include human FcγRI (CD64), FcγRIIA (CD32), FcγRIIB (CD32), FcγRIIB (CD32), FcγRIIB (CD16).

The polynucleotide sequence and amino acid sequence of FcγRI are set forth in SEQ ID NOs: 1 (NM_000566.3) and 2 (NP_000557.1), respectively;

the polynucleotide sequence and amino acid sequence of $Fc\gamma RIIA$ are set forth in SEQ ID NOs: 3 (BC020823.1) and 4 (AAH20823.1), respectively;

the polynucleotide sequence and amino acid sequence of FcγRIIB are set forth in SEQ ID NOs: 5 (BC146678.1) and 6 (AAI46679.1), respectively;

the polynucleotide sequence and amino acid sequence of FcγRIIIA are set forth in SEQ ID NOs: 7 (BC033678.1) and 8 (AAH33678.1), respectively; and

the polynucleotide sequence and amino acid sequence of FcγRIIIB are set forth in SEQ ID NOs
 9 (BC128562.1) and 10 (AAI28563.1), respectively (the RefSeq Registration number is indicated inside the parentheses).

In Fc γ RIIa, there are two allotypes, one where the amino acid at position 131 of Fc γ RIIa is histidine (type H) and the other where this amino acid is substituted with arginine (type R) (J. Exp. Med, 172: 19-25, 1990).

Herein, "parent polypeptide" refers to a polypeptide that will serve as the basis for the production of polypeptides comprising an antibody Fc region of the present invention. More specifically, it is a polypeptide comprising an antibody Fc region and is the polypeptide prior to alteration of at least one amino acid in the Fc region. The parent polypeptide in the present invention may be, for example, a polypeptide comprising the Fc region of a naturally-occurring

IgG, or it may be a polypeptide comprising an Fc region of an IgG to which an alteration other than the amino acid alterations of the present invention has been made to a naturally-occurring IgG.

"Naturally-occurring IgGs" refers to polypeptides belonging to a class of antibodies practically encoded by immunoglobulin gamma genes and comprising an amino acid sequence identical to those of IgGs found in nature. For example, a naturally-occurring human IgG means a naturally-occurring human IgG1, naturally-occurring human IgG2, naturally-occurring human IgG3, naturally-occurring human IgG4, or such. Naturally-occurring IgGs also include mutants spontaneously produced from them.

35

0

25

The Fc region of a naturally-occurring IgG means an Fc region comprising an amino acid sequence identical to that of the Fc region derived from an IgG found in nature. The Fc

region of a naturally-occurring IgG is shown in Fig. 5 (SEQ ID NOs: 11-14), and for example, it refers to Fc regions derived from naturally-occurring human IgG1, Fc regions derived from naturally-occurring human IgG2, Fc regions derived from naturally-occurring human IgG3, and Fc regions derived from naturally-occurring human IgG4. The Fc regions of naturally-occurring IgGs also include mutants spontaneously produced from them.

In the present invention, whether or not the binding activity towards each type of $Fc\gamma R$ is enhanced, or maintained or decreased in a polypeptide or an Fc region of the present invention can be determined, for example, by observing whether there is a decrease or an increase in the dissociation constant (KD) value obtained from the results of sensorgram analysis, where various Fc γRs are subjected to interaction as an analyte with antibodies immobilized onto the sensor chips or captured onto the sensor chips using Protein A, Protein L, Protein A/G, Protein G, antilamda chain antibodies, anti-kappa chain antibodies, antigenic peptides, antigenic proteins, or such using BIACORE which is an interaction analyzer that utilizes the surface plasmon resonance (SPR) phenomena, as shown in the Examples. Alternatively, it can also be determined

- 5 by observing whether there is an increase or a decrease in the value obtained by dividing the amount of change in the resonance unit (RU) value on the sensorgram before and after various types of FcγRs are subjected to interaction as an analyte with antibodies immobilized onto the sensor chips or captured onto the sensor chips using Protein A, Protein L, Protein A/G, Protein G, anti-lamda chain antibodies, anti-kappa chain antibodies, antigenic peptides, antigenic
- 0 proteins, or such, by the amount of change of resonance units (RU) before and after antibodies are immobilized or captured onto the sensor chip. Furthermore, it can be determined by observing an increase or a decrease in the dissociation constant (KD) values obtained from sensorgram analysis, where a sample such as an antibody to be evaluated is subjected to interaction as an analyte using a sensor chip onto which FcγR is immobilized directly or *via* an
- 25 anti-tag antibody. Alternatively, it can be determined by observing whether the amount of change in sensorgram values increases or decreases before and after a sample such as an antibody to be evaluated is subjected to interaction as an analyte with the sensor chip onto which FcγR is immobilized directly or *via* an anti-tag antibody.

Specifically, the binding activity of an Fc region towards an Fcγ receptor can be
 measured by the Amplified Luminescent Proximity Homogeneous Assay (ALPHA) screening,
 the BIACORE method which utilizes the surface plasmon resonance (SPR) phenomena, or such,
 in addition to ELISA or fluorescence activated cell sorting (FACS) (Proc. Natl. Acad. Sci. USA
 (2006) 103 (11): 4005-4010).

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.

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 mutant Fc region, the polypeptide complex comprising a wild-type Fc region interacts with the Fc γ receptor and produces 520-620 nm signals. The polypeptide complex comprising an untagged mutant Fc region competes with the polypeptide complex comprising a wild-type Fc region for interaction with the Fc γ 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 Fcγ receptor and GST in a cell carrying a fusion gene produced by fusing a polynucleotide encoding the Fcγ 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 Fcγ receptor with GST. The obtained signals are preferably analyzed, for example, by
- tagging an Fcγ 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).

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

- 30 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 dissociates). The Biacore 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
- 35 sensorgram. Kinetic parameters such as association rate constants (ka) and dissociation rate constants (kd) are determined from the curves of the sensorgram, and the dissociation constants

0

35

(KD) are determined from the ratio of these constants. In the BIACORE method, a method for measuring inhibition is preferably used. An example of the method for measuring inhibition is described in Proc. Natl. Acad. Sci USA (2006) 103 (11): 4005-4010.

A polypeptide with decreased $Fc\gamma R$ -binding activity refers to a polypeptide that binds to $Fc\gamma R$ with a substantially lower binding activity than the parent polypeptide when assay is performed by keeping the amount of the parent polypeptide and the amount of the polypeptide comprising at least one amino acid alteration in the Fc region of the parent polypeptide (also called a polypeptide variant) practically the same.

For example, in the KD values measured by the above-mentioned measurement method, the KD value ratio (KD value of a polypeptide variant / KD value of a parent polypeptide) is preferably 1.25 or more, 2 or more, or 3 or more, and more preferably, 5 or more, 10 or more, 100 or more, 1,000 or more, or 10,000 or more.

Furthermore, in the KD values measured by the above-mentioned measurement method, the KD value is preferably increased by 1 μ M or more, and more preferably increased by 2 μ M or more, 3 μ M or more, 5 μ M or more, 10 μ M or more, 20 μ M or more, 50 μ M or more, and 100 μ M or more. Furthermore, in the KD values measured by the above-mentioned measurement method, the KD value is preferably 0.0001 μ M or more, and more preferably 0.001 μ M or more, 0.01 μ M or more, 0.1 μ M or more, 0.5 μ M or more, 1 μ M or more, 2 μ M or more, 3 μ M or more, 5 μ M or more, 10 μ M or more, 100 μ M or more, or 1,000 μ M or more.

A polypeptide with enhanced $Fc\gamma R$ -binding activity refers to a polypeptide that binds to $Fc\gamma R$ with a substantially higher binding activity than the parent polypeptide when assay is performed by keeping the amount of the parent polypeptide and the amount of the polypeptide variant practically the same.

For example, in the KD values measured by the above-mentioned measurement method,
the KD value ratio (KD value of a parent polypeptide / KD value of a polypeptide variant) is
preferably 1.25 or more, 2 or more, or 3 or more, and more preferably, 5 or more, 10 or more,
100 or more, 1,000 or more, or 10,000 or more.

Furthermore, in the KD values measured by the above-mentioned measurement method, the KD value is preferably decreased by 0.001 μ M or more, and more preferably decreased by

30 0.01 μ M, 0.1 μ M, 1 μ M or more, 2 μ M or more, 3 μ M or more, 5 μ M or more, 10 μ M or more, 20 μ M or more, 50 μ M or more, and 100 μ M or more.

Furthermore, in the KD values measured by the above-mentioned measurement method, the KD value is preferably 5 μ M or less, and more preferably 3 μ M or less, 1 μ M or less, 0.5 μ M or less, 0.1 μ M or less, 0.01 μ M or less, 0.001 μ M or less, 0.001 μ M or less.

A polypeptide with unchanged (maintained) $Fc\gamma R$ -binding activity refers to a polypeptide that binds to $Fc\gamma R$ with a binding activity practically unchanged from or equivalent

0

25

30

to the parent polypeptide when assay is performed by keeping the amount of the parent polypeptide and the amount of the polypeptide comprising at least one amino acid alteration in the Fc region of the parent polypeptide (also called a polypeptide variant) practically the same.

Whether or not a polypeptide is a polypeptide having maintained or decreased $Fc\gamma RIIa$ binding activity and having enhanced $Fc\gamma RIIb$ -binding activity can be determined using the KD value of this polypeptide for $Fc\gamma RIIa$ and the KD value of this polypeptide for $Fc\gamma RIIb$ determined according to the above-mentioned examples. An example is the case where the KD value of the polypeptide of the present invention for $Fc\gamma RIIb$ is decreased compared with the KD value of the parent polypeptide for $Fc\gamma RIIb$; and the KD value of the polypeptide of the present invention for $Fc\gamma RIIa$ (type R and type H) is increased or maintained compared with the KD value of the parent polypeptide for $Fc\gamma RIIa$ (type R and type H). Furthermore, it is possible to determine by appropriately combining the KD value of the polypeptide for $Fc\gamma RIa$ and the KD value of the polypeptide for $Fc\gamma RIIa$ (type R and type H). Furthermore, it is possible to determine by appropriately combining the KD value of the polypeptide for $Fc\gamma RIa$ and the KD value of the polypeptide for $Fc\gamma RIIIa$, which were determined according to the above-mentioned example.

In the present invention, an increased $Fc\gamma RIIb$ -binding activity means that, for example, in the KD values measured by the measurement method described above, the KD ratio of [KD value of the parent polypeptide] / [KD value of the polypeptide variant] is preferably 1.6 or more, 2 or more, or 3 or more, and more preferably 5 or more, 10 or more, 20 or more, 30 or more, and 50 or more.

Maintained or decreased binding activities towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H) means that, for example, in the KD values measured by the measurement method described above, the KD ratio of [KD value for the stronger of the binding activities of a polypeptide variant towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H)] / [KD value for the stronger of the binding activities of a parent polypeptide towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H)] is preferably 0.7 or more, 1 or more, 2 or more, or 3 or more, and more preferably 5 or more, 10 or more, 20 or more, 30 or more, and 50 or more.

Polypeptides of the present invention preferably have maintained or decreased binding activities towards $Fc\gamma RIIa$ type R and $Fc\gamma RIIa$ type H. Furthermore, they preferably have maintained or decreased binding activities towards $Fc\gamma RIIa$ type R and $Fc\gamma RIIa$ type H, as well as a maintained or decreased $Fc\gamma RIIa$ -binding activity. In addition, they preferably have a

maintained or decreased binding activity towards FcyRIa.

A maintained or decreased binding activity towards FcγRIIIa or FcγRIa means that, for example, in the KD values measured by the measurement method described above, the KD ratio of [KD value of the polypeptide variant] / [KD value of the parent polypeptide] is preferably 1 or

35 more, 2 or more, or 3 or more, and more preferably 5 or more, 10 or more, 20 or more, 30 or more, and 50 or more.

Furthermore, whether or not a polypeptide of the present invention is a polypeptide with improved binding selectivity for $Fc\gamma RIIb$ rather than for $Fc\gamma RIIa$ can be determined by comparing the ratio of the KD value for $Fc\gamma RIIa$ to the KD value for $Fc\gamma RIIb$ of the polypeptide of the present invention (KD value for $Fc\gamma RIIa$ / KD value 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 peptide (KD value for $Fc\gamma RIIa$ / KD value for $Fc\gamma RIIb$), which were determined according to the above-mentioned examples. Specifically, when the value of the KD ratio for the polypeptide of the present invention is greater than that of the parent polypeptide, the polypeptide of the present invention can be determined to have an improved binding selectivity for $Fc\gamma RIIb$ rather than for $Fc\gamma RIIa$ in comparison with the parent polypeptide.

The binding selectivity between $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIb$ is, for example, a KD value ratio [KD value of the polypeptide variant for $Fc\gamma RIIa$ (type R)] / [KD value of the polypeptide variant for $Fc\gamma RIIb$] of preferably 1.2 or more, 2 or more, or 3 or more for the KD values measured by the measurement method described above, and more preferably 5 or more, 10

5 10 or more, 20 or more, or 30 or more.

The binding selectivity between $Fc\gamma RIIa$ (type H) and $Fc\gamma RIIb$ is, for example, a KD value ratio [KD value of the polypeptide variant for $Fc\gamma RIIa$ (type H)] / [KD value of the polypeptide variant for $Fc\gamma RIIb$] of preferably 4.2 or more, 5 or more, or 10 or more for the KD values measured by the measurement method described above, and more preferably 20 or more, 30 or more, 50 or more, 100 or more, or 200 or more.

Furthermore, whether or not the binding activities of the polypeptides of the present invention towards various $Fc\gamma Rs$ were maintained, enhanced, or decreased can be determined from the increase or decrease in the amount of binding of the various $Fc\gamma Rs$ to the polypeptides of the present invention, which were determined according to the examples described above.

25 Here, the amount of binding of the various FcγRs to the polypeptides refers to values obtained by determining the difference in the RU values of sensorgrams that changed before and after interaction of various FcγRs as the analyte with each polypeptide, and dividing them by differences in the RU values of sensorgrams that changed before and after capturing polypeptides to the sensor chips.

30 Whether or not the polypeptides of the present invention is a polypeptide having maintained or decreased binding activities towards FcγRIIa (type R and type H), and having increased binding activity towards FcγRIIb can be determined by using the amount of FcγRIIa binding of the polypeptide and the amount of FcγRIIb binding of the polypeptide, which were determined according to the examples described above.

35

0

An example is the case where the amount of $Fc\gamma RIIb$ binding of a polypeptide of the present invention is increased compared with the amount of $Fc\gamma RIIb$ binding of a parent

25

polypeptide, and the amount of $Fc\gamma RIIa$ (type R and type H) binding of a polypeptide of the present invention is equivalent to (maintained at) or preferably decreased from the amount of binding of a parent polypeptide towards $Fc\gamma RIIa$ (type R and type H). Furthermore, it is possible to determine by appropriately combining the amount of $Fc\gamma RIIa$ binding and the amount of $Fc\gamma RIIIa$ binding of the polypeptide determined according to the examples described above.

"Fc region" refers to the region comprising a fragment consisting of a hinge portion or a part thereof, CH2 domain, or CH3 domain in an antibody molecule. According to EU numbering (herein, also called the EU INDEX) (see Fig. 5), an IgG-class Fc region refers to, for example, the region from cysteine at position 226 to the C terminus, or from proline at position 230 to the C terminus, but is not limited thereto.

The Fc region may be obtained preferably 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.

The present invention provides an antibody constant region comprising an Fc region which comprises an alteration produced by substituting Pro at position 238 (EU numbering) with Asp or substituting Leu at position 328 (EU numbering) with Glu in human IgG (IgG1, IgG2,

IgG3, and IgG4). Polypeptides with maintained or decreased binding activities towards FcγRIa, FcγRIIa, and both allotypes of FcγRIIa, types R and H, as well as enhanced FcγRIIb-binding activity in comparison with a parent polypeptide can be provided by introducing alteration of substituting Pro at position 238 (EU numbering) with Asp or substituting Leu at position 328 (EU numbering) with Glu in human IgG.

In the present invention, at least one alteration can be further added to the human IgG Fc region comprising the alteration produced by substituting Pro at position 238 (EU numbering) with Asp or substituting Leu at position 328 (EU numbering) with Glu. Here, alteration refers to any one of, or a combination of substitutions, deletions, additions, and insertions. Additional alterations can be further included with these alterations. The additional alteration can be

- 30 selected from any one of, or combinations of amino acid substitutions, deletions, or modifications. For example, alterations that enhance the binding activity to FcγRIIb, as well as maintain or decrease binding activities towards FcγRIIa (type H) and FcγRIIa (type R) can be added. Adding such alterations improves the binding selectivity for FcγRIIb rather than for FcγRIIa.
- 35 Among them, alterations that improve the binding selectivity for FcγRIIb rather than for FcγRIIa (type R) are preferred, and alterations that improve the binding selectivity for FcγRIIb

rather than for FcγRIIa (type H) are more preferred. Preferred examples of alterations of substituting an amino acid include,

the alteration of substituting Gly at position 237 (EU numbering) with Trp, the alteration of substituting Gly at position 237 (EU numbering) with Phe, the alteration of substituting Pro at position 238 (EU numbering) with Phe, the alteration of substituting Asn at position 325 (EU numbering) with Met, the alteration of substituting Ser at position 267 (EU numbering) with Ile, the alteration of substituting Leu at position 328 (EU numbering) with Asp, the alteration of substituting Ser at position 267 (EU numbering) with Val, the alteration of substituting Leu at position 328 (EU numbering) with Val, the alteration of substituting Ser at position 328 (EU numbering) with Trp, the alteration of substituting Ser at position 267 (EU numbering) with Gln, the alteration of substituting Ser at position 267 (EU numbering) with Met, the alteration of substituting Ser at position 267 (EU numbering) with Asp, the alteration of substituting Ser at position 267 (EU numbering) with Asp, the alteration of substituting Ser at position 267 (EU numbering) with Asp, the alteration of substituting Ser at position 267 (EU numbering) with Asp, the alteration of substituting Gly at position 236 (EU numbering) with Asp, the alteration of substituting Ala at position 327 (EU numbering) with Asp,

5 the alteration of substituting Asn at position 325 (EU numbering) with Ser, the alteration of substituting Leu at position 235 (EU numbering) with Tyr, the alteration of substituting Val at position 266 (EU numbering) with Met, the alteration of substituting Leu at position 328 (EU numbering) with Tyr, the alteration of substituting Leu at position 235 (EU numbering) with Tyr,

- 0 the alteration of substituting Leu at position 235 (EU numbering) with Phe, the alteration of substituting Ser at position 239 (EU numbering) with Gly, the alteration of substituting Ala at position 327 (EU numbering) with Glu, the alteration of substituting Ala at position 327 (EU numbering) with Gly, the alteration of substituting Pro at position 238 (EU numbering) with Leu,
- 25 the alteration of substituting Ser at position 239 (EU numbering) with Leu, the alteration of substituting Leu at position 328 (EU numbering) with Thr, the alteration of substituting Leu at position 328 (EU numbering) with Ser, the alteration of substituting Leu at position 328 (EU numbering) with Met, the alteration of substituting Pro at position 331 (EU numbering) with Trp,
- 30 the alteration of substituting Pro at position 331 (EU numbering) with Tyr, the alteration of substituting Pro at position 331 (EU numbering) with Phe, the alteration of substituting Ala at position 327 (EU numbering) with Asp, the alteration of substituting Leu at position 328 (EU numbering) with Phe, the alteration of substituting Pro at position 271 (EU numbering) with Leu,
- 35 the alteration of substituting Ser at position 267 (EU numbering) with Glu, the alteration of substituting Leu at position 328 (EU numbering) with Ala,

the alteration of substituting Leu at position 328 (EU numbering) with Ile, the alteration of substituting Leu at position 328 (EU numbering) with Gln, the alteration of substituting Leu at position 328 (EU numbering) with Val, the alteration of substituting Lys at position 326 (EU numbering) with Trp, the alteration of substituting His at position 268 (EU numbering) with Arg, the alteration of substituting His at position 268 (EU numbering) with Gly, the alteration of substituting Ser at position 324 (EU numbering) with Asn, the alteration of substituting Val at position 266 (EU numbering) with Val, the alteration of substituting Pro at position 271 (EU numbering) with Gly, the alteration of substituting Ile at position 332 (EU numbering) with Phe, the alteration of substituting Ser at position 332 (EU numbering) with Phe, the alteration of substituting Tyr at position 333 (EU numbering) with Asn,

- 5 the alteration of substituting Ser at position 337 (EU numbering) with Asp, the alteration of substituting Tyr at position 300 (EU numbering) with Gln, the alteration of substituting Thr at position 335 (EU numbering) with Asp, the alteration of substituting Ser at position 239 (EU numbering) with Asn, the alteration of substituting Lys at position 326 (EU numbering) with Leu,
- 0 the alteration of substituting Lys at position 326 (EU numbering) with Ile, the alteration of substituting Ser at position 239 (EU numbering) with Glu, the alteration of substituting Lys at position 326 (EU numbering) with Phe, the alteration of substituting Lys at position 326 (EU numbering) with Val, the alteration of substituting Lys at position 326 (EU numbering) with Tyr,
- 25 the alteration of substituting Ser at position 267 (EU numbering) with Asp, the alteration of substituting Lys at position 326 (EU numbering) with Pro, the alteration of substituting Lys at position 326 (EU numbering) with His, the alteration of substituting Lys at position 334 (EU numbering) with Ala, the alteration of substituting Lys at position 334 (EU numbering) with Trp,
- 30 the alteration of substituting His at position 268 (EU numbering) with Gln, the alteration of substituting Lys at position 326 (EU numbering) with Gln, the alteration of substituting Lys at position 326 (EU numbering) with Glu, the alteration of substituting Lys at position 326 (EU numbering) with Met, the alteration of substituting Val at position 266 (EU numbering) with Ile,
- 35 the alteration of substituting Lys at position 334 (EU numbering) with Glu, the alteration of substituting Tyr at position 300 (EU numbering) with Glu,

0

the alteration of substituting Lys at position 334 (EU numbering) with Met, the alteration of substituting Lys at position 334 (EU numbering) with Val, the alteration of substituting Lys at position 334 (EU numbering) with Thr, the alteration of substituting Lys at position 334 (EU numbering) with Ser, the alteration of substituting Lys at position 334 (EU numbering) with His, the alteration of substituting Lys at position 334 (EU numbering) with Phe, the alteration of substituting Lys at position 334 (EU numbering) with Gln, the alteration of substituting Lys at position 334 (EU numbering) with Pro, the alteration of substituting Lys at position 334 (EU numbering) with Tyr, the alteration of substituting Lys at position 334 (EU numbering) with Ile, the alteration of substituting Gln at position 295 (EU numbering) with Leu, the alteration of substituting Lys at position 334 (EU numbering) with Leu, the alteration of substituting Lys at position 334 (EU numbering) with Asn, the alteration of substituting His at position 268 (EU numbering) with Ala, the alteration of substituting Ser at position 239 (EU numbering) with Asp, the alteration of substituting Ser at position 267 (EU numbering) with Ala, the alteration of substituting Leu at position 234 (EU numbering) with Trp, the alteration of substituting Leu at position 234 (EU numbering) with Tyr, the alteration of substituting Gly at position 237 (EU numbering) with Ala, the alteration of substituting Gly at position 237 (EU numbering) with Asp,

- the alteration of substituting Gly at position 237 (EU numbering) with Glu, the alteration of substituting Gly at position 237 (EU numbering) with Leu, the alteration of substituting Gly at position 237 (EU numbering) with Met, the alteration of substituting Gly at position 237 (EU numbering) with Tyr,
- 25 the alteration of substituting Ala at position 330 (EU numbering) with Lys, the alteration of substituting Ala at position 330 (EU numbering) with Arg, the alteration of substituting Glu at position 233 (EU numbering) with Asp, the alteration of substituting His at position 268 (EU numbering) with Asp, the alteration of substituting His at position 268 (EU numbering) with Glu,
- the alteration of substituting Lys at position 326 (EU numbering) with Asp,
 the alteration of substituting Lys with Ser at position 326 (EU numbering),
 the alteration of substituting Lys with Thr at position 326 (EU numbering),
 the alteration of substituting Val with Ile at position 323 (EU numbering),
 the alteration of substituting Val with Leu at position 323 (EU numbering),
- 35 the alteration of substituting Val at position 323 (EU numbering) with Met, the alteration of substituting Tyr at position 296 (EU numbering) with Asp,

the alteration of substituting Lys at position 326 (EU numbering) with Ala, the alteration of substituting Lys at position 326 (EU numbering) with Asn, and the alteration of substituting Ala at position 330 (EU numbering) with Met.

Furthermore, examples of preferred amino acid substitutions among these alterations include

the alteration of substituting Gly at position 237 (EU numbering) with Trp, the alteration of substituting Gly at position 237 (EU numbering) with Phe, the alteration of substituting Ser at position 267 (EU numbering) with Val, the alteration of substituting Ser at position 267 (EU numbering) with Gln, the alteration of substituting His at position 268 (EU numbering) with Asn, the alteration of substituting Pro at position 271 (EU numbering) with Gly, the alteration of substituting Lys at position 326 (EU numbering) with Gln, the alteration of substituting Lys at position 326 (EU numbering) with Gln, the alteration of substituting Lys at position 326 (EU numbering) with Gln,

5 the alteration of substituting Lys at position 326 (EU numbering) with Met, the alteration of substituting Ser at position 239 (EU numbering) with Asp, the alteration of substituting Ser at position 267 (EU numbering) with Ala, the alteration of substituting Leu at position 234 (EU numbering) with Trp, the alteration of substituting Leu at position 234 (EU numbering) with Tyr,

0 the alteration of substituting Gly at position 237 (EU numbering) with Ala, the alteration of substituting Gly at position 237 (EU numbering) with Asp, the alteration of substituting Gly at position 237 (EU numbering) with Glu, the alteration of substituting Gly at position 237 (EU numbering) with Leu, the alteration of substituting Gly at position 237 (EU numbering) with Met,

25 the alteration of substituting Gly at position 237 (EU numbering) with Tyr, the alteration of substituting Ala at position 330 (EU numbering) with Lys, the alteration of substituting Ala at position 330 (EU numbering) with Arg, the alteration of substituting Glu at position 233 (EU numbering) with Asp, the alteration of substituting His at position 268 (EU numbering) with Asp,

30 the alteration of substituting His at position 268 (EU numbering) with Glu, the alteration of substituting Lys at position 326 (EU numbering) with Asp, the alteration of substituting Lys at position 326 (EU numbering) with Ser, the alteration of substituting Lys at position 326 (EU numbering) with Thr, the alteration of substituting Val at position 323 (EU numbering) with Ile,

35 the alteration of substituting Val at position 323 (EU numbering) with Leu, the alteration of substituting Val at position 323 (EU numbering) with Met, the alteration of substituting Tyr at position 296 (EU numbering) with Asp, the alteration of substituting Lys at position 326 (EU numbering) with Ala, the alteration of substituting Lys at position 326 (EU numbering) with Asn, and the alteration of substituting Ala at position 330 (EU numbering) with Met.

The alteration mentioned above may be an alteration introduced at one position, and alternatively, or alterations at two or more positions can be combined. Preferred examples of such alterations include those mentioned in Tables 6-7 and Tables 9-12.

Furthermore, for example, amino acid substitutions that improve FcRn-binding activity (J. Immunol. 2006 Jan 1; 176(1): 346-56; J Biol Chem. 2006 Aug 18; 281(33): 23514-24; Int. Immunol. 2006 Dec; 18(12): 1759-69; Nat Biotechnol. 2010 Feb; 28(2): 157-9.; 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 introduced into an antibody constant region portion. Alternatively, polypeptides produced by conferring polypeptides of the present invention with the property of promoting disappearance of antigens,

5 which are described in WO 2011/122011 or PCT/JP2011/072550, and polypeptides conferring the property for repeated binding to a plurality of antigen molecules, which are described in WO 2009/125825 or PCT/JP2011/077619, are also included in the present invention.

Preferred examples of polypeptides of the present invention include IgG antibodies.
When an IgG antibody is used as the antibody, the type of constant region is not limited, and an
IgG isotypes (subclasses) such as IgG1, IgG2, IgG3, and IgG4 can be used. IgG antibodies of the present invention are preferably human IgG, and more preferably human IgG1 and human IgG4. The amino acid sequences of the heavy-chain constant regions of human IgG1 and human IgG4 are known. A plurality of allotype sequences due to genetic polymorphisms have been described in Sequences of Proteins of Immunological Interest, NIH Publication No. 91-3242 for the human IgG1 constant region, and any of the sequences may be used in the present invention.

<Substitution>

When substituting amino acid residues, substitution to a different amino acid residue is carried out with the objective of altering aspects such as (a)-(c) described below:

- 30 (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.

Amino acid residues are classified into the following groups based on their general side chain properties:

- 35 (1) hydrophobic: norleucine, met, ala, val, leu, and ile;
 - (2) neutral hydrophilic: cys, ser, thr, asn, and gln;

(3) acidic: asp and glu;

(4) basic: his, lys, and arg;

(5) residues that affect the chain orientation: gly and pro; and

(6) aromatic: trp, tyr, and phe.

Substitution between amino acid residues within each of these amino acid groups is referred to as conservative substitution, and amino acid residue substitution between different groups is referred to as non-conservative substitution. Substitutions in the present invention may be conservative substitutions or non-conservative substitutions, or a combination of conservative substitutions and non-conservative substitutions.

Amino acid sequence alterations are produced by various methods known to those skilled in the art. Such methods include the site-directed mutagenesis method (Hashimoto-Gotoh, T, Mizuno, T, Ogasahara, Y, and Nakagawa, M. (1995) An oligodeoxyribonucleotidedirected dual amber method for site-directed mutagenesis. Gene 152: 271-275; Zoller, MJ, and Smith, M. (1983) Oligonucleotide-directed mutagenesis of DNA fragments cloned into M13

- 5 vectors. Methods Enzymol. 100: 468-500; Kramer, W, Drutsa, V, Jansen, HW, Kramer, B, Pflugfelder, M, and Fritz, HJ (1984) The gapped duplex DNA approach to oligonucleotidedirected mutation construction. Nucleic Acids Res. 12: 9441-9456; Kramer W, and Fritz HJ (1987) Oligonucleotide-directed construction of mutations via gapped duplex DNA Methods. Enzymol. 154, 350-367; and Kunkel, TA (1985) Rapid and efficient site-specific mutagenesis
- 0 without phenotypic selection. Proc Natl Acad Sci U S A. 82: 488-492), the PCR mutation method, and the cassette mutation method, but are not limited thereto.

Amino acid modification of the present invention includes post-translational modification. A specific post-translational modification may be addition or deletion of a sugar chain. For example, in the IgG1 constant region consisting of the amino acid sequence of SEQ

- 25 ID NO: 11, the amino acid residue at position 297 (EU numbering) may be sugar chainmodified. The sugar-chain structure for the modification is not limited. Generally, antibodies expressed in eukaryotic cells comprise glycosylation in the constant region. Therefore, antibodies expressed in cells such as those below are normally modified by some type of sugar chain:
- 30 antibody-producing cells of mammals
 - eukaryotic cells transformed with an expression vector comprising a DNA encoding an antibody

Eukaryotic cells shown here include yeast and animal cells. For example, CHO cells and HEK293H cells are representative animal cells used in transformation with an expression

35 vector comprising an antibody-encoding DNA. On the other hand, those without glycosylation at this site are also included in the constant region of 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*.

Specifically, for example, sialic acid may be added to the sugar chain of an Fc region (MAbs. 2010 Sep-Oct; 2(5): 519-27).

<Antibody>

Furthermore, the present invention provides antibodies comprising an Fc region in which any of the above-mentioned amino acid sequences is altered.

The term "antibody/antibodies" in the present invention is used in the broadest sense, and as long as the desired biological activity is shown, it comprises any antibody such as monoclonal antibodies (including full-length monoclonal antibodies), polyclonal antibodies, antibody variants, antibody fragments, polyspecific antibodies (multi-specific antibodies) (for example, bispecific antibodies (diabodies)), chimeric antibodies, and humanized antibodies.

Regarding the antibodies of the present invention, the antigen type and antibody origin are not limited, and they may be any type of antibodies. The origin of the antibodies is not particularly limited, but examples include human antibodies, mouse antibodies, rat antibodies, and rabbit antibodies.

Methods for producing the antibodies are well known to those skilled in the art, and for example, monoclonal antibodies may be produced by the hybridoma method (Kohler and Milstein, Nature 256: 495 (1975)), or the recombination method (U.S. Patent No. 4,816,567).

Alternatively, they may be isolated from a phage antibody library (Clackson *et al.*, Nature 352: 624-628 (1991); Marks *et al.*, J.Mol.Biol. 222: 581-597 (1991)).

A humanized antibody is also called a reshaped human antibody. Specifically, humanized antibodies prepared by grafting the CDRs of a non-human animal antibody such as a 25 mouse antibody to a human antibody and such are known. Common genetic engineering techniques for obtaining humanized antibodies are also known. Specifically, for example, overlap extension PCR is known as a method for grafting mouse antibody CDRs to human FRs.

A vector for expressing a humanized antibody can be produced by inserting a DNA encoding an antibody variable region in which three CDRs and four FRs are ligated and a DNA 30 encoding a human antibody constant region into an expression vector so that these DNAs are fused in frame. After this integration vector is transfected into a host to establish recombinant cells, these cells are cultured, and the DNA encoding the humanized antibody is expressed to produce the humanized antibody in the culture of the cells (see, European Patent Publication No. EP 239,400, and International Patent Publication No. WO 1996/002576).

35 As necessary, an amino acid residue in an FR may be substituted so that the CDRs of a reshaped human antibody form an appropriate antigen-binding site. For example, a mutation can

be introduced into the amino acid sequence of an FR by applying the PCR method used for grafting mouse CDRs to human FRs.

A desired human antibody can be obtained by DNA immunization using a transgenic animal having the complete repertoire of human antibody genes (see International Publication Nos. WO 1993/012227, WO 1992/003918, WO 1994/02602, WO 1994/025585, WO 1996/034096, and WO 1996/033735) as an animal for immunization.

Furthermore, technologies for obtaining a human antibody by panning using a human antibody library are known. For example, a human antibody V region is expressed on the surface of a phage as a single-chain antibody (scFv) by the phage display method. The scFvexpressing phage that binds to the antigen can be selected. The DNA sequence that encodes the V region of the antigen-bound human antibody can be determined by analyzing the genes of the selected phage. After determining the DNA sequence of the scFv that binds to the antigen, an expression vector can be prepared by fusing the V-region sequence in-frame with the sequence of a desired human antibody C region, and then inserting this into a suitable expression vector.

5 The expression vector is introduced into suitable expression cells such as those described above, and the human antibody can be obtained by expressing the human antibody-encoding gene. These methods are already known (see, International Publication Nos. WO 1992/001047, WO 1992/020791, WO 1993/006213, WO 1993/011236, WO 1993/019172, WO 1995/001438, and WO 1995/15388).

0

25

Variable regions constituting the antibodies of the present invention can be variable regions that recognize any antigen.

Herein, there is no particular limitation on the antigen, and it may be any antigens. Examples of such antigens preferably include ligands (cytokines, chemokines, and such), receptors, cancer antigens, MHC antigens, differentiation antigens, immunoglobulins, and immune complexes partly containing immunoglobulins.

Examples of cytokines include interleukins 1 to 18, colony stimulating factors (G-CSF, M-CSF, GM-CSF, etc.), interferons (IFN- α , IFN- β , IFN- γ , etc.), growth factors (EGF, FGF, IGF, NGF, PDGF, TGF, HGF, etc.), tumor necrosis factors (TNF- α and TNF- β), lymphotoxin, erythropoietin, leptin, SCF, TPO, MCAF, and BMP.

30 Examples of chemokines include CC chemokines such as CCL1 to CCL28, CXC chemokines such as CXCL1 to CXCL17, C chemokines such as XCL1 and XCL2, and CX3C chemokines such as CX3CL1.

Examples of receptors include receptors belonging to receptor families such as the hematopoietic growth factor receptor family, cytokine receptor family, tyrosine kinase-type

35 receptor family, serine/threonine kinase-type receptor family, TNF receptor family, G proteincoupled 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 BA., King RJB., van der Molen HJ. ed. New Comprehesive Biochemistry Vol.18B "Hormones and their Actions Part II" pp.1-46 (1988) Elsevier Science Publishers BV; Patthy (Cell (1990) 61 (1): 13-14); Ullrich *et al.* (Cell (1990) 61 (2): 203-212); Massagué (Cell (1992) 69 (6): 1067-1070); Miyajima *et al.* (Annu. Rev. Immunol. (1992) 10: 295-331); Taga *et al.* (FASEB J. (1992) 6, 3387-3396); Fantl *et al.* (Annu. Rev. Biochem. (1993), 62: 453-481); Smith *et al.* (Cell (1994) 76 (6): 959-962); and Flower DR. Flower (Biochim. Biophys. Acta (1999) 1422 (3): 207-234).

Examples of specific receptors belonging to the above-mentioned receptor families preferably include human or mouse erythropoietin (EPO) receptors (Blood (1990) 76 (1): 31-35; and Cell (1989) 57 (2): 277-285), human or mouse granulocyte-colony stimulating factor (G-CSF) receptors (Proc. Natl. Acad. Sci. USA. (1990) 87 (22): 8702-8706, mG-CSFR; Cell (1990) 61 (2): 341-350), human or mouse thrombopoietin (TPO) receptors (Proc Natl Acad Sci U S A. (1992) 89 (12): 5640-5644; EMBO J. (1993) 12(7): 2645-53), human or mouse insulin receptors

5 (Nature (1985) 313 (6005): 756-761), human or mouse Flt-3 ligand receptors (Proc. Natl. Acad. Sci. USA. (1994) 91 (2): 459-463), human or mouse platelet-derived growth factor (PDGF) receptors (Proc. Natl. Acad. Sci. USA. (1988) 85 (10): 3435-3439), human or mouse interferon (IFN)- α and β receptors (Cell (1990) 60 (2): 225-234; and Cell (1994) 77 (3): 391-400), human or mouse leptin receptors, human or mouse growth hormone (GH) receptors, human or mouse

0 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.

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 preferably include 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 (Int J Cancer. (2003) 103 (4): 455-65), as well as EpCAM which is expressed in several cancers including lung cancer (Proc Natl Acad Sci

30 USA. (1989) 86 (1): 27-31), CA19-9, CA15-3, and sialyl SSEA-1 (SLX).

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.

Differentiation antigens may include CD1, CD2, CD4, CD5, CD6, CD7, CD8, CD10,
35 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.

Immunoglobulins include IgA, IgM, IgD, IgG, and IgE. Immunocomplexes include a component of at least any of the immunoglobulins.

Other antigens include, for example, the molecules below: 17-IA, 4-1BB, 4Dc, 6-keto-PGF1a, 8iso-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-1antitrypsin, 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,
- 5 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, CCR10, CCR2, CCR3, CCR4,
- 25 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,
- 30 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
- 35 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), GDF-8 (myostatin), GDF-9, GDF-15 (MIC-1), GDNF, 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-5 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 (INF)-alpha, INF-beta, INF-gamma, inhibin, iNOS, insulin 0 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, 25 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, 30 MARC, MCAM, 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-C adherin, NCA 90,
- 35 NCAM, 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,

0

OX40L, OX40R, p150, p95, PADPr, parathyroid hormone, PARC, PARP, PBR, PBSF, PCAD, P-cadherin, PCNA, PDGF, PDGF, PDK-1, PECAM, PEM, PF4, PGE, PGF, PGI2, PGJ2, PIN, PLA2, placental alkaline phosphatase (PLAP), PlGF, PLP, PP14, proinsulin, prorelaxin, protein C, PS, PSA, PSCA, prostate-specific membrane antigen (PSMA), PTEN, PTHrp, Ptk, PTN, R51, RANK, RANKL, RANTES, 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 (tumorassociated 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, TNFc, 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, TRUNDD), 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),

25 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

TNFRSF7 (CD27), TNFRSF8 (CD30), TNFRSF9 (4-1BB CD137, ILA), TNFRSF21 (DR6),

 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

35 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, VEFGR-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, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, WNT16, XCL1, XCL2, XCR1, XCR1, XEDAR, XIAP, XPD, HMGB1, IgA, Aβ, 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 XIII, factor XIII, factor XIIIa, TFPI, antithrombin III, EPCR, thrombomodulin, TAPI, tPA, plasminogen, plasmin, PAI-1, PAI-2, GPC3, Syndecan-1,

5 Syndecan-2, Syndecan-3, Syndecan-4, LPA, and S1P; and receptors for hormone and growth factors.

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 is 50% or more, preferably 80% or more, and more preferably 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. In the antibodies of the present invention, alteration of amino acid sequence may be at least one of amino acid residue substitution, addition, deletion, and modification.

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, the antibodies of the present invention comprise the variable regions in which the glutamine is modified to pyroglutamic acid.

Antibody variable regions of the present invention 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

35 these non-human antibodies, and human antibodies. "Humanized antibodies", also referred to as "reshaped human antibodies", are antibodies in which the complementarity determining regions (CDRs) of an antibody derived from a non-human mammal, for example, a mouse antibody, are transplanted into the CDRs of a human antibody. Methods for identifying CDRs are known (Kabat *et al.*, Sequence of Proteins of Immunological Interest (1987), National Institute of Health, Bethesda, Md.; Chothia *et al.*, Nature (1989) 342: 877). Their common genetic recombination techniques are also known (see, European Patent Application Publication No. EP 125023 and WO 96/02576). Furthermore, these antibodies may have various amino acid substitutions introduced into their variable regions to improve their antigen binding, pharmacokinetics, stability, and antigenicity. Variable regions of the antibodies of the present invention may be able to bind antigens repeatedly due to their pH dependability in antigen binding (WO 2009/125825).

 κ chain and λ chain-type constant regions are present in antibody light-chain constant regions, but either one of the light chain constant regions is acceptable. Furthermore, light-chain constant regions of the present invention may be light-chain constant regions with amino acid alterations such as substitutions, deletions, additions, and/or insertions.

For example, for the heavy chain constant regions of an antibody of the present invention, heavy chain constant regions of human IgG antibodies may be used and heavy chain constant regions of human IgG1 antibodies and those of human IgG4 antibodies are preferred.

Furthermore, polypeptides of the present invention may be made into Fc fusion protein molecules by linking to other proteins, physiologically active peptides, and such.

Examples of the other proteins and biologically active peptides include receptors, adhesion molecules, ligands, and enzymes, but are not limited thereto.

Preferred examples of Fc fusion protein molecules of the present invention include proteins with Fc domain fused to a receptor protein that binds to a target, and such examples include TNFR-Fc fusion protein, IL1R-Fc fusion protein, VEGFR-Fc fusion protein, and CTLA4-Fc fusion protein (Nat Med. 2003 Jan; 9(1): 47-52; BioDrugs. 2006; 20(3): 151-60). Furthermore, a protein to be fused to a polypeptide of the present invention may be any molecule as long as it binds to a target molecule, and examples include scFv molecules (WO 2005/037989), single-domain antibody molecules (WO 2004/058821; WO 2003/002609), antibody-like molecules (Current Opinion in Biotechnology 2006, 17: 653-658; Current Opinion

 in Biotechnology 2007, 18: 1-10; Current Opinion in Structural Biology 1997, 7: 463-469; and Protein Science 2006, 15: 14-27) such as DARPins (WO 2002/020565), Affibody (WO 1995/001937), Avimer (WO 2004/044011; WO 2005/040229), and Adnectin (WO 2002/032925). Furthermore, antibodies and Fc fusion protein molecules may be multispecific antibodies that bind to multiple types of target molecules or epitopes.

35 Furthermore, the antibodies of the present invention include antibody modification products. Such antibody modification products include, for example, antibodies linked with

39

0

25

various molecules such as polyethylene glycol (PEG) and cytotoxic substances. Such antibody modification products can be obtained by chemically modifying antibodies of the present invention. Methods for modifying antibodies are already established in this field.

The antibodies of the present invention may also be bispecific antibodies. "Bispecific antibody" refers to an antibody that has in a single molecule variable regions that recognize different epitopes. The epitopes may be present in a single molecule or in different molecules.

The polypeptides of the present invention can be prepared by the methods known to those skilled in the art. For example, the antibodies can be prepared by the methods described below, but the methods are not limited thereto.

A DNA encoding an antibody heavy chain in which one or more amino acid residues in the Fc region have been substituted with other amino acids of interest and DNA encoding an antibody light chain, are expressed. A DNA encoding a heavy chain in which one or more amino acid residues in the Fc region are substituted with other amino acids of interest can be prepared, for example, by obtaining a DNA encoding the Fc region of a natural heavy chain, and

5 introducing an appropriate substitution so that a codon encoding a particular amino acid in the Fc region encodes another amino acid of interest.

Alternatively, a DNA encoding a heavy chain in which one or more amino acid residues in the Fc region are substituted with other amino acids of interest can also be prepared by designing and then chemically synthesizing a DNA encoding a protein in which one or more

amino acid residues in the Fc region of the natural heavy chain are substituted with other amino acids of interest. The position and type of amino acid substitution are not particularly limited.
 Furthermore, alteration is not limited to substitution, and alteration may be any of deletion, addition, or insertion, or combination thereof.

Alternatively, a DNA encoding a heavy chain in which one or more amino acid residues in the Fc region are substituted with other amino acids of interest can be prepared as a combination of partial DNAs. Such combinations of partial DNAs include, for example, the combination of a DNA encoding a variable region and a DNA encoding a constant region, and the combination of a DNA encoding an Fab region and a DNA encoding an Fc region, but are not limited thereto. Furthermore, a DNA encoding a light chain can similarly be prepared as a

30 combination of partial DNAs.

Methods for expressing the above-described DNAs include the methods described below. For example, a heavy chain expression vector is constructed by inserting a DNA encoding a heavy chain variable region into an expression vector along with a DNA encoding a heavy chain constant region. Likewise, a light chain expression vector is constructed by

35 inserting a DNA encoding a light chain variable region into an expression vector along with a DNA encoding a light chain constant region. Alternatively, these heavy and light chain genes

may be inserted into a single vector.

When inserting a DNA encoding the antibody of interest into an expression vector, the DNA is inserted so that the antibody is expressed under the control of an expression-regulating region such as an enhancer or promoter. Next, host cells are transformed with this expression vector to express the antibody. In such cases, an appropriate combination of host and expression vector may be used.

Examples of the vectors include M13 vectors, pUC vectors, pBR322, pBluescript, and pCR-Script. Alternatively, when aiming to subclone and excise cDNA, in addition to the vectors described above, pGEM-T, pDIRECT, pT7, and such can be used.

Expression vectors are particularly useful when using vectors for producing the polypeptides of the present invention. For example, when a host cell is *E. coli* such as JM109, DH5 α , HB101, and XL1-Blue, the expression vectors must carry a promoter that allows efficient expression in *E. coli*, for example, lacZ promoter (Ward *et al.*, Nature (1989) 341: 544-546; FASEB J. (1992) 6: 2422-2427; its entirety are incorporated herein by reference), araB promoter

5 (Better *et al.*, Science (1988) 240: 1041-1043; its entirety are incorporated herein by reference), T7 promoter, or such. Such vectors include pGEX-5X-1 (Pharmacia), "QIAexpress system" (Qiagen), pEGFP, or pET (in this case, the host is preferably BL21 that expresses T7 RNA polymerase) in addition to the vectors described above.

The vectors may contain signal sequences for polypeptide secretion. As a signal sequence for polypeptide secretion, a pelB signal sequence (Lei, S. P. *et al* J. Bacteriol. (1987) 169: 4379; its entirety are incorporated herein by reference) may be used when a polypeptide is secreted into the *E. coli* periplasm. The vector can be introduced into host cells by lipofectin method, calcium phosphate method, and DEAE-Dextran method, for example.

In addition to *E. coli* expression vectors, the vectors for producing the polypeptides of the present invention include mammalian expression vectors (for example, pcDNA3 (Invitrogen), pEGF-BOS (Nucleic Acids. Res. 1990, 18(17): p5322; its entirety are incorporated herein by reference), pEF, and pCDM8), insect cell-derived expression vectors (for example, the "Bac-to-BAC baculovirus expression system" (Gibco-BRL) and pBacPAK8), plant-derived expression vectors (for example, pMH1 and pMH2), animal virus-derived expression vectors (for example,

30 pHSV, pMV, and pAdexLcw), retroviral expression vectors (for example, pZIPneo), yeast expression vectors (for example, "Pichia Expression Kit" (Invitrogen), pNV11, and SP-Q01), and *Bacillus subtilis* expression vectors (for example, pPL608 and pKTH50), for example.

When aiming for expression in animal cells such as CHO, COS, and NIH3T3 cells, the vectors must have a promoter essential for expression in cells, for example, SV40 promoter

35 (Mulligan *et al.*, Nature (1979) 277: 108; its entirety are incorporated herein by reference),
 MMTV-LTR promoter, EF1α promoter (Mizushima *et al.*, Nucleic Acids Res. (1990) 18: 5322;

its entirety are incorporated herein by reference), CAG promoter (Gene. (1990) 18: 5322; its entirety are incorporated herein by reference), and CMV promoter, and more preferably they have a gene for selecting transformed cells (for example, a drug resistance gene that allows evaluation using an agent (neomycin, G418, or such)). Vectors with such characteristics include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, and pOP13, for example.

In addition, the following method can be used for stable gene expression and gene copy number amplification in cells: CHO cells deficient in a nucleic acid synthesis pathway are introduced with a vector that carries a DHFR gene which compensates for the deficiency (for example, pCHOI), and the vector is amplified using methotrexate (MTX). Alternatively, the following method can be used for transient gene expression: COS cells with a gene expressing SV40 T antigen on their chromosome are transformed with a vector with an SV40 replication origin (pcD and such). Replication origins derived from polyoma virus, adenovirus, bovine papilloma virus (BPV), and such can also be used. To amplify gene copy number in host cells, the expression vectors may further carry selection markers such as aminoglycoside transferase

5 (APH) gene, thymidine kinase (TK) gene, *E. coli* xanthine-guanine phosphoribosyltransferase (Ecogpt) gene, and dihydrofolate reductase (dhfr) gene.

Antibodies can be collected, for example, by culturing transformed cells, and then separating the antibodies from the inside of the transformed cells or from the culture media. Antibodies can be separated and purified using an appropriate combination of methods such as

0 centrifugation, ammonium sulfate fractionation, salting out, ultrafiltration, 1q, FcRn, protein A, protein G column, affinity chromatography, ion exchange chromatography, and gel filtration chromatography.

Furthermore, the present invention provides methods for producing a polypeptide comprising an antibody Fc region having maintained or decreased FcγRIIa-binding activity, and enhanced FcγRIIb-binding activity in comparison with a parent polypeptide, which comprises adding at least one amino acid alteration to the Fc region of the polypeptide.

Examples include production methods comprising the following steps: (a) adding at least one amino acid alteration to the Fc region of polypeptides comprising an antibody Fc region;

30 (b) measuring the FcγRIIa-binding activity and FcγRIIb-binding activity of the polypeptides altered in step (a); and

(c) selecting polypeptides having maintained or decreased FcγRIIa-binding activity, and enhanced FcγRIIb-binding activity in comparison with a parent polypeptide.

A preferred embodiment is a method for producing a polypeptide comprising an antibody Fc region, which comprises the steps of:

(a) altering a nucleic acid encoding the polypeptide so that the FcyRIIa-binding activity is

maintained or decreased, and the $Fc\gamma RIIb$ -binding activity is enhanced in comparison with the parent peptide;

(b) introducing the nucleic acid into host cells and culturing them to induce expression; and

(c) collecting the polypeptide from the host cell culture.

Furthermore, antibodies and Fc fusion protein molecules produced by this production method are also included in the present invention.

The present invention also provides methods for producing a polypeptide in which antibody production against the polypeptide is suppressed compared with its parent polypeptide when administered *in vivo*, which comprise adding at least one amino acid alteration in the Fc region of a polypeptide comprising an antibody Fc region.

Examples include a production method comprising the following steps: (a) adding at least one amino acid alteration in the Fc region of a polypeptide comprising an antibody Fc region; and

(b) confirming that antibody production is suppressed when the polypeptide altered in step (a) is administered *in vivo* in comparison with a parent polypeptide.

Whether or not production of antibodies against the polypeptide has been suppressed can be confirmed by methods of administering the polypeptide to an animal and such. Alternatively, suppression of antibody production can be determined by measuring the binding activities towards $Fc\gamma RIIa$ and $Fc\gamma RIIb$, and observing an increase in the value obtained by

0 dividing the KD value for $Fc\gamma RIIa$ by the KD value for $Fc\gamma RIIb$. Such polypeptides are considered to be useful as pharmaceuticals since they can suppress antibody production without activating activating $Fc\gamma R$.

In the above-mentioned production method, it is preferable to enhance the $Fc\gamma RIIb$ binding activity, and maintain or decrease the binding activities towards $Fc\gamma RIIa$ (type R) and

25 FcγRIIa (type H); and it is preferable to additionally reduce binding activities towards FcγRIa and/or FcγRIIIa.

In a preferred embodiment in the above-mentioned production method, for example, a polypeptide comprising a human IgG Fc region is altered so that Pro at position 238 (EU numbering) is substituted with Asp or Leu at position 328 (EU numbering) is substituted with

Glu. Other preferred embodiments include altering the polypeptide so that at least one substitution selected from the group consisting of:
 substitution of Gly at position 237 (EU numbering) with Trp;
 substitution of Gly at position 237 (EU numbering) with Phe;

substitution of Ser at position 267 (EU numbering) with Val;

35 substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn;

0

substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu; substitution of Lys at position 326 (EU numbering) with Gln; substitution of Lys at position 326 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala; substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; substitution of Gly at position 237 (EU numbering) with Leu; substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; substitution of Glu at position 233 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser;

substitution of Lys at position 326 (EC numbering) with Ser,
substitution of Lys at position 326 (EU numbering) with Thr;
substitution of Val at position 323 (EU numbering) with Ile;
substitution of Val at position 323 (EU numbering) with Leu;

- substitution of Val at position 323 (EU numbering) with Met; substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ala; substitution of Lys at position 326 (EU numbering) with Asn; and
- 30 substitution of Ala at position 330 (EU numbering) with Met, in addition to substitution of Pro at position 238 (EU numbering) with Asp.

Furthermore, the present invention provides methods for altering a polypeptide for the production of a polypeptide having maintained or decreased FcγRIIa-binding activity, and having enhanced FcγRIIb-binding activity in comparison with its parent polypeptide.

35

The present invention also provides methods for altering a polypeptide for the production of a polypeptide whose antibody production is suppressed compared with that of a

parent polypeptide when it is administered in vivo.

In a preferred embodiment, for example, a polypeptide comprising a human IgG Fc region is altered so that Pro at position 238 (EU numbering) is substituted with Asp or Leu at position 328 (EU numbering) is substituted with Glu. Other preferred embodiments include altering the polypeptide so that at least one substitution selected from the group consisting of:

substitution of Gly at position 237 (EU numbering) with Trp; substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn; substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu; substitution of Lys at position 326 (EU numbering) with Gln;

- 5 substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr;
- substitution of Gly at position 237 (EU numbering) with Ala;
 substitution of Gly at position 237 (EU numbering) with Asp;
 substitution of Gly at position 237 (EU numbering) with Glu;
 substitution of Gly at position 237 (EU numbering) with Leu;
 substitution of Gly at position 237 (EU numbering) with Met;
- 25 substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; substitution of Glu at position 233 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Asp;
- 30 substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser; substitution of Lys at position 326 (EU numbering) with Thr; substitution of Val at position 323 (EU numbering) with Ile;
- 35 substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Met;

0

25

substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ala; substitution of Lys at position 326 (EU numbering) with Asn; and substitution of Ala at position 330 (EU numbering) with Met, in addition to substitution of Pro at position 238 (EU numbering) with Asp.

Furthermore, the present invention provides a nucleic acid encoding a polypeptide comprising an antibody Fc region with at least one amino acid alteration, which has maintained or decreased Fc γ RIIa-binding activity, and enhanced Fc γ RIIb-binding activity in comparison with a parent polypeptide. The nucleic acid of the present invention may be in any form such as DNA or RNA.

The present invention also provides vectors carrying the above-described nucleic acids of the present invention. The type of vector can be appropriately selected by those skilled in the art depending on the host cells to be introduced with the vector. The vectors include, for example, those described above.

Furthermore, the present invention relates to host cells transformed with the abovedescribed vectors of the present invention. Appropriate host cells can be selected by those skilled in the art. The host cells include, for example, those described above.

Furthermore, the present invention provides methods for maintaining or decreasing $Fc\gamma RIIa$ -binding activity and enhancing $Fc\gamma RIIb$ -binding activity of a polypeptide comprising an antibody Fc region in comparison with a parent polypeptide, wherein the method comprises adding at least one amino acid alteration to the Fc region.

The present invention also provides methods for suppressing production of antibodies against a polypeptide compared with a parent polypeptide when the polypeptide is administered *in vivo*, wherein the method comprises adding at least one amino acid alteration in the Fc region of the polypeptide comprising an antibody Fc region.

In a preferred embodiment, for example, a polypeptide comprising a human IgG Fc region is altered so that Pro at position 238 (EU numbering) is substituted with Asp or Leu at position 328 (EU numbering) is substituted with Glu. Other preferred embodiments include altering the polypeptide so that at least one substitution selected from the group consisting of:

- 30 substitution of Gly at position 237 (EU numbering) with Trp; substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn;
- 35 substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu;

substitution of Lys at position 326 (EU numbering) with Gln; substitution of Lys at position 326 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala; substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; substitution of Gly at position 237 (EU numbering) with Leu; substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; substitution of Glu at position 233 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Asp;

- substitution of His at position 268 (EU numbering) with Glu;
 substitution of Lys at position 326 (EU numbering) with Asp;
 substitution of Lys at position 326 (EU numbering) with Ser;
- substitution of Lys at position 326 (EU numbering) with Thr; substitution of Val at position 323 (EU numbering) with Ile; substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Met;
- 25 substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ala; substitution of Lys at position 326 (EU numbering) with Asn; and substitution of Ala at position 330 (EU numbering) with Met, in addition to substitution of Pro at position 238 (EU numbering) with Asp.
- 30 In the above-mentioned method, it is preferable to enhance the FcγRIIb-binding activity, and maintain or decrease binding activities towards FcγRIIa (type R) and FcγRIIa (type H); and it is preferable to additionally maintain or decrease binding activities towards FcγRIa and/or FcγRIIIa.

Polypeptides produced by any of the above-mentioned methods are also included in the 35 present invention. <Pharmaceutical compositions>

The present invention provides pharmaceutical compositions comprising the polypeptide of the present invention.

The pharmaceutical compositions of the present invention can be formulated, in addition to the antibody or Fc-fusion protein molecules of the present invention described above, with pharmaceutically acceptable carriers by known methods. For example, the compositions can be used parenterally, when the antibodies are formulated in a sterile solution or suspension for injection using water or any other pharmaceutically acceptable liquid. For example, the compositions can be formulated by appropriately combining the antibodies or Fc-fusion protein molecules with pharmaceutically acceptable carriers or media, specifically, sterile water or physiological saline, vegetable oils, emulsifiers, suspending agents, surfactants, stabilizers, flavoring agents, excipients, vehicles, preservatives, binding agents, and such, by mixing them at a unit dose and form required by generally accepted pharmaceutical implementations. Specific examples of the carriers include light anhydrous silicic acid, lactose, crystalline cellulose,

5 mannitol, starch, carmellose calcium, carmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylacetal diethylaminoacetate, polyvinylpyrrolidone, gelatin, medium-chain triglyceride, polyoxyethylene hardened castor oil 60, saccharose, carboxymethyl cellulose, corn starch, inorganic salt, and such. The content of the active ingredient in such a formulation is adjusted so that an appropriate dose within the required range

0 can be obtained.

> Sterile compositions for injection can be formulated using vehicles such as distilled water for injection, according to standard protocols.

Aqueous solutions used for injection include, for example, physiological saline and isotonic solutions containing glucose or other adjuvants such as D-sorbitol, D-mannose, D-25 mannitol, and sodium chloride. These can be used in conjunction with suitable solubilizers such as alcohol, specifically ethanol, polyalcohols such as propylene glycol and polyethylene glycol, and non-ionic surfactants such as Polysorbate 80TM and HCO-50.

Oils include sesame oils and soybean oils, and can be combined with solubilizers such as benzyl benzoate or benzyl alcohol. These may also be formulated with buffers, for example, 30 phosphate buffers or sodium acetate buffers; analgesics, for example, procaine hydrochloride; stabilizers, for example, benzyl alcohol or phenol; or antioxidants. The prepared injections are typically aliquoted into appropriate ampules.

The administration is preferably carried out parenterally, and specifically includes injection, intranasal administration, intrapulmonary administration, and percutaneous

35 administration. For example, injections can be administered systemically or locally by intravenous injection, intramuscular injection, intraperitoneal injection, or subcutaneous

injection.

Furthermore, the method of administration can be appropriately selected according to the age and symptoms of the patient. A single dosage of the pharmaceutical composition containing an antibody or a polynucleotide encoding an antibody can be selected, for example, from the range of 0.0001 to 1,000 mg per kg of body weight. Alternatively, the dosage may be, for example, in the range of 0.001 to 100,000 mg/patient. However, the dosage is not limited to these values. The dosage and method of administration vary depending on the patient's body weight, age, and symptoms, and can be appropriately selected by those skilled in the art.

The above-mentioned polypeptides of the present invention are useful as active ingredients of pharmaceutical agents that suppress the activation of B cells, mast cells, dendritic cells, and/or basophils. Polypeptides of the present invention can suppress the activation of B cells, mast cells, dendritic cells, and/or basophils, by selectively working on FcγRIIb without activating activating FcγR. B cell activation includes proliferation, IgE production, IgM production, and IgA production. The above-mentioned polypeptides of the present invention

- 5 cross-link FcγRIIb with IgE to suppress IgE production of B cells, with IgM to suppress IgM production of B cells, and with IgA to suppress IgA production. Other than the above, suppressive effects similar to those mentioned above are exhibited by directly or indirectly cross-linking FcγRIIb with molecules that are expressed on B cells and comprise the ITAM domain inside the cell or interact with the ITAM domain such as BCR, CD19, and CD79b. Furthermore,
- activation of mast cells includes proliferation, activation by IgE and such, and degranulation. In mast cells, the above-mentioned polypeptides of the present invention can suppress proliferation, activation by IgE and such, and degranulation by directly or indirectly cross-linking FcγRIIb with IgE receptor molecules that are expressed on mast cells and comprise the ITAM domain or interact with the ITAM domain such as FcεRI, DAP12, and CD200R3. Activation of basophils
- 25 includes proliferation and degranulation of basophils. Also in basophils, the above-mentioned polypeptides of the present invention can suppress proliferation, activation, and degranulation by directly or indirectly cross-linking FcγRIIb with molecules on the cell membrane, which comprise the ITAM domain inside the cell or interact with the ITAM domain. Activation of dendritic cells includes proliferation and degranulation of dendritic cells. Also in dendritic cells,
- 30 the above-mentioned polypeptides of the present invention can suppress activation, degranulation, and proliferation by directly or indirectly cross-linking FcγRIIb with molecules on the cell membrane, which comprise the ITAM domain inside the cell or interact with the ITAM domain.

In the present invention, the polypeptides of the present invention mentioned above are useful as an active ingredient of therapeutic agents or preventive agents for immunological inflammatory diseases. As described above, since polypeptides of the present invention can suppress activation of B cells, mast cells, dendritic cells and/or basophils, administration of the polypeptides of the present invention as a result can treat or prevent immunological inflammatory diseases. Without being limited thereto, the term "immunological inflammatory diseases" comprises , rheumatoid arthritis, autoimmune hepatitis, autoimmune thyroiditis, autoimmune blistering diseases, autoimmune adrenocortical disease, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, megalocytic anemia, autoimmune atrophic gastritis, autoimmune neutropenia, autoimmune orchitis, autoimmune encephalomyelitis, autoimmune receptor disease, autoimmune infertility, chronic active hepatitis, glomerulonephritis, interstitial pulmonary fibrosis, multiple sclerosis, Paget's disease, osteoporosis, multiple myeloma, uveitis, acute and chronic spondylitis, gouty arthritis,

inflammatory bowel disease, adult respiratory distress syndrome (ARDS), psoriasis, Crohn's disease, Basedow's disease, juvenile diabetes, Addison's disease, myasthenia gravis, lens-induced uveitis, systemic lupus erythematosus, allergic rhinitis, allergic dermatitis, ulcerative colitis, hypersensitivity, muscle degeneration, cachexia, systemic scleroderma, localized scleroderma,

- 5 Sjogren's syndrome, Behchet's disease, Reiter's syndrome, type I and type II diabetes, bone resorption disorder, graft-versus-host reaction, ischemia-reperfusion injury, atherosclerosis, brain trauma, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, malgias due to staining, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia, Goodpasture's syndrome, Guillain-Barre syndrome, Hashimoto's thyroiditis, pemphigus, IgA nephropathy,
- 0 pollinosis, antiphospholipid antibody syndrome, polymyositis, Wegener's granulomatosis, arteritis nodosa, mixed connective tissue disease, fibromyalgia, asthma, atopic dermatitis, chronic atrophic gastritis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune pancreatitis, aortitis syndrome, rapidly progressive glomerulonephritis, megaloblastic anemia, idiopathic thrombocytopenic purpura, primary hypothyroidism, idiopathic Addison's disease,
- 25 insulin-dependent diabetes mellitus, chronic discoid lupus erythematosus, pemphigoid, herpes gestationis, linear IgA bullous dermatosis, epidermolysis bullosa acquisita, alopecia areata, vitiligo vulgaris, leukoderma acquisitum centrifugum of Sutton, Harada's disease, autoimmune optic neuropathy, idiopathic azoospermia, habitual abortion, hypoglycemia, chronic urticaria, ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis, reactive arthritis,
- 30 spondyloarthropathy, enthesopathy, irritable bowel syndrome, chronic fatigue syndrome, dermatomyositis, inclusion body myositis, Schmidt's syndrome, Graves' disease, pernicious anemia, lupoid hepatitis, presenile dementia, Alzheimer's disease, demyelinating disorder, amyotrophic lateral sclerosis, hypoparathyroidism, Dressler's syndrome, Eaton-Lambert syndrome, dermatitis herpetiformis, alopecia, progressive systemic sclerosis, CREST syndrome
- 35 (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), sarcoidosis, rheumatic fever, erythema multiforme, Cushing's syndrome, transfusion reaction,

Hansen's disease, Takayasu arteritis, polymyalgia rheumatica, temporal arteritis, giant cell arthritis, eczema, lymphomatoid granulomatosis, Kawasaki disease, endocarditis, endomyocardial fibrosis, endophthalmitis, fetal erythroblastosis, eosinophilic fasciitis, Felty syndrome, Henoch-Schonlein purpura, transplant rejection, mumps, cardiomyopathy, purulent arthritis, familial Mediterranean fever, Muckle-Wells syndrome, and hyper-IgD syndrome.

Furthermore, in autoimmune diseases which may be caused by production of antibodies against autoantigens (autoantibodies), the polypeptides of the present invention mentioned above are useful as an active ingredient of pharmaceutical agents for treating or preventing the autoimmune diseases by suppressing production of those autoantibodies. Use of a molecule produced by fusing an antibody Fc portion with AchR (an autoantigen of myasthenia gravis) has been reported to suppress proliferation of B cells which express AchR-recognizing BCR, and induce apoptosis (J. Neuroimmunol, 227: 35-43, 2010). Use of a fusion protein formed between an antigen recognized by an autoantibody and an antibody Fc region of the present invention enables crosslinking of FcyRIIb with BCR of a B cell expressing BCR for that autoantigen,

5 suppression of proliferation of B cells expressing BCR for the autoantigen, and induction of apoptosis. Such autoimmune diseases include Guillain-Barre syndrome, myasthenia gravis, chronic atrophic gastritis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune pancreatitis, aortitis syndrome, Goodpasture's syndrome, rapidly progressive glomerulonephritis, megaloblastic anemia, autoimmune hemolytic anemia,

0 autoimmune neutropenia, idiopathic thrombocytopenic purpura, Basedow's disease, Hashimoto's thyroiditis, primary hypothyroidism, idiopathic Addison's disease, insulin-dependent diabetes mellitus, chronic discoid lupus erythematosus, localized scleroderma, pemphigus, pemphigoid, herpes gestationis, linear IgA bullous dermatosis, epidermolysis bullosa acquisita, alopecia areata, vitiligo vulgaris, leukoderma acquisitum centrifugum of Sutton, Harada's disease,

25 autoimmune optic neuropathy, idiopathic azoospermia, habitual abortion, type II diabetes, hypoglycemia, and chronic urticaria; but are not limited thereto.

Furthermore, the above-mentioned polypeptides of the present invention are useful as an active ingredient in therapeutic agents for diseases with deficiency of a biologically essential protein. For diseases with deficiency of a biologically essential protein, therapeutic methods that

- 30 administer and supplement the protein as a pharmaceutical agent are used. However, since the patient lacks the protein from the beginning, the externally supplemented protein is recognized as a foreign substance and antibodies against that protein are produced. As a result, the protein becomes easily removed, and the effect as a pharmaceutical is reduced. Use of a fusion protein comprising such a protein and an antibody Fc region of the present invention enables
- 35 crosslinking between FcγRIIb and BCR on B cells that recognize the protein, and enables suppression of antibody production against the protein. The proteins to be supplemented include

Factor VIII, Factor IX, TPO, EPO, α -iduronidase, iduronate sulfatase, A-type heparan *N*-sulfatase, B type α -*N*-acetylglucosaminidase, C type acetyl CoA: α -glucosaminidase acetyltransferase, D type *N*-acetylglucosamine 6-sulfatase, galactose 6-sulfatase, *N*-acetylgalactosamine 4-sulfatase, β -glucuronidase, α -galactosidase, acidic α -galactosidase, and glucocerebrosidase. These proteins may be supplemented for diseases such as hemophilia, idiopathic thrombocytopenic purpura, renal anemia, and lysosomal disease (mucopolysaccharidosis, Fabry's disease, Pompe disease, and Gaucher's disease), without being limited thereto.

Furthermore, the above-mentioned polypeptides of the present invention are useful as an active ingredient for antiviral agents. Antibodies that comprise an Fc region of the present invention and are anti-virus antibodies can suppress antibody-dependent enhancement observed with anti-virus antibodies. Antibody-dependent enhancement is a phenomenon where a virus uses neutralizing antibodies against the virus to become phagocytosed *via* activating Fc γ Rs, and infects Fc γ R-expressing cells so that the infection spreads. Binding of anti-dengue-virus

neutralizing antibodies to FcγRIIb has been reported to play an important role in suppressing antibody-dependent enhancement (Proc. Natl. Acad. Sci. USA, 108: 12479-12484, 2011).
 Crosslinking FcγRIIb with an immunocomplex with dengue virus, which is formed by the anti-dengue-virus neutralizing antibodies, inhibits FcγR-mediated phagocytosis, resulting in the suppression of antibody-dependent enhancement. Examples of such viruses include dengue virus (DENV1, DENV2, and DENV4) and HIV, but are not limited thereto.

Furthermore, polypeptides of the present invention described above are useful as an active ingredient in preventive agents or therapeutic agents for arteriosclerosis. Antibodies against oxidized LDL, *i.e.*, a cause for arteriosclerosis, which are antibodies comprising an Fc region of the present invention, can prevent FcγRIIa-dependent adhesion of inflammatory cells. It has been reported that while anti-oxidized LDL antibodies inhibit the interaction between oxidized LDL and CD36, anti-oxidized LDL antibodies bind to endothelial cells, and monocytes recognize their Fc portion in an FcγRIIa-dependent or FcγRI-dependent manner; and this leads to adhesion (Immunol. Lett., 108: 52-61, 2007). Using antibodies comprising an Fc region of the present invention for such antibodies may inhibit FcγRIIa-dependent binding and suppress

30 monocyte adhesion by FcyRIIb-mediated inhibitory signals.

Herein, polypeptides of the present invention described above are useful as an active ingredient in therapeutic agents or preventive agents for cancer. As described above, it is known that enhancing the $Fc\gamma RIIb$ binding enhances the agonistic activity of an agonist antibody, and enhances the antitumor effect of the antibody. Therefore, agonist antibodies using the Fc region

35 of the present invention are useful for treatment or prevention of cancer. The Fc region of the present invention enhances the agonistic activity of agonist antibodies against receptors of the

TNF receptor family such as Aliases, CD120a, CD120b, Lymphotoxin β receptor, CD134, CD40, FAS, TNFRSF6B, CD27, CD30, CD137, TNFRSF10A, TNFRSF10B, TNFRSF10C, TNFRSF10D, RANK, Osteoprotegerin, TNFRSF12A, TNFRSF13B, TNFRSF13C, TNFRSF14, Nerve growth factor receptor, TNFRSF17, TNFRSF18, TNFRSF19, TNFRSF21, TNFRSF25, and Ectodysplasin A2 receptor. Furthermore, the agonistic activity of agonist antibodies other than those described above is also enhanced. Without being limited thereto, cancer includes lung cancer (including small cell lung cancer, non-small cell lung cancer, pulmonary adenocarcinoma, and squamous cell carcinoma of the lung), large intestine cancer, rectal cancer, colon cancer, breast cancer, liver cancer, gastric cancer, pancreatic cancer, renal cancer, mesothelioma, squamous cell carcinoma, cervical cancer, endometrial cancer, bladder cancer, esophageal cancer, head and neck cancer, nasopharyngeal cancer, salivary gland tumor, thymoma, skin cancer, basal cell

tumor, malignant melanoma, anal cancer, penile cancer, testicular cancer, Wilms' tumor, acute myeloid leukemia (including acute myeloleukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, and acute monocytic leukemia),

- chronic myelogenous leukemia, acute lymphoblastic leukemia, chronic lymphatic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma (Burkitt's lymphoma, chronic lymphocytic leukemia, mycosis fungoides, mantle cell lymphoma, follicular lymphoma, diffuse large-cell lymphoma, marginal zone lymphoma, pilocytic leukemia plasmacytoma, peripheral T-cell
- 0 lymphoma, and adult T cell leukemia/lymphoma), Langerhans cell histiocytosis, multiple myeloma, myelodysplastic syndrome, brain tumor (including glioma, astroglioma, glioblastoma, meningioma, and ependymoma), neuroblastoma, retinoblastoma, osteosarcoma, Kaposi's sarcoma, Ewing's sarcoma, angiosarcoma, and hemangiopericytoma.

Furthermore, the present invention relates to methods for treating or preventing 25 immunological inflammatory diseases, which comprise the step of administering to a subject (patient) a polypeptide of the present invention or a polypeptide produced by production methods of the present invention.

The present invention also provides kits for use in the therapeutic methods or preventive methods of the present invention, which comprises at least a polypeptide of the present invention

- 30 or a polypeptide produced by production methods of the present invention, or a pharmaceutical composition of the present invention. In addition, pharmaceutically acceptable carriers, media, instructions on the method of use, and such may be included in the kit. Furthermore, the present invention relates to use of a polypeptide of the present invention or a polypeptide produced by production methods of the present invention in the production of agents for treating or
- 35 preventing immunological inflammatory diseases. The present invention also relates to polypeptides of the present invention or polypeptides produced by production methods of the

present invention for use in the therapeutic methods or preventive methods of the present invention.

As used herein, the three-letter and single-letter codes for respective amino acids are as follows:

- Alanine: Ala (A)
- Arginine: Arg (R)

Asparagine: Asn (N)

Aspartic acid: Asp (D)

- Cysteine: Cys (C)
-) Glutamine: Gln (Q) Glutamic acid: Glu (E) Glycine: Gly (G)

Histidine: His (H)

Isoleucine: Ile (I)

- 5 Leucine: Leu (L)
 Lysine: Lys (K)
 Methionine: Met (M)
 Phenylalanine: Phe (F)
 Proline: Pro (P)
- 0 Serine: Ser (S) Threonine: Thr (T) Tryptophan: Trp (W) Tyrosine: Tyr (Y) Valine: Val (V)

25

All prior art documents cited herein are incorporated by reference in their entirety.

Examples

Herein below, the present invention will be specifically described further with reference to the Examples, but it is not to be construed as being limited thereto.

30

[Example 1] Comprehensive analysis of the binding of Fc variants to $Fc\gamma R$

Mutations were introduced into IgG1 antibodies to generate antibodies that have decreased Fc-mediated binding towards activating FcγR, specifically both allotypes of FcγRIIa, types H and R, as well as enhanced FcγRIIb binding relative to IgG1; and binding to each FcγR was analyzed comprehensively.

35 was analyzed comprehensively.

The variable region (SEQ ID NO: 15) of a glypican 3 antibody comprising the CDR of

25

35

GpH7 which is an anti-glypican 3 antibody with improved plasma kinetics disclosed in WO 2009/041062 was used as the common antibody H chain. Similarly, for the common antibody L chain, GpL16-k0 (SEQ ID NO: 16) of the glypican 3 antibody with improved plasma kinetics disclosed in WO 2009/041062 was used. Furthermore, B3 (SEQ ID NO: 17) in which a K439E mutation has been introduced into G1d produced by removing the C terminal Gly and Lys of IgG1 was used as the antibody H chain constant region. This H chain is referred to as GpH7-B3 (SEQ ID NO: 18), and the L chain is referred to as GpL16-k0 (SEQ ID NO: 16).

With respect to GpH7-B3, the amino acids that are considered to be involved in Fc γ R binding and the surrounding amino acids (positions 234 to 239, 265 to 271, 295, 296, 298, 300, and 324 to 337, according to EU numbering) were substituted respectively with 18 types of amino acids excluding the original amino acids and Cys. These Fc variants are referred to as B3 variants. B3 variants were expressed and purified using the method of Reference Example 1, and the binding to each Fc γ R (Fc γ RIa, Fc γ RIIa type H, Fc γ RIIa type R, Fc γ RIIb, and Fc γ RIIIa) was comprehensively evaluated using the method of Reference Example 2.

Figures were produced based on the results of interaction analysis with each $Fc\gamma R$ by the method below. The value of the amount of $Fc\gamma R$ binding of each B3 variant-derived antibody was divided by the value of the amount of $Fc\gamma R$ binding of the antibody used for comparison which does not have mutations introduced into B3 (an antibody having the sequence of a naturally-occurring human IgG1 at positions 234 to 239, 265 to 271, 295, 296, 298, 300, and

0 324 to 337, according to EU numbering). The value obtained by multiplying this value by 100 was used as an indicator of the relative FcγR-binding activity of each variant. The horizontal axis shows the value of the relative FcγRIIb-binding activity of each variant, and the vertical axis shows the value of the respective relative binding activity of each variant towards activating FcγRs: FcγRIa, FcγRIIa type H, FcγRIIa type R, and FcγRIIIa (Figs. 1, 2, 3, and 4).

As shown by labels in Figs. 1-4, the results show that of all alterations, when only mutations called mutation A (alteration produced by substituting Pro at position 238 (EU numbering) with Asp) and mutation B (alteration produced by substituting Leu at position 328 (EU numbering) with Glu) were introduced, there were remarkable enhancement of binding to Fc γ RIIb and remarkable suppression of binding to both types of Fc γ RIIa compared with before the introduction

30 the introduction.

[Example 2] SPR analysis of variants that selectively bind to FcyRIIb

With regard to the alteration identified in Example 1 where Pro at position 238 (EU numbering) is substituted with Asp, the binding to each FcγR was analyzed in detail.

The variable region of IL6R-H (SEQ ID NO: 19), which is the variable region of the antibody against the human interleukin 6 receptor disclosed in WO 2009/125825, was used as

the antibody H chain variable region, and IL6R-G1d (SEQ ID NO: 20) which comprises G1d with deletion of C-terminal Gly and Lys of human IgG1was used as the antibody H chain constant region in the IgG1 H chain. Pro at position 238 (EU numbering) in IL6R-G1d was substituted with Asp to produce IL6R-G1d-v1 (SEQ ID NO: 21). Next, Leu at position 328 (EU numbering) in IL6R-G1d was substituted with Glu to produce IL6R-G1d-v2 (SEQ ID NO: 23). Furthermore, for comparison, Ser at position 267 (EU numbering) was substituted with Glu, and Leu at position 328 (EU numbering) was substituted with Phe in IL6R-G1d to produce IL6R-G1d-v3 (SEQ ID NO: 24) as described in Non-patent Document 27. IL6R-L (SEQ ID NO: 22), which is the L chain of tocilizumab, was utilized as a mutual antibody L chain; and together with each H chain, the antibodies were expressed and purified according to the method of Reference Example 1. The obtained antibodies which comprise an amino acid sequence derived from IL6R-G1d-v1, IgG1-v2, and IgG1-v3, respectively.

Next, kinetic analysis of interactions between these antibodies and FcγR was carried out
using Biacore T100 (GE Healthcare). HBS-EP+ (GE Healthcare) was used as the running
buffer, and the measurement temperature was set to 25°C. A chip produced by immobilizing
Protein A onto a Series S Sensor Chip CM5 (GE Healthcare) by the amine-coupling method was
used. An antibody of interest was captured onto this chip to interact with each FcγR 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, pH 1.5, and 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 Evaluation Software to calculate the binding rate constant ka (L/mol/s) and dissociation rate constant kd (1/s), and the dissociation constant KD (mol/L) was calculated from these
 values.

This time, since the binding of IgG1-v1 and IgG1-v2 to $Fc\gamma RIIa$ type H and to $Fc\gamma RIIa$ was weak, kinetic parameters such as KD could not be calculated from the above-mentioned analytical method. Regarding such interactions, KD values were calculated using the following 1:1 binding model described in Biacore T100 Software Handbook BR1006-48 Edition AE.

30 The behavior of interacting molecules according to the 1:1 binding model on Biacore can be described by Equation 1 shown below.

[Equation 1]

$$R_{eq} = C \bullet R_{max} / (KD + C) + RI$$

 R_{eq} : a plot of steady-state binding levels against analyte concentration

35 C: concentration

RI: bulk refractive index contribution in the sample R_{max} : analyte binding capacity of the surface

When this equation is rearranged, KD can be expressed as Equation 2 shown below. [Equation 2]

$KD = C \bullet R_{max} / (R_{eq} - RI) - C$

KD can be calculated by substituting the values of R_{max} , RI, and C into this equation. From the current measurement conditions, RI = 0, $C = 2 \mu mol/L$ 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 γ R with IgG1 using the 1:1 Langmuir binding model was divided by the amount of IgG1 captured, this was multiplied by the amount of IgG1-v1 and IgG1-v2 captured, and the resulting value was used as R_{max} . This calculation is based on the hypothesis that the limit quantity of each Fc γ R that can be bound by IgG1 remains unchanged for all variants produced by introducing mutations into IgG1, 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.

Under these measurement conditions, the amount of binding (R_{eq}) of IgG1-v1 and IgG1-v2 to Fc γ RIIa type H was approximately 2.5 RU and 10 RU, respectively, and the amount of

binding (R_{eq}) of IgG1-v1 and IgG1-v2 to FcγRIIIa was approximately 2.5 RU and 5 RU, respectively. The amount of IgG1, IgG1-v1, and IgG1-v2 captured in the analysis of interactions with H-type FcγRIIa was 452 RU, 469.2 RU, and 444.2 RU, respectively, and the amount of IgG1, IgG1-v1, and IgG1-v2 captured in the analysis of interactions with FcγRIIIa was 454.5 RU, 470.8 RU, and 447.1 RU, respectively. The R_{max} values obtained from global fitting of sensorgrams obtained as a result of analyzing the interaction of IgG1 with H-type FcγRIIa and FcγRIIIa using the 1:1 Langmuir binding model were 69.8 RU and 63.8 RU, respectively. When these values were used, the calculated R_{max} values of IgG1-v1 and IgG1-v2 to FcγRIIa type H were 72.5 RU and 68.6 RU, respectively, and the calculated R_{max} values of IgG1-v1 and IgG1-v1

to FcγRIIIa were 66.0 RU and 62.7 RU, respectively. These values were substituted into
Equation 2 to calculate the KD of IgG1-v1 and IgG1-v2 for FcγRIIa type H and FcγRIIIa.
[Equation 2]

$$KD = C \bullet R_{max} / (R_{eq} - RI) - C$$

The KD values of IgG1, IgG1-v1, IgG1-v2, and IgG1-v3 for each $Fc\gamma R$ (the KD values of each antibody for each $Fc\gamma R$) are shown in Table 1, and the relative KD values of IgG1-v1,

IgG1-v2, and IgG1-v3 obtained by taking the KD values of IgG1 for each Fc γ R and dividing them by the KD values of IgG1-v1, IgG1-v2, and IgG1-v3 for each Fc γ R (the relative KD values of each antibody for each Fc γ R) are shown in Table 2.

[Table 1]

	lgG1	lgG1-v1	lgG1-v2	lgG1-v3
FcγRla	3.4E-10	7.3E-09	4.6E-10	1.9E-10
FcγRIIa R	1.2E-06	1.2E-05	2.9E-06	2.3E-09
FcγRIIa H	7.7E-07	5.6E-05*	1.2E-05*	1.5E-06
FcγRIIb	5.3E-06	1.1E-06	2.3E-06	1.3E-08
FcγRIIIa	3.1E-06	5.1E-05*	2.3E-05*	8.8E-06
(mol/L)				nol/L)

In Table 1 shown above, "*" means that the KD value was calculated using Equation 2 because binding of FcyR to IgG was not sufficiently observed.

0 [Equation 2]

$$KD = C \bullet R_{max} / (R_{eq} - RI) - C$$

[Table 2]

	lgG1-v1	lgG1-v2	lgG1-v3
FcγRla	0.047	0.74	1.8
FcγRIIa R	0.10	0.41	522
FcγRIIa H	0.014	0.064	0.51
FcγRIIb	4.8	2.3	408
FcγRIIIa	0.061	0.14	0.35

(THE VALUE OBTAINED BY DIVIDING THE KD VALUE OF IgG1 FOR EACH Fc γ R BY THE KD VALUE OF EACH ANTIBODY IgG1 FOR EACH Fc γ R)

According to Table 2, when compared with that of IgG1, the binding activity of IgG1-v1 was decreased to 0.047-fold for Fc γ RIa, decreased to 0.10-fold for Fc γ RIIa type R, decreased to 0.014-fold for Fc γ RIIa type H, decreased to 0.061-fold for Fc γ RIIa, and increased to 4.8-fold for Fc γ RIIb.

Furthermore, according to Table 2, when compared with that of IgG1, the binding activity of IgG1-v2 was decreased to 0.74-fold for Fc γ RIa, decreased to 0.41-fold for Fc γ RIIa type R, decreased to 0.064-fold for Fc γ RIIa type H, decreased to 0.14-fold for Fc γ RIIa, and increased to 2.3-fold for Fc γ RIIb.

More specifically, these results demonstrated that IgG1-v1 having an alteration of substituting Pro at position 238 (EU numbering) with Asp and IgG1-v2 having an alteration of substituting Leu at position 328 (EU numbering) with Glu have the properties of weakening the binding to all activating Fc γ Rs including both allotypes of Fc γ RIIa, while enhancing the binding to Fc γ RIIb which is an inhibitory Fc γ R.

- Next, selectivity of the obtained variant to FcγRIIb was evaluated by using the ratio of
 5 FcγRIIb-binding activity to the binding activity towards type R or type H of FcγRIIa as the indicator. Specifically, I/A(R) or I/A(H), which is a value obtained by dividing the KD value for FcγRIIa type R or type H by the KD value for FcγRIIb, was used as an indicator for the selectivity of FcγRIIb with respect to each FcγRIIa. This indicator has a greater value when the KD value for FcγRIIb becomes smaller or when the KD value for FcγRIIa becomes larger. That
- 0 is, a variant that shows a larger value shows an increased binding activity for FcγRIIb relative to
 FcγRIIa. These indicators are summarized in Table 3 for each variant.

	lgG1	lgG1-v1	lgG1-v2	lgG1-v3
I/A (R)	0.23	11	1.3	0.18
I/A (H)	0.15	51	5.2	115

[Table 3]

FcyRIIb over both allotypes of FcyRIIa.

25

According to the results of Table 3, in comparison with IgG1, IgG1-v3 which was produced by applying the existing technology showed a greater 1/A(H) value than that of IgG1 and a greater selectivity for Fc γ RIIb, but a smaller 1/A(R) value than that of IgG1 and an improved selectivity for Fc γ RIIb. On the other hand, IgG1-v1 and IgG1-v2 found in the Examples have larger I/A(R) and I/A(H) values than those of IgG1, and improved selectivity for

30

So far, alterations having such properties have not been reported, and they are in fact very rare as shown in Figs. 1, 2, 3, and 4. Alterations produced by substituting Pro at position

238 (EU numbering) with Asp or substituting Leu at position 328 (EU numbering) with Glu are very useful for the development of therapeutic agents for immunological inflammatory diseases and such.

Furthermore, Table 2 shows that IgG1-v3 described in Non-Patent Document 27 certainly shows a 408-fold enhanced binding to $Fc\gamma RIIb$, while the binding to $Fc\gamma RIIa$ type H is decreased to 0.51 fold, and the binding to $Fc\gamma RIIa$ type R is enhanced to 522 fold. According to these results, since IgG1-v1 and IgG1-v2 suppress their binding to both $Fc\gamma RIIa$ types R and H, and enhance their binding to $Fc\gamma RIIb$, they are considered to be variants that bind with a greater $Fc\gamma RIIb$ selectivity compared with IgG1-v3. Specifically, alterations produced by substituting Pro at position 238 (EU numbering) with Asp or substituting Leu at position 328 (EU numbering) with Glu are very useful for the development of therapeutic agents for immunological inflammatory diseases and such.

[Example 3] Effects of combining FcyRIIb-selective binding alterations with other Fc region amino acid substitutions

Further enhancement of the selectivity for $Fc\gamma RIIb$ was attempted based on the variant which has improved selectivity for $Fc\gamma RIIb$ and has a substitution of Pro at position 238 (EU numbering) with Asp found in Examples 1 and 2.

First, into IL6R-G1d_v1 (SEQ ID NO: 21) produced by introducing into IL6R-G1d the
alteration produced by substituting Pro at position 238 (EU numbering) with Asp, the substitution of Leu at position 328 (EU numbering) with Glu as described in Example 2 which enhances selectivity for FcγRIIb was introduced to produce the IL6R-G1d-v4 variant (SEQ ID NO: 25). This was combined with IL6R-L (SEQ ID NO: 22) and prepared according to the method of Reference Example 1. The obtained antibody having the amino acid sequence derived
from IL6R-G1d-v4 as the antibody H chain has been named IgG1-v4. The binding activities of IgG1, IgG1-v1, IgG1-v2, and IgG1-v4 to FcγRIIb were evaluated according to the method of Reference Example 2, and those results are shown in Table 4.

Variant	Alteration	KD for FcγRIIb (mol/L)	Relative KD for FcγRIIb (KD of IgG1 / KD of each variant)
IgG1	-	5.30E-06	1
IgG1-v1	Substitution of Pro at position 238 (EU numbering) with Asp	1.10E-06	4.8
IgG1-v2	Substitution of Leu at position 328 (EU numbering) with Glu	2.30E-06	2.3
IgG1-v4	Substitution of Pro at position	1.10E-05	0.47

[Table 4]

238 (EU numbering) with Asp	
and substitution of Leu at	
position 328 (EU numbering)	
with Glu	

From the results of Table 4, since L328E improves the Fc γ RIIb-binding activity by 2.3 fold compared with IgG1, combining it with P238D which similarly improves the Fc γ RIIb-binding activity by 4.8 fold compared with IgG1 was anticipated to further increase the degree of improvement of Fc γ RIIb-binding activity; however, in reality, the Fc γ RIIb-binding activity of the variant containing a combination of these alterations was decreased to 0.47 fold compared with that of IgG1. This result is an effect that could not have been predicted from the respective alterations.

- Similarly, into IL6R-G1d-v1 (SEQ ID NO: 21) produced by introducing into IL6R-G1d
 the alteration produced by substituting Pro at position 238 (EU numbering) with Asp, the substitutions of Ser at position 267 (EU numbering) with Glu and of Leu at position 328 (EU numbering) with Phe as described in Example 2 which improve FcγRIIb-binding activity were introduced, and the IL6R-G1d-v5 variant (SEQ ID NO: 26) was prepared according to the method of Reference Example 1. The obtained antibody having the amino acid sequence derived
- 5 from IL6R-G1d-v5 as the antibody H chain has been named IgG1-v5. The FcγRIIb-binding activities of IgG1, IgG1-v1, IgG1-v3, and IgG1-v5 were evaluated according to the method of Reference Example 2, and those results are shown in Table 5.

S267E/L328F which had an enhancing effect on FcγRIIb in Example 2 was introduced into the P238D variant, and its FcγRIIb-binding activities before and after introducing this alteration were evaluated. The results are shown in Table 5.

Variant	Alteration	KD for FcγRIIb (mol/L)	Relative KD for FcγRIIb (KD of IgG1 / KD of each variant)
IgG1	-	5.30E-06	1
IgG1-v1	Substitution of Pro at position 238 (EU numbering) with Asp	1.10E-06	4.8
IgG1-v3	Substitution of Ser at position 267 (EU numbering) with Glu and substitution of Leu at position 328 (EU numbering) with Phe	1.30E-08	408
IgG1-v5	Substitution of Pro at position 238 (EU numbering) with Asp, substitution of Ser at position 267 (EU numbering) with Glu, and	4.50E-07	12

[Table 5]

substitution of Leu at position 328	
(EU numbering) with Phe	

From the results of Table 5, since S267E/L328F improves the Fc γ RIIb-binding activity by 408 fold compared with IgG1, combining it with P238D which similarly improves the Fc γ RIIb-binding activity by 4.8 fold as compared with IgG1 was anticipated to further increase the degree of improvement of Fc γ RIIb-binding activity; however, in reality, in a similar manner to the former example, the Fc γ RIIb-binding activity of the variant containing a combination of these alterations was improved only 12 fold or so as compared with that of IgG1. This result is also an effect that could not have been predicted from the effects of the respective alterations.

These results showed that while the substitution of Pro at position 238 (EU numbering) with Asp alone improves $Fc\gamma RIIb$ -binding activity, the effect is not exhibited when it is combined with other alterations that improve the $Fc\gamma RIIb$ -binding activity. A reason for this may be that the structure at the interacting interface between Fc and $Fc\gamma R$ is changed by introducing the substitution of Pro at position 238 (EU numbering) with Asp and the effects of alterations observed in the naturally-occurring antibody are no longer reflected in the results. Accordingly, it was considered to be extremely difficult to create an Fc with excellent selectivity for $Fc\gamma RIIb$ using an Fc comprising substitution of Pro at position 238 (EU numbering) with Asp as a template, since the information on effects of alterations obtained with naturally-occurring antibodies could not be applied.

0 [Example 4] Comprehensive analysis of FcγRIIb binding of variants introduced with an alteration at the hinge portion in addition to the P238D alteration

As shown in Example 3, in an Fc produced by substituting Pro at position 238 (EU numbering) with Asp in a naturally-occurring human IgG1, an anticipated combinatorial effect could not be obtained even by combining it with another alteration predicted to further increase

25 FcγRIIb binding. Therefore, based on the altered Fc produced by substituting Pro at position 238 (EU numbering) with Asp, examination was carried out by comprehensively introducing alterations into the Fc to find variants that further enhance FcγRIIb binding. For the antibody H chains, IL6R-F11 (SEQ ID NO: 27) was produced by introducing an alteration of substituting Met at position 252 (EU numbering) with Tyr and an alteration of substituting Asn at position

30 434 (EU numbering) with Tyr into IL6R-G1d (SEQ ID NO: 20), and IL6R-F652 (SEQ ID NO: 28) was prepared by introducing an additional alteration of substituting Pro at position 238 (EU numbering) with Asp. Expression plasmids containing an antibody H chain sequence were prepared for each of the antibody H chain sequences produced by substituting the region near the residue at position 238 (EU numbering) (positions 234 to 237, and 239 (EU numbering)) in

0

IL6R-F652 each with 18 amino acids excluding the original amino acids and Cys. IL6R-L (SEQ ID NO: 22) was utilized as a common antibody L chain for all of the antibodies. These variants were expressed, purified, and expressed by the method of Reference Example 1. These Fc variants are called PD variants. Interactions of each PD variant with Fc γ RIIa type R and Fc γ RIIb were comprehensively evaluated by the method of Reference Example 2.

With regard to the results of analyzing the interaction with the respective Fc γ Rs, a figure was produced according to the following method. The value obtained by dividing the value for the amount of binding of each PD variant to each Fc γ R by the value for the amount of Fc γ R binding of the pre-altered antibody which is used as the control (IL6R-F652/IL6R-L, which has an alteration of substituting Pro at position 238 (EU numbering) with Asp and then multiplying the result by 100, was used as the relative binding activity value of each PD variant to each Fc γ R. The horizontal axis shows relative values of the Fc γ RIIb-binding activity of each PD variant, and the vertical axis shows relative values of the Fc γ RIIa type R-binding activity values of each PD variant (Fig. 6).

As a result, eleven types of alterations were found to have the effects of enhancing $Fc\gamma RIIb$ binding and maintaining or enhancing $Fc\gamma RIIa$ type R-binding in comparison with the antibody before introducing alterations. The activities of these eleven variants to bind $Fc\gamma RIIb$ and $Fc\gamma RIIa$ R are summarized in Table 6. In the table, SEQ ID NO refers to the SEQ ID NO of the H chain of the evaluated variant, and alteration refers to the alteration introduced into IL6R-F11 (SEQ ID NO: 27).

[Table 6]

SEQ ID NO	VARIANT NAME	ALTERATION		RELATIVE FcγRIIaR- BINDING ACTIVITY
28	IL6R-F652/IL6R-L	P238D	100	100
29	IL6R-PD042/IL6R-L	P238D/L234W	106	240
30	IL6R-PD043/IL6R-L	P238D/L234Y	112	175
31	IL6R-PD079/IL6R-L	P238D/G237A	101	138
32	IL6R-PD080/IL6R-L	P238D/G237D	127	222
33	IL6R-PD081/IL6R-L	P238D/G237E	101	117
34	IL6R-PD082/IL6R-L	P238D/G237F	108	380
35	IL6R-PD086/IL6R-L	P238D/G237L	112	268
36	IL6R-PD087/IL6R-L	P238D/G237M	109	196
37	IL6R-PD094/IL6R-L	P238D/G237W	122	593
38	IL6R-PD095/IL6R-L	P238D/G237Y	124	543
39	IL6R-PD097/IL6R-L	P238D/S239D	139	844

Fig. 7 shows relative values for the FcγRIIb-binding activity obtained by additionally introducing these eleven alterations into a variant carrying the P238D alteration, and relative
values for the FcγRIIb-binding activity obtained by introducing these alterations into an Fc that does not contain the P238D alteration in Example 1. These eleven alterations enhanced the amount of FcγRIIb binding compared with before introduction when they were further introduced into the P238D variant, but on the contrary, the effect of lowering FcγRIIb binding was observed for eight of those alterations except G237F, G237W, and S239D, when they were introduced into the variant that does not contain P238D (GpH7-B3/GpL16-k0) used in Example 1. Example 3 and these results showed that from the effects of introducing alterations into a naturally-occurring IgG1, it is difficult to predict the effects of introducing the same alterations into the variant containing an Fc with the P238D alteration. In other words, it would not have

15 The results of measuring KD values of the variants indicated in Table 6 for FcγRIa, FcγRIIaR, FcγRIIaH, FcγRIIb, and FcγRIIIaV by the method of Reference Example 2 are summarized in Table 7. In the table, SEQ ID NO refers to the SEQ ID NO of the H chain of the evaluated variant, and alteration refers to the alteration introduced into IL6R-F11 (SEQ ID NO: 27). The template used for producing IL6R-F11, IL6R-G1d/IL6R-L, is indicated with an asterisk

been possible to discover these eight alterations identified this time without this investigation.

20 (*). Furthermore, KD(IIaR)/KD(IIb) and KD(IIaH)/KD(IIb) in the table respectively show the

value obtained by dividing the KD value of each variant for Fc γ RIIaR by the KD value of each variant for Fc γ RIIb, and the value obtained by dividing the KD value of each variant for Fc γ RIIaH by the KD value of each variant for Fc γ RIIb. KD(IIb) of the parent polypeptide / KD(IIb) of the altered polypeptide refers to a value obtained by dividing the KD value of the parent polypeptide for Fc γ RIIb by the KD value of each variant for Fc γ RIIb. In addition, Table 7 shows KD values for the stronger of the Fc γ RIIaR- and Fc γ RIIaH-binding activities of each variant / KD values for the stronger of the Fc γ RIIaR- and Fc γ RIIaH-binding activities of the parent polypeptide. Here, parent polypeptide refers to a variant which has IL6R-F11 (SEQ ID NO: 27) as the H chain. It was determined that due to weak binding of Fc γ R to IgG, it was impossible to accurately analyze by kinetic analysis, and thus the gray-filled cells in Table 7 show values calculated by using Equation 2 of Reference Example 2. [Equation 2]

$KD = C \bullet R_{max} / (R_{eq} - RI) - C$

- Table 7 shows that all variants improved their affinity for FcγRIIb in comparison with
 IL6R-F11, and the range of improvement was 1.9 fold to 5.0 fold. The ratio of KD value of each variant for FcγRIIaR / KD value of each variant for FcγRIIb, and the ratio of KD value of each variant for FcγRIIaH / KD value of each variant for FcγRIIb represent an FcγRIIb-binding activity relative to the FcγRIIaR-binding activity and FcγRIIaH-binding activity, respectively. That is, these values show the degree of binding selectivity of each variant for FcγRIIb, and a
 larger value indicates a higher binding selectivity for FcγRIIb. For the parent polypeptide IL6R-F11/IL6R-L, the ratio of KD value for FcγRIIaR / KD value for FcγRIIaR / KD value for FcγRIIb
- value for $Fc\gamma RIIaH / KD$ value for $Fc\gamma RIIb$ are both 0.7, and accordingly all variants in Table 7 showed improvement of binding selectivity for $Fc\gamma RIIb$ in comparison with the parent polypeptide. When the KD value for the stronger of the $Fc\gamma RIIaR$ - and $Fc\gamma RIIaH$ -binding
- 25 activities of a variant / KD value for the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the parent polypeptide is 1 or more, this means that the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of a variant has equivalent or reduced binding compared with the binding by the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the parent polypeptide. Since this value was 0.7 to 5.0 for the variants obtained this time, one may say that
- binding by the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the variants obtained this time was nearly the same or decreased in comparison with the parent polypeptide. These results showed that compared with the parent polypeptide, the variants obtained this time have maintained or decreased binding activities to FcγRIIa type R and type H, and improved selectivity for FcγRIIb. Furthermore, compared with IL6R-F11, all variants had lower affinity to
- 35 FcγRIa and FcγRIIIaV.

2016262766 25 Nov 2016

[Table 7]													
KO VALUE FOR THE STRONGER OF THE FESELLAR- AND FESELLAR- BINDING ACTIVITIES OF A BINDING ACTIVITIES OF A STRONGER OF THE FESELLARD STRONGER OF THE FESELLARD FESELLARDINDING ACTIVITIES OF FESELLARDINDING ACTIVITIES OF	01	Ω \$	S S S S S S S S S S S S S S S S S S S	90 P	57 7	22	O JA	80 80	87 87	07	14	3,6	67
KO (11b) OF PARENT POLYPEPTIDE/ KD (11b) OF ALTERED POLYFEPTIDE	28	С1 Г	*: 0	\$2	23	67 67	\$3	02	27	43	8 <i>3</i>	53	5.0
KD(IIIA+1/ KD(IIIA+1/	80 0	53 2,7	5.5	144	20	123	0 <u>2</u>	4.7	£2	3.0	52	6.9	14.0
(911)CX (11 ² 551)CX	04	0.7	00	15.9	105	107				22	те Ге	3,4	2.6
KD AGATNIST Foeritiav (mot/L)	3.56-07	125-361	376-06	455.05	375-08		415-08		416-08			4.25-08	1,75-06
KD AGAINST FOURTID (mol/L)	2.68-06	6.8E-08								238-00	2.3E-08	225-08	46-08
KD AGAINST FogR11aH (mo1/L)	6.7E-07	80-30's	1 85-05					1 66-36		2.06-05	126-13	1.55-05	1 26-063
KO AGAINST Foor I ar	1.05-06	5.0E-06	1.85-05			21 2-05	3.85-05	1.4E−05	1 85-05	228-00	7.25-06	138-06	355-08
KD AGAINST KD A FugBla Fog (mol/L) (m	32E-10	975-10	63E-08	756-08	1 48-07	1 25-07	3.4E-07	5.2E-08	128-03	5 28-08	3.65-38	80-368	\$ \$E-8
	×		L234W/P238D	12347/72300	G237A/P238D	G23707P2380	G237E/P23ED	GZ37F/P2380	C237L/P238D	G23744/P238D	G237W//P238D	G237Y/P238D	06023/08024
sed id no variant name	LBP-GAd/ILBR-L	LSR-F11/1L&R-L	LER-FEOME/EER-L	LBR-PD043/RBR-L	1.68	L6R-FD080/7L68-L	L6R-PD081/11.8R-L	L6R-PD082/3L68-L	1.5R-PDX85/11.5R-1.	188-90087/3169-1.	L5R-PD034/1L5R-L	L6R-PE006/3162-L	R.BR-PD087/368-L
SED ID NO	20 JR	27 III.		30 11		32 JR			39 39	~~~		38 18	W 68

[Example 5] X-ray crystallographic analysis of a complex formed between an Fc containing P238D and an extracellular region of FcγRIIb

As indicated earlier in Example 3, even though an alteration that improves $Fc\gamma RIIb$ binding activity or selectivity for $Fc\gamma RIIb$ is introduced into an Fc containing P238D, the $Fc\gamma RIIb$ -binding activity was found to decrease, and the reason for this may be that the structure at the interacting interface between Fc and $Fc\gamma RIIb$ is changed due to introduction of P238D. Therefore, to pursue the reason for this phenomena, the three-dimensional structure of the complex formed between an IgG1 Fc containing the P238D mutation (hereinafter, Fc(P238D)) and the extracellular region of $Fc\gamma RIIb$ was elucidated by X-ray crystallographic analysis, and the three-dimensional structure and binding mode were compared to those of the complex formed between the Fc of a naturally-occurring IgG1 (hereinafter, Fc(WT)) and the extracellular region of $Fc\gamma RIIb$. Many reports have been made on the three-dimensional structure of a complex formed between an Fc and an $Fc\gamma R$ extracellular region; and the three-dimensional

- 5 structures of the Fc(WT) / FcγRIIIb extracellular region complex (Nature, 2000, 400: 267-273; J. Biol. Chem. 2011, 276: 16469-16477), the Fc(WT) / FcγRIIIa extracellular region complex (Proc. Natl. Acad. Sci. USA, 2011, 108: 12669-126674), and the Fc(WT) / FcγRIIa extracellular region complex (J. Imunol. 2011, 187: 3208-3217) have been analyzed. While the three-dimensional structure of the Fc(WT) / FcγRIIb extracellular region complex has not been
- analyzed, the three-dimensional structure of a complex formed with Fc(WT) is known for FcγRIIa, and the extracellular regions of FcγRIIa and FcγRIIb match 93% in amino acid sequence and have very high homology. Thus, the three-dimensional structure of the Fc(WT) / FcγRIIb extracellular region complex was predicted by modeling using the crystal structure of the Fc(WT) / FcγRIIa extracellular region complex.

The three-dimensional structure of the Fc(P238D) / Fc γ RIIb extracellular region complex was determined by X-ray crystallographic analysis at 2.6 Å resolution. The structure obtained as a result of this analysis is shown in Fig. 8. The Fc γ RIIb extracellular region is bound between two Fc CH2 domains, and this is similar to the three-dimensional structures of complexes formed between Fc(WT) and the respective extracellular region of Fc γ RIIIa,

30 Fc γ RIIIb, or Fc γ RIIa analyzed so far.

Next, for detailed comparison, the crystal structure of the Fc(P238D) / Fc γ RIIb extracellular region complex and the model structure of the Fc(WT) / Fc γ RIIb extracellular region complex were superimposed by the least squares fitting based on the C α atom pair distances with respect to the Fc γ RIIb extracellular region and the Fc CH2 domain A (Fig. 9). In

35 that case, the degree of overlap between Fc CH2 domains B was not satisfactory, and conformational differences were found in this portion. Furthermore, using the crystal structure

of the Fc(P238D) / Fc γ RIIb extracellular region complex and the model structure of the Fc(WT) / Fc γ RIIb extracellular region complex, pairs of atoms that have a distance of 3.7 Å or less between the Fc γ RIIb extracellular region and Fc CH2 domain B were extracted and compared in order to observe the differences in interatomic interactions between Fc γ RIIb and Fc CH2 domain B in Fc(WT) and Fc(P238D). As shown in Table 8, the interatomic interactions between Fc CH2 domain B and Fc γ RIIb in Fc(P238D) and Fc(WT) do not match.

[Table 8]

FegRi	etb ATC	MC	INTER	ACTION	PARTN	MAIN B Er Atoms, Å)	INTER	C(WT) CH2 DOMAIN B NTERACTION PARTNER DISTANCE BETWEEN ATOMS, A)								
Val	116	CG2					Asp Gly			(3.47) (3.65)						
Ser	126	ÖĞ	Ser Ser Tyr	298 298 296	N CB O	(3.31) (3.32) (3.05)										
Lys	128	CĂ	Ser	298	OG	(3.50)										
Phe	129	CB	Ser	298	0	(3.36)										
Phe	129	CD2					Asn Asn	297 297	CB CG	(3.50) (3.43)						
Lys	128	С	Ser	298	OG	(3.47)										
Phe	129	N	Ser	298	OG	(3.30)										
Phe	129	0	Ser	267	OG .	(3.54)										
Arg	131	CB					Val	266	0	(3.02)						
Arg	131	CG					Val	266	0	(3.22)						
Arg	131	CD					Val Val Val	266 266 266	CG1 C O	(3.45) (3.55) (3.10)						
Arg	131	NE	Ala	327	0	(3.60)	Val Val Val	266 266 266	C O N	(3.66) (3.01) (3.49)						
Arg	131	ÇZ	Asp Asp Asp Ala	270 270 270 327	CG OD2 OD1 CB	(3.64) (3.22) (3.27) (3.63)	Val	266	N	(3.13)						
Arg	131	NH1	Asp Asp Asp Ser	270 270 270 267	CG OD2 OD1 CB	(3.19) (2.83) (2.99) (3.56)	Val Val Thr Ser	266 266 299 298	CG1 N OG1 O	(3.47) (3.43) (3.66) (3.11)						

Arg	131	NH2	Asp Asp Asp Ala	270 270 270 327	CG OD2 OD1 CB	(3.20) (2.80) (2.87) (3.66)	Asp Val	265 266	CA N	(3.16) (3.37)
Tyr	157	CE1					Leu Leu	234 234	CG CD1	(3.64) (3.61)
Tyr	157	OH					Gly Leu Leu	236 234 234	O CA CG	(3.62) (3.48) (3.45)

Furthermore, the X-ray crystal structure of the $Fc(P238D) / Fc\gamma RIIb$ extracellular region complex and the model structure of the $Fc(WT) / Fc\gamma RIIb$ extracellular region complex were superimposed by the least squares fitting based on the C α atom pair distances with respect to the only Fc CH2 domain A or the only Fc CH2 domain B, and the detailed structures near P238D were compared. The location of the amino acid residue at position 238 (EU numbering), which is mutation introduction position, is changed between Fc(P238D) and Fc(WT), one can see that along with this change, the nearby loop structure continuing from this hinge region is changed

- 0 between Fc(P238D) and Fc(WT) (Fig. 10). Originally in Fc(WT), Pro at position 238 (EU numbering) is present on the inner side of the protein, and forms a hydrophobic core with the surrounding residues. However, when this residue is changed to a charged and very hydrophilic Asp, the presence in the same hydrophobic core would cause energetical disadvantage in terms of desolvation. Therefore, in Fc(P238D), to cancel this energetically disadvantageous situation,
- 5 the amino acid residue at position 238 (EU numbering) changes its orientation to face the solvent side, and this may have caused this change in the nearby loop structure. Furthermore, since this loop continues from the hinge region crosslinked by an S-S bond, its structural change will not be limited to a local change, and will affect the relative positioning of the FcCH2 domain A and domain B. As a result, the interatomic interactions between FcγRIIb and Fc CH2 domain B have been changed. Therefore, predicted effects could not be observed when alterations that improve selectivity and binding activity towards FcγRIIb in a naturally-occurring IgG were combined with an Fc containing the P238D alteration.

Furthermore, as a result of structural changes due to introduction of P238D in Fc CH2 domain A, a hydrogen bond has been found between the main chain of Gly at adjacent position
25 237 (EU numbering) and Tyr at position 160 in FcγRIIb (Fig. 11). The residue in FcγRIIa that corresponds to this Tyr 160 is Phe; and when the binding is to FcγRIIa, this hydrogen bond is not formed. The amino acid at position 160 is one of the few differences between FcγRIIa and FcγRIIb at the interface of interaction with Fc, the presence of this hydrogen bond which is specific to FcγRIIb is presumed to have led to improvement of FcγRIIb-binding activity and

30 decrease of FcyRIIa-binding activity in Fc(P238D), and improvement of its selectivity.

Furthermore, in Fc CH2 domain B, an electrostatic interaction is observed between Asp at position 270 (EU numbering) and Arg at position 131 in Fc γ RIIb (Fig. 12). In Fc γ RIIa type H, which is one of the allotypes of Fc γ RIIa, the corresponding residue is His, and therefore cannot form this electrostatic interaction. This can explain why the Fc(P238D)-binding activity is lowered in Fc γ RIIa type H compared with Fc γ RIIa type R. Observations based on such results of X-ray crystallographic analysis showed that the change of the loop structure beside P238D due to P238D introduction and the accompanying change in the relative domain positioning causes formation of new interactions not found in the naturally-occurring IgG, and this led to a selective binding profile of P238D variants for Fc γ RIIb.

[Expression and Purification of Fc(P238D)]

An Fc containing the P238D alteration was prepared as follows. First, Cys at position 220 (EU numbering) of hIL6R-IgG1-v1 (SEQ ID NO: 21) was substituted with Ser. Then, genetic sequence of Fc(P238D) from Glu at position 236 (EU numbering) to its C terminal was

5 cloned by PCR. Using this cloned genetic sequence, production of expression vectors, and expression and purification of Fc(P238D) were carried out according to the method of Reference Example 1. Cys at position 220 (EU numbering) forms a disulfide bond with Cys of the L chain in general IgG1. The L chain is not co-expressed when Fc alone is prepared, and therefore, this residue was substituted with Ser to avoid formation of unnecessary disulfide bonds.

0

25

[Expression and purification of the FcyRIIb extracellular region]

This was prepared according to the method of Reference Example 2.

[Purification of the Fc(P238D) / FcyRIIb extracellular region complex]

To 2 mg of the FcγRIIb extracellular region sample obtained for crystallization, 0.29 mg of Endo F1 (Protein Science 1996, 5: 2617-2622) expressed and purified from *Escherichia coli* as a glutathione S-transferase fusion protein was added. This was allowed to remain at room temperature for three days in 0.1 M Bis-Tris buffer at pH 6.5, and the N-linked oligosaccharide was cleaved, leaving *N*-acetylglucosamine directly bound to Asn. Next, this FcγRIIb

- 30 extracellular domain sample subjected to carbohydrate cleavage treatment was concentrated by ultrafiltration with 5000 MWCO, and purified by gel filtration chromatography (Superdex200 10/300) using a column equilibrated in 20 mM HEPS at pH 7.5 containing 0.05 M NaCl. Furthermore, to the obtained carbohydrate-cleaved FcγRIIb extracellular region fraction, Fc(P238D) was added so that the molar ratio of the FcγRIIb extracellular region would be
- 35 present in slight excess, and after concentration by ultrafiltration with 10,000 MWCO, a sample of the Fc(P238D) / FcγRIIb extracellular region complex was obtained through purification by

gel filtration chromatography (Superdex200 10/300) using a column equilibrated in 20 mM HEPS at pH 7.5 containing 0.05 M NaCl.

[Crystallization of the Fc(P238D) / FcyRIIb extracellular region complex]

A sample of the Fc(P238D) / Fc γ RIIb extracellular region complex was concentrated to approximately 10 mg/mL by ultrafiltration with 10,000 MWCO, and crystallization was carried out by the sitting drop vapor diffusion method. Hydra II Plus One (MATRIX) was used for crystallization; and for a reservoir solution containing 100 mM Bis-Tris pH 6.5, 17% PEG3350, 0.2 M ammonium acetate, and 2.7% (w/v) D-Galactose, a crystallization drop was produced by mixing at a ratio of reservoir solution : crystallization sample = 0.2 μ L : 0.2 μ L, and after sealing, this was allowed to remain at 20°C, and thin plate-like crystals were successfully obtained.

[Measurement of X-ray diffraction data from an Fc(P238D) / FcγRIIb extracellular region

5 complex crystal]

One of the obtained single crystals of the Fc(P238D) / FcyRIIb extracellular region complex was soaked into a solution of 100 mM Bis-Tris pH 6.5, 20% PEG3350, ammonium acetate, 2.7% (w/v) D-Galactose, 22.5% (v/v) ethylene glycol. The crystal was fished out of the solution using a pin with attached tiny nylon loop, and frozen in liquid nitrogen; and then X-ray 0 diffraction data was measured at synchrotron radiation facility Photon Factory BL-1A in High Energy Accelerator Research Organization. During the measurement, the crystal was constantly placed in a nitrogen stream at -178°C to maintain in a frozen state, and a total of 225 X ray diffraction images were collected using Quantum 270 CCD detector (ADSC) attached to a beam line with rotating the crystal 0.8° at a time. Determination of cell parameters, indexing of 25 diffraction spots, and diffraction data processing from the obtained diffraction images were performed using the Xia2 program (CCP4 Software Suite), XDS Package (Walfgang Kabsch) and Scala (CCP4 Software Suite); and finally, diffraction intensity data up to 2.46 Å resolution was obtained. The crystal belongs to the space group $P2_1$, and has the following cell parameters; $a = 48.85 \text{ Å}, b = 76.01 \text{ Å}, c = 115.09 \text{ Å}, \alpha = 90^{\circ}, \beta = 100.70^{\circ}, \gamma = 90^{\circ}.$

30

[X ray crystallographic analysis of the Fc(P238D) / FcγRIIb extracellular region complex]

Crystal structure of the $Fc(P238D) / Fc\gamma RIIb$ extracellular region complex was determined by the molecular replacement method using the program Phaser (CCP4 Software Suite). From the size of the obtained crystal lattice and the molecular weight of the Fc(P238D) /

35 FcγRIIb extracellular region complex, the number of complexes in the asymmetric unit was predicted to be one. From the structural coordinates of PDB code: 3SGJ which is the crystal

- structure of the Fc(WT) / Fc γ RIIIa extracellular region complex, the amino acid residue portions of the A chain positions 239-340 and the B chain positions 239-340 were taken out as separate coordinates, and they were used respectively as models for searching the Fc CH2 domains. The amino acid residue portions of the A chain positions 341-444 and the B chain positions 341-443 were taken out as a single set of coordinates from the same structural coordinates of PDB code: 3SGJ; and this was used as a model for searching the Fc CH3 domains. Finally, from the structural coordinates of PDB code: 2FCB which is a crystal structure of the Fc γ RIIb extracellular region, the amino acid residue portions of the A chain positions 6-178 was taken out and used as a model for searching the Fc γ RIIb extracellular region. The orientation and position of each search model in the crystal lattice were determined in the order of Fc CH3 domain, Fc γ RIIb extracellular region, and Fc CH2 domain, based on the rotation function and translation function to obtain the initial model for the crystal structure of the Fc(P238D) / Fc γ RIIb extracellular region complex. When rigid body refinement which moves the two Fc CH2 domains, the two Fc CH3 domains, and the Fc γ RIIb extracellular region was performed on the
- 5 obtained initial model, the crystallographic reliability factor, R value became 40.4%, and the Free R value became 41.9% to diffraction intensity data from 25 Å to 3.0 Å at this point. Furthermore, structural refinement using the program Refmac5 (CCP4 Software Suite), and revision of the model to observe the electron density maps whose coefficient have 2Fo-Fc or Fo-Fc, which are calculated based on the experimentally determined structural factor Fo, the
- calculated structural factor Fc and the calculated phase using the model, was carried out by the Coot program (Paul Emsley), and model refinement was carried out by repeating these steps. Finally, as a result of incorporation of water molecules into the model based on the electron density maps which use 2Fo-Fc or Fo-Fc as the coefficient, and the following refinement, the crystallographic reliability factor, R values and the Free R value of the model containing 4846
 non-hydrogen atoms became 23.7% and 27.6% to 24291 diffraction intensity data from 25 Å to
- 23

[Production of a model structure of the $Fc(WT) / Fc\gamma RIIb$ extracellular region complex]

Based on the structural coordinates of PDB code: 3RY6 which is a crystal structure of
the Fc(WT) / FcγRIIa extracellular region complex, the Build Mutants function of the Discovery
Studio 3.1 program (Accelrys) was used to introduce mutations to match the amino acid
sequence of FcγRIIb into FcγRIIa in this structural coordinates. In that case, the Optimization
Level was set to High, Cut Radius was set to 4.5, five models were generated, and the one with
the best energy score from among them was employed as the model structure for the Fc(WT)/

35 FcyRIIb extracellular region complex.

2.6 Å resolution, respectively.

[Example 6] Analysis of $Fc\gamma R$ binding of Fc variants whose alteration sites were determined based on crystal structures.

Based on the results of X-ray crystallographic analysis on the complex formed between Fc(P238D) and the FcγRIIb extracellular region obtained in Example 5, comprehensive alterations were introduced into sites on the altered Fc having substitution of Pro at position 238 (EU numbering) with Asp that were predicted to affect interaction with FcγRIIb, (residues of positions 233, 240, 241, 263, 265, 266, 267, 268, 271, 273, 295, 296, 298, 300, 323, 325, 326, 327, 328, 330, 332, and 334 (EU numbering)) and variants with a combination of alterations that enhance FcγRIIb binding were examined.

IL6R-B3 (SEQ ID NO: 40) was produced by introducing into IL6R-G1d (SEQ ID NO: 20) produced in Example 2, the alteration produced by substituting Lys at position 439 (EU numbering) with Glu. Next, IL6R-BF648 (SEQ ID NO: 41) was produced by introducing into IL6R-B3, the alteration produced by substituting Pro at position 238 (EU numbering) with Asp. IL6R-L (SEQ ID NO: 22) was utilized as the common antibody L chain for all of the antibodies.

5 These antibody variants were expressed and purified according to the method of Reference Example 1, and binding to each of the FcγRs (FcγRIa, FcγRIIa type H, FcγRIIa type R, FcγRIIb, and FcγRIIIa type V) was comprehensively evaluated by the method of Reference Example 2.

A figure was produced according to the following method for the results of analyzing the interactions with the respective FcγRs. The value for the amount of binding of each variant to each FcγR was divided by the value for the amount of binding of the pre-altered control antibody (IL6R-BF648/IL6R-L with Pro at position 238 (EU numbering) substituted with Asp) to each FcγR, and the obtained was then multiplied by 100 and used as the relative binding activity value of each variant to each FcγR. The horizontal axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of each variant to FcγRIIb, and the vertical axis shows the relative binding activity value of e

As shown in Fig. 13, the results show that of all the alterations, 24 types of alterations were found to have an effect of maintaining or enhancing $Fc\gamma RIIb$ binding in comparison with the pre-altered antibody. The binding of these variants to each of the $Fc\gamma Rs$ are shown in Table 9. In the table, SEQ ID NO refers to the SEQ ID NO of the H chain of the evaluated variant, and

alteration refers to the alteration introduced into IL6R-B3 (SEQ ID NO: 40). The template used for producing IL6R-B3, IL6R-G1d/IL6R-L, is indicated with an asterisk (*).

[Table 9]

74

SEQ ID NO	VARIANT NAME	ALTERNATION	RELATIVE FogRia- BINDING ACTIVITY		RELATIVE FcgRIIaH BINDING ACTIVITY	RELATIVE FcgRIIb- BINDING ACTIVITY	RELATIVE FcgRIIIaV- BINDING ACTIVITY
20	IL6R-G1d/IL6R-L	*	140	650	1670	62	3348
40	IL6R-2B999/IL6R-L	and the second second second	145	625	1601	58	3264
41	IL6R-BF648/IL6R-L	P238D	100	100	100	100	100
42	IL6R-2B002/IL6R-L	P238D/E233D	118	103	147	116	147
43	IL6R-BP100/IL6R-L	P238D/S267A	121	197	128	110	138
44	IL6R-BP102/IL6R-L	P238D/S267Q	104	165	66	106	86
45	IL6R-BP103/IL6R-L	P238D/S267V	56	163	69	107	77
46	IL6R-BP106/IL6R-L	P238D/H268D	127	150	110	116	127
47	IL6R-BP107/IL6R-L	P238D/H268E	123	147	114	118	129
48	IL6R-BP110/IL6R-L	P238D/H268N	105	128	127	101	127
49	IL6R-BP112/IL6R-L	P238D/P271G	119	340	113	157	102
50	IL6R-2B128/IL6R-L	P238D/Y296D	95	87	37	103	96
51	IL6R-2B169/IL6R-L	P238D/V3231	73	92	83	104	94
52	IL6R-2B171/IL6R-L	P238D/V323L	116	117	115	113	122
53	IL6R-2B172/IL6R-L	P238D/V323M	140	244	179	132	144
54	IL6R-BP136/IL6R-L	P238D/K326A	117	159	103	119	102
55	IL6R-BP117/IL6R-L	P238D/K326D	124	166	96	118	105
56	IL6R-BP120/IL6R-L	P238D/K326E	125	175	92	114	103
57	IL6R-BP126/IL6R-L	P238D/K326L	113	167	132	103	146
58	IL6R-BP119/IL6R-L	P238D/K326M	117	181	133	110	145
59	IL6R-BP142/IL6R-L	P238D/K326N	98	103	97	106	102
60	IL6R-BP121/IL6R-L	P238D/K326Q	118	155	135	113	157
61	IL6R-BP118/IL6R-L	P238D/K326S	101	132	128	104	144
62	IL6R-BP116/IL6R-L	P238D/K326T	110	126	110	108	114
63	IL6R-BP911/IL6R-L	P238D/A330K	52	101	108	119	120
64	IL6R-BP078/IL6R-L	P238D/A330M	106	101	89	105	91
65	IL6R-BP912/IL6R-L	P238D/A330R	60	81	93	103	97

The results of measuring KD values of the variants shown in Table 9 for FcγRIa,
FcγRIIaR, FcγRIIaH, FcγRIIb, and FcγRIIIa type V by the method of Reference Example 2 are summarized in Table 10. In the table, SEQ ID NO refers to the SEQ ID NO of the H chain of the evaluated variant, and alteration refers to the alteration introduced into IL6R-B3 (SEQ ID NO: 40). The template used for producing IL6R-B3, IL6R-G1d/IL6R-L, is indicated with an asterisk (*). Furthermore, KD(IIaR)/KD(IIb) and KD(IIaH)/KD(IIb) in the table respectively represent the value obtained by dividing the KD value of each variant for FcγRIIaR by the KD value of each variant for FcγRIIB, and the value obtained by dividing the KD value of each variant for FcγRIIAR by the KD value of

- each variant for FcγRIIb, and the value obtained by dividing the KD value of each variant for
 FcγRIIaH by the KD value of each variant for FcγRIIb. KD(IIb) of the parent polypeptide /
 KD(IIb) of the altered polypeptide refers to the value obtained by dividing the KD value of the
 parent polypeptide for FcγRIIb by the KD value of each variant for FcγRIIb. In addition, the KD
 value for the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of each variant / KD
- value for the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the parent polypeptide are shown in Table 10. Here, parent polypeptide refers to the variant which has IL6R-B3 (SEQ ID NO: 40) as the H chain. It was determined that due to weak binding of FcγR to IgG, it was

impossible to accurately analyze by kinetic analysis, and thus the gray-filled cells in Table 10 show values calculated by using Equation 2 of Reference Example 2.

[Equation 2]

$KD = C \bullet R_{max} / (R_{eq} - RI) - C$

Table 10 shows that in comparison with IL6R-B3, all variants showed improvement of affinity for Fc γ RIIb, and the range of improvement was 2.1 fold to 9.7 fold. The ratio of KD value of each variant for Fc γ RIIaR / KD value of each variant for Fc γ RIIb, and the ratio of KD value of each variant for Fc γ RIIaH / KD value of each variant for Fc γ RIIb represent an Fc γ RIIb-binding activity relative to the Fc γ RIIaR-binding activity and Fc γ RIIaH-binding activity, respectively. That is, these values show the degree of binding selectivity of each variant for Fc γ RIIb, and a greater value indicates a higher binding selectivity for Fc γ RIIb. Since the ratio of KD value for Fc γ RIIaR / KD value for Fc γ RIIb, and the ratio of KD value for Fc γ RIIaR / KD value for Fc γ RIIb, and the ratio of KD value for Fc γ RIIb, and the ratio of KD value for Fc γ RIIaR / KD value for Fc γ RIIb, and 0.2, respectively, all

- 5 variants in Table 10 showed improvement of binding selectivity for FcγRIIb in comparison with the parent polypeptide. When the KD value for the stronger of the FcγRIIaR- and FcγRIIaHbinding activities of a variant / KD value for the stronger of the FcγRIIaR- and FcγRIIaHbinding activities of the parent polypeptide is 1 or more, this means that the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of a variant has equivalent or decreased binding
- 0 compared with the binding by the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the parent polypeptide. Since this value was 4.6 to 34.0 for the variants obtained this time, one may say that in comparison with the parent polypeptide, the variants obtained this time had reduced binding by the stronger of the FcγRIIaR- and FcγRIIaH-binding activities. These results showed that compared with the parent polypeptide, the variants obtained this time have
- 25 maintained or decreased FcγRIIa type R- and type H-binding activities, enhanced FcγRIIbbinding activity, and improved selectivity for FcγRIIb. Furthermore, compared with IL6R-B3, all variants had lower affinity to FcγRIa and FcγRIIIaV.

[Table 10]

2016262766 25 Nov 2016

E STRONGER - AND 6 ACTIVITIES D VALUE FOR THE ES OF THE IDE	60	40	19.9	24.7	102	11.0	14.4	14.0	153	22.6	46	33.1 33.1	543	20.6	0.6	11.8	12.0	125	14.4	128	235	16.6	19.7	19.4	213	19.0	34.0
KD VALIE FOR THE STRONGER OF THE FORTLAR- AND FORRIAH-BINDING ACTIVITIES OF A VARIANT/ KD VALUE FOR THE STRONGER OF THE FORRIAR- AND FORMLAH- BINDING ACTIVITIES OF THE PARENT POLVFEPTIDE																											
ko (11b) of Parent Polyreptide/ Ko (11b) G Altered Polyreptide	1 2	31	2.6		2.9	3.4	23	S.S.	88	2.4	24	23	2.6	29	40				22	2.7	2.6	28	23	28	22 57	88	21
KD(IIaH)/ KD(IIb)	03	02	33.9	823	42.8		19 12		56.1	5 5	1004	23.6	40.7	31.8	27.3	47.6	51.4	63.1	31.7	385	561	40,4	40.0	482	41.7	4 4	25.9
KD(IIIaR)/ KD(IIIa)	04				73		08		12.3			17.7		15.0						6. 8				133			
KD AGAINST FcgAliiav (mol/L)	358-03	336-07	716-06		¥.						○ 63E-0€]												565-05			785-06	
KD AGAINST Fogrila (mol/1.)	286-38	316-06	125-06		115-06						326-07			1.1 E-06			8.0E-07	1.05-06				1.16-00		116-06		•	1 26-36
KD AGAINST FcgRIIaH (mol/L)	6.7E-07	7.76-07	4.05-06	3988-08	165-05	616-05	335-328	30400	52E-06	4 7E-OS	355-36	346-06	43E-06	348-05	216-06	388-06	41E-0E	635-05	486-05	458-36	935-38	446-06	4 8 1-36	54E-06	37E-06	458-06	395-36
KD AGAINST FcgRilaR (mol/1)	1.05-05	1.1 6-06	1 58-05	1 86-05	7.8E-36[3.4E~O6[115-8	115-35	1 28-06	1.7E-06	356-06	2.65-36	1 85-06	1.65-05	á.1 E06 [9.1 E06 [32E-06	9.3E-06	11E-36	33E-36[1 38-05	135-36	1.5E-05	1 56-36 [1.86-05.	1.5E-05	2.85-05
KD AGAINST FogRIa (mol/L)	325-10	425-10	115-06	64E-09	116-00	825-09	355-08	4.05-08	1.56-09	73E-09	9255-09	135-08	255-00	31E-00	3.05-09	5 8 E- C0	41E08	6.6509	7.46-08	7.0E-09	535-09	89-311	1.25-08	2.85-09	495-06	82E-00	385-38
ALTERATION	×	The second secon	P238D	P238D/E233D	P238D/5267A	P2380/S267G	P238D/S267V	P238D/H268D	P238D/H268E	P238D/H268N	P2380/P271G	P236D/Y296D	P236D/V3231	P238D//523L	P238D//323M	P238D/K328A	P2380/K3280	P238D/K328E	P238D/K326L	P238D/K828M	P2380/K326N	P238D/K3260	P238D/k326S	P238D/F316T	P238D/A330K	P236D/A330M	P238D/A330R
VARIANT NAME	Leg-Ctd/ILER-L	L6R-28993/IL6R-L	L8R-3F643/1L6R-L	L6R-2E002/IL6R-L	LSR-BP1 CO/ILSR-L	L6R-BP1 (2/JL6R-L	LOR-BP103//LOR-L	L6R-8P1 (%/IL6R-L	L&R-BPI (77 / IL & R-L	L&R-8P110/IL&R-L	L6R-BP112/IL6R-L	1.68-28128/1.68-1	1-68-2E1 68/11/68-L	L6R-28171/IL6R-L	L68-28172/1L6P-L	1.3R-3P136/11.5R-1.	L6R-BP117/IL6R-L	LSR-BP120/IL3R-L	L6R-8P1 26/1L6R-L	1.0R-8P119/11.0R-1	L&R-BP142/JL&R-1.	1.6R-6P121 / 11.6R-1.	1.6R8P118/11.6R-L	L68-8P116/IL6R-L	L68-8P911/R68-1	L6R-BP078/IL6R-L	L&R-BP912/IL&R-L
SEQ ID NO	20 10 10 10			42	43		<u>چ</u> ې				1] 6¥			52						58 11				62 11			

With regard to the promising variants among the obtained combination variants, the factors leading to their effects were studied using the crystal structure . Fig. 14 shows the crystal structure of the $Fc(P238D) / Fc\gamma RIIb$ extracellular region complex. In this figure, the H chain positioned on the left side is Fc Chain A, and the H chain positioned on the right side is Fc Chain B. Here, one can see that the site at position 233 (EU numbering) in Fc Chain A is located near Lys at position 113 (EU numbering) of $Fc\gamma RIIb$. However, in this crystal structure, the E233 side chain is in a condition of considerably high mobility, and its electron density is not well observed. Therefore, the alteration produced by substituting Glu at position 233 (EU numbering) with Asp leads to decrease in the degree of freedom of the side chain since the side chain becomes one carbon shorter. As a result, the entropy loss when forming an interaction with Lys at position 113 (EU numbering) of $Fc\gamma RIIb$ may be decreased, and consequently this is speculated to contribute to improvement of binding free energy.

Similarly, Fig. 15 shows the environment near the site at position 330 (EU numbering)
in the structure of the Fc(P238D) / FcγRIIb extracellular region complex. This figure shows that the environment around the site at position 330 (EU numbering) of Fc Chain A of Fc (P238D) is a hydrophilic environment composed of Ser at position 85, Glu at position 86, Lys at position 163, and such (EU numbering) of FcγRIIb. Therefore, the alteration produced by substituting Ala at position 330 (EU numbering) with Lys or Arg is speculated to contribute to strengthening the interaction with Ser at position 85 (EU numbering) or Glu at position 86 (EU numbering) in FcγRIIb.

Fig. 16 depicts the structures of Pro at position 271 (EU numbering) of Fc Chain B after superimposing the crystal structures of the Fc(P238D) / Fc γ RIIb extracellular region complex and the Fc(WT) / Fc γ RIIIa extracellular region complex by the least squares fitting based on the C α atom pair distances with respect to Fc Chain B. These two structures match well, but have different three-dimensional structures of Pro at position 271 (EU numbering). When the weak electron density around this area in the crystal structure of the Fc(P238D)/Fc γ RIIb extracellular region complex is also taken into consideration, it is suggested that there is possibility that Pro at position 271 (EU numbering) in Fc(P238D) / Fc γ RIIb causes a large strain on the structure, thus

- 30 disturbing the loop structure to attain an optimal structure. Therefore, the alteration produced by substituting Pro at position 271 (EU numbering) with Gly gives flexibility to this loop structure, and is speculated to contribute to enhancement of binding by reducing the energetic barrier when allowing an optimum structure to form during interaction with FcγRIIb.
- 35 [Example 7] Examination of the combinatorial effect of alterations that enhance FcγRIIb binding when combined with P238D.

Of the alterations obtained in Examples 4 and 6, those that enhanced $Fc\gamma RIIb$ binding or maintained $Fc\gamma RIIb$ binding and showed effects of suppressing binding to other $Fc\gamma Rs$ were combined with each other, and their effects were examined.

Particularly good alterations were selected from Tables 6 and 9, and they were combined and introduced into the antibody H chain IL6R-BF648 in a similar manner to the method of Example 6. IL6R-L was utilized as the common antibody L chain for all of the antibodies, the antibodies were expressed and purified according to the method of Reference Example 1, and binding to each of the Fc γ Rs (Fc γ RIa, Fc γ RIIa H type, Fc γ RIIa R type, Fc γ RIIb, and Fc γ RIIIa V type) was comprehensively evaluated by the method of Reference Example 2.

Relative binding activities were calculated for the results of analyzing interactions with the respective Fc γ Rs according to the following method. The value for the amount of binding of each variant to each Fc γ R was divided by the value for the amount of binding of the pre-altered control antibody (IL6R-BF648/IL6R-L with substitution of Pro at position 238 (EU numbering) with Asp to each Fc γ R, and multiplied by 100; and then the value was used as the relative

5 binding activity value of each variant to each $Fc\gamma R$. The horizontal axis shows the relative binding activity value of each variant to $Fc\gamma RIIb$, and the vertical axis shows the relative binding activity value of each variant to $Fc\gamma RIIa$ type R (Table 11).

In the table, SEQ ID NO refers to the SEQ ID NO of the H chain of the evaluated variant, and alteration refers to the alteration introduced into IL6R-B3 (SEQ ID NO: 40). The template used for producing IL6R-B3, IL6R-G1d/IL6R-L, is indicated with an asterisk (*).

[Table 11]

0

seq ID No	VARIANT NAME	AL TERNATION	FogRia			RELATIVE FogRilb- BINDING ACTIVITY	RELATIVE FogRillav- BINDING ACTIVITY
20	11.6P-Gt i/11.6P-1.		148	850	1570	62	3348
	0.6P-B3/il8P-i.		148	\$25	1601	56	3264
	RL697-87048/3L0R-L	P238D	100	1.00	100	100	300
	R.6P-25253/1.6R-1_	E233D/P2380/V323M		266	ļ <u>20</u> 7	156	<u>981</u>
	0.69-26261/3.68-1	E233D/PC38D/V238D			<u></u>	115	ļ
	8.69-89082/8.68-1. 8.69-89082/8.68-1.	P233D/P238D/A330K P235D/Y286G/A330K		126	108	136	
	1.69-5904/1.68-(PERSUA CONTRACT ANNO A		<u>97</u> 253	91 182	122	1 <u>07</u> 106
	11.68-8P088/11.68-L	G237D/ P238D/ A330K	19	278	158	152	104
	ILOR-BROSS/ILOR-L	P225ED/Y326A/A330K	72	155	115	197	123
78	1108-89087/1108-1	1234Y/P238D/A380K	33	168	179	137	156
	1.68-87088/1.68-1	<u>{02370/P2280/K326A/A330K</u>		377	168	161	122
	ILSR-89089/ILSR-L	JL234Y/P238D/K828A/A930K		ļ <u>222</u> .	186	147	136
	11.68-69129/11.68-1.	ES280/F238D/3296D/A3308		111	38	1.88	85
	BL6R-8P130/IL6R-L	ES380/F2380/V323M/A830K	164	222.	224	160	115
	81.68-82131/8.68-1 81.68-82132/8.68-1	E3330/02370/192380/4330K		<u>364</u> 191	259 130	160 150	118 120
	N 69-DEI 33/0 62-0	192930/1/2941/292357/4530K	41	124	151	137	114
	R.69-82133/R.59-L R.69-82143/R.59-L	E233D/F238D/F326A/A330K E233D/1234 V/P235D/A330K L234V/P238D/K325A	88	238	143	137 133	114
	1689-8P144/1689-L	(02370/P2330/K326A	64	204	1.08	121	(28
83	8.62-82145/8.62-1	10347/02310/22360		\$50		150	159.
<u>84</u>	8L69-8P146/1L69-L	12347/0237D/9238D/Y326A	50	445	208	156	180
	8.62-BP147/0.6R-L	12347/02370/P2380/F326A/A330K		<u>650</u>	582	172	<u> </u>
	11.69-89148/11.68-C	1235D/L234Y/G251O/F238D/NR/6A/A330#	33	6936	482	178	<u> </u>
	8.69-6P149/0.68-C	12235D/1284Y/62370/P288D/Y2860/K828A/A880K		<u>839</u>	401	173	186
	8.69-69150/1188-1	L234 V/G237D/P238D/K326A/A330R E233D/L234 V/G237D/P238D/K326A/A330R		787 705	821	1 <i>8</i> 3 180	2014 221
	11.68-69182/11.68-L	E2350/L234V/02570/P2380/V2360/K326A/A330R	34	538	\$48	178	146
	8.68-8FI 76/116R-C	E2390/P2380/X3280/A330K	102	253	128	147	131
82	11.6R-6F177/11.6R-L	E2350/L2341//02570/F2380/P271G/K3250/A530K	\$7	<u>681</u>	409	177	186
33	LOR-8F178/1LOR-L	[E2330/G237D/P238D/P27VS/A330K	51	633	259	173	110
	11.08-85170/11.0R-L	02370/P2380/P271G/P320A/A330K		5?0	228	172	125
	11.68-67180/1.68-1	62370/P2380/P2710/A380K		802	203	1 73	100
<u> </u>	11.08-8F181/(1.68-1 11.08-8F182/(1.68-1	E2380/F238D/P271G/X328A/A330K	168	<u>362</u> 413	150	170 128	22
	RL68-EP183/R.68-L	E0380/P2380/P271 G/Y2980/ 4680K E0380/L234 Y/P2380/P271 G/Y328A/A330K	99 83	423	139 191	164	120 113
	R.6R-02134/R.6R-L	E233D/RC36D/P171G/A330K		436	131	171	1.96
	1088-02185/108-0	E2330/L254 Y/G2370/P2380/P271 G/V526A/A330K	47		448	178	181
101	RL6R-BP185/RL5R-L	JE283D/L284Y/G237D/P288D/P271G/Y286D/N326A/A830K.	43		368	175	143
	1.68-69197/1.68-L	L234V/P238D/P271G/V326A/A330K	80	387.	208	157	124
	8.6P-BP188/31.6R-1	E283D/6237D/P286D/H268D/P271G/A830K		<u> 636</u>	284	179	181
	11.69-89189/11.68-C	G2370/P235D/H2980/P271G/K326A/A350K	<u> </u>	587	183	177	141
<u>168</u> 168	8.6P-8P190/8.6R-1. 8.6P-8P191/88R-1.	CC37D/P235D/P088D/P271G/A330K 2235D/P238D/P258D/P271G/K325A/A330K	\$0 125	615 382	224 145	181 170	195. 142
	B.69-BP192/B.6R-(E235D/P236D/H2565D/P271G/Y285D/A330K	109	458	122	172	118
	1.69-89193/11.68-0	E2330/P236D/F258D/P271G/A3304	113		184	178	138
<u>109</u>	10.68-05194/11.66-1	E2350/L234V/02570/P2380/H2680/P2710/K526A/A530K	69	672	395	178	249
110	11.6R-8F195/11.0R-L	[E2350/L2341/G2570/P2380/R2580/P271G/V2860/K326A/A830K	48	551	344	151	<u> </u>
	11.69-87196/11.68-1	L234Y/P23ED/H258D/P2710/K320A/AS30K	<u>. 69</u>	462	195	157	137
	10.08-8F197/0.06-0	E2350/L234V/02370/P2380/H2680/P2710/Y2860/K3260/A330K			294	173	
	R.6R-8F198/R.6R-1 R.6R-8F199/R.6R-1	E2350/L234 V/P2350/H2880/P2710/K325A/A830K	104	443	188	104	187
4 4 12	The experimentation of the second	jegaso/P2380/P3280/A3300		172.	116	144 188	106.
116	ROR-BEZO: ALSR-1.	E335/G237D/P238D/P27NB/A330R	57	586	359	186	121
117	IL68-87202/IL58-L	52370/P2380/P271 G/K328A/A390R	48	\$15	28%	185	100
<u>118</u>	<u> .08-05203/ .08- </u>	0237D/P233D/P271 G/A330P	40	897	205 255	185	56
119	8L68-02204/8L68-L	122330/P230D/P2710/X026A/A330R		<u></u>	ļ	165	121
	1069-8P205/105P-C	182330/P2880/P2710/V2960/A330P		335	108	167	<u></u>
121	RL6R-BP2C6/RL6P-L	E233D/F238D/P271 0/A390R	101	362	123	166	<u>82</u>
122	R.69-89207/R.88-L	E233D/P288D/A330R	74		108	124	97
<u>. 123</u> 194	11.69~87208/11.98~1_ 11.69~67209/11.68~1_	E233D/G237D/P233D/H295D/P271G/A330R C227D/P233D/H265D/P271G/K306A/A330R		690 825	<u>310</u> 267	186 186	118. 158
	8.69-89210/1L8R-L	G237D/P235D/H2850/P271G/A008	\$7	<u>561</u>	\$28	187	125
	0.69-89211/0.68-0	E2330/P2380/H2680/P27EG/K325A/A330R	128	312	111	(65	87
127	0.68-89212/R.6R-L	E2330/P2380/H2580/P271G/Y2860/A3998	117		135	175	122
	0.68-89213/1188-1	E2330/P238D/H053D/P271G/A330R	1:3		123	168	100
128	ILOR-OF214/ILOR-L	E2350/L234V/G2570/P2580/V2960/K5250/A390K	36	498	285	174	185

The results of measuring KD values of the variants shown in Table 11 for FcγRIa, FcγRIIaR, FcγRIIaH, FcγRIIb, and FcγRIIIa type V by the method of Reference Example 2 are summarized in Table 12. In the table, SEQ ID NO refers to the SEQ ID NO of the H chain of the evaluated variant, and alteration refers to the alteration introduced into IL6R-B3 (SEQ ID NO: 40). The template used for producing IL6R-B3, IL6R-G1d/IL6R-L, is indicated with an asterisk

(*). Furthermore, KD(IIaR)/KD(IIb) and KD(IIaH)/KD(IIb) in the table respectively represent the value obtained by dividing the KD value of each variant for Fc γ RIIaR by the KD value of each variant for Fc γ RIIb, and the value obtained by dividing the KD value of each variant for Fc γ RIIaH by the KD value of each variant for Fc γ RIIb. KD(IIb) of the parent polypeptide / KD(IIb) of the altered polypeptide refers to the value obtained by dividing the KD value of the parent polypeptide for Fc γ RIIb by the KD value of each variant for Fc γ RIIb. In addition, the KD value for the stronger of the Fc γ RIIaR- and Fc γ RIIaH-binding activities of each variant / KD value for the stronger of the Fc γ RIIaR- and Fc γ RIIaH-binding activities of the parent polypeptide are shown in Table 12. Here, parent polypeptide refers to the variant which has IL6R-B3 (SEQ ID NO: 40) as the H chain. It was determined that due to weak binding of Fc γ R to IgG, it was impossible to accurately analyze by kinetic analysis, and thus the gray-filled cells in Table 12 show values calculated by using Equation 2 of Reference Example 2.

[Equation 2]

 $KD = C \bullet R_{max} / (R_{eq} - RI) - C$

Table 12 shows that in comparison with IL6R-B3, all variants showed improvement of affinity for FcyRIIb, and the range of improvement was 3.0 fold to 99.0 fold. The ratio of KD value of each variant for FcyRIIaR / KD value of each variant for FcyRIIb, and the ratio of KD value of each variant for FcyRIIaH / KD value of each variant for FcyRIIb represent an FcyRIIbbinding activity relative to the FcyRIIaR-binding activity and FcyRIIaH-binding activity, 0 respectively. That is, those values show the degree of binding selectivity of each variant for FcyRIIb, and a greater value indicates a higher binding selectivity for FcyRIIb. Since the ratio of KD value for FcyRIIaR / KD value for FcyRIIb, and the ratio of KD value for FcyRIIaH / KD value for FcyRIIb of the parent polypeptide IL6R-B3/IL6R-L were 0.3 and 0.2, respectively, all 25 variants in Table 12 showed improvement of binding selectivity for FcyRIIb in comparison with the parent polypeptide. When the KD value for the stronger of the FcyRIIaR- and FcyRIIaHbinding activities of a variant / KD value for the stronger of the FcyRIIaR- and FcyRIIaHbinding activities of the parent polypeptide is 1 or more, this means that the stronger of the FcyRIIaR- and FcyRIIaH-binding activities of a variant has equivalent or decreased binding compared with the binding by the stronger of the FcyRIIaR- and FcyRIIaH-binding activities of

- 30 compared with the binding by the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the parent polypeptide. Since this value was 0.7 to 29.9 for the variants obtained this time, one may say that binding by the stronger of the FcγRIIaR- and FcγRIIaH-binding activities of the variants obtained this time was nearly equivalent or decreased compared with that of the parent polypeptide. These results showed that compared with the parent polypeptide, the variants
- 35 obtained this time have maintained or decreased FcγRIIa type R- and type H-binding activities,

enhanced FcγRIIb-binding activity, and improved selectivity for FcγRIIb. Furthermore, compared with IL6R-B3, all variants had lower affinity for FcγRIa and FcγRIIIaV.

[Table 12]

2016262766 25 Nov 2016

, K	22	6	8.8	2.5	22.5	20	28.6	3.4	92 82	28	20 20 20	1.2	6.00	44	22	2.5	33	- 1	4.	63	5 5	2.2		ж 4	12:	32	22.	1.0
AU PRIOF FOR THE STRAWARD OF THE FORMA AND FORMERS PORTHER THE THE FORMER OF AND AFT, AND WALE FOR THE THE STRAMER OF THE FORMERS OF THE PAREME FOR THEFORMER OF ANTIVITIES OF THE PAREME FOR THEFORMER OF					~		~3			PT				~				4°										
AND FORM	2	~	e }	12 {	36}	8	38 {	54 } 24 }	990 1	NA {	5.1 {	21	108	1 1 1 1	22 {	18 - E	34 }	58 {	4	88 [~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	52 } 52 }	\$ F /	14	51	05 (24 {	2.6
ko (116) of Parent Polypertik/ko (118 of Altreed Polypertik					~~																	33			25	ж 		×:
x(1891)/ XD(18)	33	305	838	303	32.4	385	225	42.6	392	583	2,43	102.5	8 %s	212	6'93 	6.35	513	48.8	328	45.8	35.5	202	1.12	525	883	3000		100 m
(10)2% (10)2%	94	03	(38)	24.5	24.8 1	30	280	243	2	1 833	0.55	13.5	191	29.8	323	32.5 22.5	3.5	155	100	82	23	523	18.6.1	145	92)	37.2	8.85	202
KD ASAENSE Focgettiev (mol/L)	3.55-07	10-38.5	10-3V	100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100 - 100	30.32.4	10-1212	- 585-36	30-33 X	682-68	100-38-9 100-100-100-100-100-100-100-100-100-100	100 100 V	8 32 3	30-313	133-452	34 C (%	190-383 (20-222	625-26	10.000	32-32	2000	100	32-32	() (\$756.0K)	335-06	300	1. A. Street
KO AGAINST Focklib (sol/U)	262-26	338-02	1 22-06	4.26-07	1.05-05	5.58-63	0-36.	S CE-623	328-07	20-340 X	63.6-07	226-03	3.96-62	80 8-0 0	3:06-90	256-03	20.328	5.6E-03	578-03	2.85-52	378-03	232-07	5566-03	358-03	83E-68	336-05	4.05-79	43.8-08
KE ACARASE FOCRATARI (ROL/U)	678-07	20-401 1	X.06-05-	1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 - 1961 -	S	375-20	10-37 P	236-36	4.0-4.2	1900-340 Sec.	80.3 C	20-322	306-305	3C3C 9	285.28	17-32 ×		200 V	2.45-26	10-43 X	1.0-4/ S	1. SE-6	2.3.3	1. N	345-24	3.46-36	1000	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1
C AGAINST FockHIRK (mot/L)	100-301		1 28-05	505-005	228-082	(201)	2.38-05	8-97	420-265	336-366	392-32.6	205-005	0.55-06	1.58-36.5	8 3 3 3	316-065	926-326	365-398	236-365	668-000	3.00-96.8	218-28	3.00-238.0	18-31.	1.45-05	358-003	10-31.9	318-005
KC AGATASTY Freffia (seef./l)	325-30	2.5-3.8	1128-08	1.48-361	\$02:09	87-381	189385	102-201	20-362	180-37 1	325-09	20-34 5	6.36-08:	SC-33.2	1.82-58	10-374	1.52-08	135-07	180-23 F	3,245-38	10-321	142-58	10-34-6	190-300 I	125-00	3 25-07	6.46.9	190-301
NG 12471 104	.×.	AD (82.8-68/1.00-5	\$6.67~89%440./1.98~5. [F05:81]	82/330/44/34/07/42/242		11.69-13062/1639-6. [E25333/P2366V/X330K	(P336E/1938D/ 4330)	22800/2828W/28800	1592), PS/25/79/350/45/08/	[P253813/V2328.62/423608.	73 R.G.R.B.M.R.R.R. R.2384(P2330/4333)	3.5.7-67.68.11.52-1. 02370/72330/Y328.6/A33(K.	75 _ 18.62+18.0204/22+4 _ 12.84/19/38.02/13.826/45.89/6	E2860/14280/143654/238/K	77 BLER 13-1 USF 4. B228307 P33107 282004 282004	25 R. R. P. P. S. VILSP-C. 122/230 (20310 (2030) //03.24	88.84~854.86.45~5{	E228D/L2947/P428D/X330K	M & P ~ P ~ M & P ~ 1, 1344/14208/14206.	52 (5) 55-553 43/18/24-5 (52/310/18/98/18/26/8	1.1344/52530/52300	alor and 40/10.00°a.	01.04-804 %1.01.03-1, %2347/C28710/P230Q4/3365//2300K	E2830/1234Y/C2870/Y2980/K226A/W300K	64-4. [2050201/2041/CC370/705801/12660145684/46908	81.88-82M 59-4 1. 2947/722310/72380/V326A/4350R	10 14 63 - 32 64 54 74 54 - 10 93 17 42 34 7 12 35 01 19 19 10 10 10 10 10 10 10 10 10 10 10 10 10	\$0 BL&PERTSZALSPL FEISO/LZ34V/32372/F238D/Y288D/K286A/8233
so d no valati na	LEEP DAMORT	0.5.8~63/5.58~.	R.61-BP648/1158-1	01.69-2625(3/11.66-1	W&R-23261/2.6K-L	1.68-B7062/W/3-6.	38.82-8008 ALSP-L	R.C.P.B. 062, R.J. 8-6.	R. 8. 8. 65 (19.69-1.	W.&H-434036/W.S.&-4.	N.68-9503/N.68-1.	1.52-67.65/11.52-4	1.62-BPX52/IU/2-6	3-20-20-20-20-20-20-20-20-20-20-20-20-20-	R.68-19:420/1056-5	REP-8931 / R.62-4	WAR-105532/11:05-1.	8) 8168-BM 33/8/59-6 8	1-45 W 52 K 64-43 B	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	8.88-585 35 19.99-1 8	1.68-397.48/1.28-4.	1.02-89-91/10/2-1.	N 82 KB-1983	67 100-100 40/10-0-0	1.22-22456/1.62-1.	162-2025/1620-4	3.58-86152.A.58-1
2 2 2 2	300	08	20. 19	ž		\$	28 28	4 02	 С		s S	20 20	34	2	~	8	8. 8.	3	ö	52 8	20 20	83 23	88 88	200 200	23 23	88 8	100 miles	3

0.9E-06 3.0E-05 7.1 E-07 8.2E-06
4E-06 1.6E-05
.2E-06 1.8E-05
2E-06 2.6E-05
E-06 2.8E-05
3E-06 3.0E-05
6E-07 9.3E-06
8E-06 1.8E-05
.0E-06 1.8E-05
1.4E-06 2.1E-05
11E-06 17E-05
3.0E-06 2.7E-05
2.6E-06 3.2E-05
2.2E-06) 2
8.2E-07, 8.5E-06
91E-07
3 0E-06
.BE-07
.2E-06
8
5
8.4E-07
1.2E-06
9.9E-07
4.5E-06
3.5E-06
31E-06[
.9E-06
8.5E-07
2E-06
0E-06
<u>8</u>
356-06
921

[Reference Example 1] 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 µm MILLEX(R)-GV filter (Millipore), or through a 0.45 µm 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

0 to calculate the antibody concentration (Protein Science 1995; 4: 2411-2423).

[Reference Example 2] Method for preparing $Fc\gamma R$ and method for analyzing the interaction between an altered antibody and $Fc\gamma R$

Extracellular domains of FcγRs were prepared by the following method. First, a gene of the extracellular domain of FcγR was synthesized by a method well known to those skilled in the art. At that time, the sequence of each FcγR was produced based on the information registered at NCBI. Specifically, FcγRI was produced based on the sequence of NCBI Accession No. NM_000566.3, FcγRIIa was produced based on the sequence of NCBI Accession No. NM_001136219.1, FcγRIIb was produced based on the sequence of NCBI Accession No.

- 30 NM_004001.3, FcγRIIIa was produced based on the sequence of NCBI Accession No. NM_001127593.1, and FcγRIIIb was produced based on the sequence of NCBI Accession No. NM_000570.3, and a His tag was attached to the C terminus. Furthermore, polymorphism is known for FcγRIIa, FcγRIIIa, and FcγRIIIb, and the polymorphic sites were produced by referring to J. Exp. Med., 1990, 172: 19-25 for FcγRIIa; J. Clin. Invest., 1997, 100 (5): 1059-
- 35 1070 for FcγRIIIa; and J. Clin. Invest., 1989, 84, 1688-1691 for FcγRIIIb.
 The obtained gene fragments were inserted into an animal cell expression vector, and

30

35

expression vectors were produced. The produced expression vectors were introduced transiently into human embryonic kidney cancer cell line-derived FreeStyle293 cells (Invitrogen) to express the proteins of interest. Regarding Fc γ RIIb used for crystallographic analysis, the protein of interest was expressed in the presence of Kifunensine at a final concentration of 10 µg/mL, so that the sugar chain added to Fc γ RIIb will be the high-mannose type. Cells were cultured, and after collection of the obtained culture supernatant, this was passed through a 0.22 µm filter to obtain the culture supernatant. In principle, the obtained culture supernatants were purified in the following four steps. The steps carried out were, cation exchange column chromatography (SP Sepharose FF) in step 1, affinity column chromatography (HisTrap HP) for His tag in step 2, gel filtration column chromatography (Superdex200) in step 3, and aseptic chromatography in step 4. However, for Fc γ RI, anion exchange column chromatography using Q sepharose FF was performed as step 1. The purified proteins were subjected to absorbance measurements at 280 nm using a spectrophotometer; and from the obtained values, the concentrations of the purified proteins were calculated using the absorption coefficient calculated using methods such as PACE

5 (Protein Science 1995; 4: 2411-2423).

Analysis of interaction between each altered antibody and the Fcγ receptor prepared as mentioned above was carried out using Biacore T100 (GE Healthcare), Biacore T200 (GE Healthcare), Biacore A100, and Biacore 4000. HBS-EP+ (GE Healthcare) was used as the running buffer, and the measurement temperature was set to 25°C. Chips produced by

0 immobilizing the antigen peptide, Protein A (Thermo Scientific), Protein A/G (Thermo Scientific), and Protein L (ACTIGEN or BioVision) by the amine coupling method to a Series S sensor Chip CM5 (GE Healthcare) or Series S sensor Chip CM4 (GE Healthcare), or alternatively, chips produced by allowing preliminarily biotinylated antigen peptides to interact with and immobilize onto a Series S Sensor Chip SA (certified) (GE Healthcare) were used.

After capturing of antibodies of interest onto these sensor chips, an Fc γ receptor diluted with the running buffer was allowed to interact, the amount bound to an antibody was measured, and the antibodies were compared. However, since the amount of Fc γ receptor bound depends on the amount of the captured antibodies, the amount of Fc γ 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 reaction with 10 mM glycine-

HCl, pH 1.5, and the chips were regenerated and used repeatedly.
 Kinetic analyses for calculating the KD values of each altered antibody for FcγR were performed according to the following method. First, antibodies of interest were captured onto

the above-mentioned sensor chips, and an $Fc\gamma$ receptor diluted with the running buffer was allowed to interact. The Biacore Evaluation Software was used to globally fit the measured

results to the obtained sensorgram using the 1:1 Langmuir binding model, and the association

86

rate constant ka (L/mol/s) and the dissociation rate constant kd (1/s) were calculated; and from those values the dissociation constants KD (mol/L) were calculated.

When the interaction between each of the altered antibodies and $Fc\gamma R$ was weak, and correct analysis was determined to be impossible by the above-mentioned kinetic analysis, the KD for such interactions were calculated using the following 1:1 binding model equation described in the Biacore T100 Software Handbook BR1006-48 Edition AE.

The behavior of interacting molecules according to the 1:1 binding model on Biacore can be described by Equation 1 shown below.

[Equation 1]

$$R_{eq} = C \bullet R_{max} / (KD + C) + RI$$

 R_{eq} : a plot of steady-state binding levels against analyte concentration

C: concentration

RI: bulk refractive index contribution in the sample

R_{max}: analyte binding capacity of the surface

5

When this equation is rearranged, KD can be expressed as Equation 2 shown below. [Equation 2]

$$KD = C \bullet R_{max} / (R_{eq} - RI) - C$$

- KD can be calculated by substituting the values of R_{max}, RI, and C into this equation.
 The values of RI and C can be determined from the sensorgram of the measurement results and measurement conditions. R_{max} was calculated according to the following method. As a target of comparison, for antibodies that had sufficiently strong interactions as evaluated simultaneously in the same round of measurement, the R_{max} value was obtained through global fitting using the 1:1 Langmuir binding model, and then it was divided by the amount of the comparison antibody
 captured onto the sensor chip, and multiplied by the captured amount of an altered antibody to be
- 25

evaluated.

Industrial Applicability

30

Polypeptides comprising an Fc region that have maintained or decreased binding
activities towards both allotypes of FcγRIIa, types R and H, and having enhanced FcγRIIbbinding activity in comparison with the parent polypeptide are provided by the present invention.
By using the polypeptides with enhanced binding selectivity for FcγRIIb rather than for both
allotypes of FcγRIIa (types R and H), it is possible to transmit inhibitory signal of inflammatory
immune response mediated by phosphorylation of ITIM of FcγRIIb in patients carrying either of

the allotypes, types R and H. Furthermore, by conferring an antibody Fc with the property of selective $Fc\gamma RIIb$ binding, anti-antibody production may be suppressed through $Fc\gamma RIIb$ -mediated immunosuppressive actions.

CLAIMS

1. A polypeptide variant comprising an antibody Fc region with at least one amino acid alteration, which has maintained or decreased binding activities towards Fc γ RIIa (type R) and Fc γ RIIa (type H), and enhanced Fc γ RIIb-binding activity in comparison with a parent polypeptide, and wherein the value of [KD value of the polypeptide variant for Fc γ RIIa (type H)] / [KD value of the polypeptide variant for Fc γ RIIb] is 4.2 or more, wherein the amino acid alteration comprises substitution of Pro at position 238 (EU numbering) with Asp.

2. The polypeptide of claim 1, wherein the value of [KD value of the parent polypeptide for $Fc\gamma RIIb$] / [KD value of the polypeptide variant for $Fc\gamma RIIb$] is 1.6 or more.

3. The polypeptide of claim 1 or 2, wherein the value of [KD value of the stronger of the binding activities of the polypeptide variant towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H)] / [KD value of the stronger of the binding activities of the parent polypeptide towards $Fc\gamma RIIa$ (type R) and $Fc\gamma RIIa$ (type H)] is 0.7 or more.

4. The polypeptide of any one of claims 1 to 3, which has maintained or decreased FcγRIIIa-binding activity compared with that of a parent polypeptide.

5. The polypeptide of any one of claims 1 to 4, which has maintained or decreased FcγRIa-binding activity compared with that of a parent polypeptide.

6. The polypeptide of any one of claims 1 to 5, wherein the polypeptide further

comprises an additional amino acid alteration selected from the group consisting of: substitution of Gly at position 237 (EU numbering) with Trp; substitution of Gly at position 237 (EU numbering) with Phe; substitution of Ser at position 267 (EU numbering) with Val; substitution of Ser at position 267 (EU numbering) with Gln; substitution of His at position 268 (EU numbering) with Asn; substitution of Pro at position 271 (EU numbering) with Gly; substitution of Lys at position 326 (EU numbering) with Leu; substitution of Lys at position 326 (EU numbering) with Gln; substitution of Lys at position 326 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Met; substitution of Ser at position 239 (EU numbering) with Asp; substitution of Ser at position 267 (EU numbering) with Ala; substitution of Leu at position 234 (EU numbering) with Trp; substitution of Leu at position 234 (EU numbering) with Tyr; substitution of Gly at position 237 (EU numbering) with Ala; substitution of Gly at position 237 (EU numbering) with Asp; substitution of Gly at position 237 (EU numbering) with Glu; substitution of Gly at position 237 (EU numbering) with Leu; substitution of Gly at position 237 (EU numbering) with Met; substitution of Gly at position 237 (EU numbering) with Tyr; substitution of Ala at position 330 (EU numbering) with Lys; substitution of Ala at position 330 (EU numbering) with Arg; substitution of Glu at position 233 (EU numbering) with Asp;

substitution of His at position 268 (EU numbering) with Asp; substitution of His at position 268 (EU numbering) with Glu; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ser; substitution of Lys at position 326 (EU numbering) with Thr; substitution of Val at position 323 (EU numbering) with Ile; substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Leu; substitution of Val at position 323 (EU numbering) with Met; substitution of Tyr at position 296 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Ala; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp; substitution of Lys at position 326 (EU numbering) with Asp;

7. The polypeptide of any one of claims 1 to 6, wherein the polypeptide comprising the antibody Fc region is an IgG antibody.

8. The polypeptide of any one of claims 1 to 6, wherein the polypeptide comprising the antibody Fc region is an Fc fusion protein molecule.

9. A pharmaceutical composition comprising the polypeptide of any one of claims 1 to 8.

10. An agent for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils, which comprises the polypeptide of any one of claims 1 to 8 or the pharmaceutical composition of claim 9.

11. An agent for treating or preventing an immunological inflammatory disease, which comprises the polypeptide of any one of claims 1 to 8 or the pharmaceutical composition of claim 9.

12. The agent of claim 11, wherein the immunological inflammatory disease is an autoimmune disease and is a disease which may be caused by production of an antibody against an autoantigen.

13. An agent for treating a disease, which comprises the polypeptide of any one of claims 1 to 8 or the pharmaceutical composition of claim 9, wherein the disease is a disease with deficiency of a biologically essential protein.

14. An antiviral agent comprising the polypeptide of any one of claims 1 to 8 or the pharmaceutical composition of claim 9.

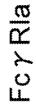
15. Use of a polypeptide according to any one of claims 1 to 8 or the pharmaceutical composition of claim 9, in the manufacture of a medicament for treating or preventing an immunological inflammatory disease.

16. Use of a polypeptide according to any one of claims 1 to 8 or the pharmaceutical composition of claim 9, in the manufacture of a medicament for suppressing activation of B cells, mast cells, dendritic cells, and/or basophils.

Chugai Seiyaku Kabushiki Kaisha

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON



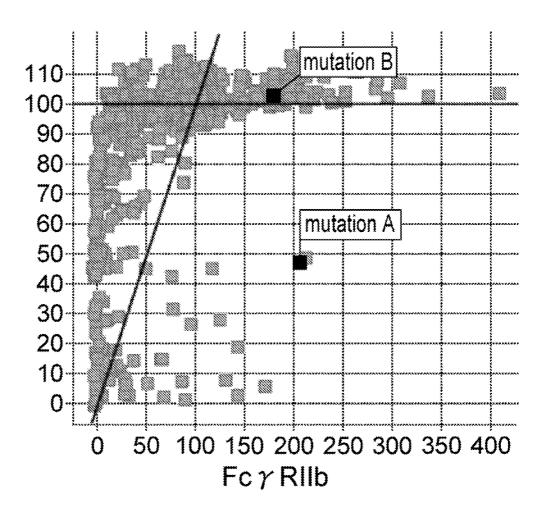
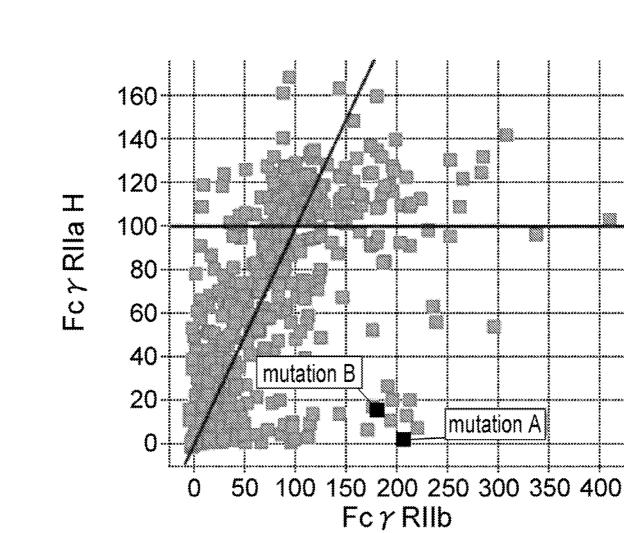


FIG. 1

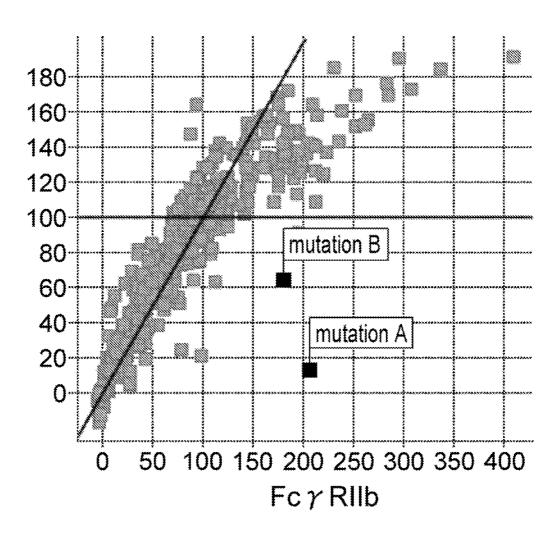


TVAATUAN

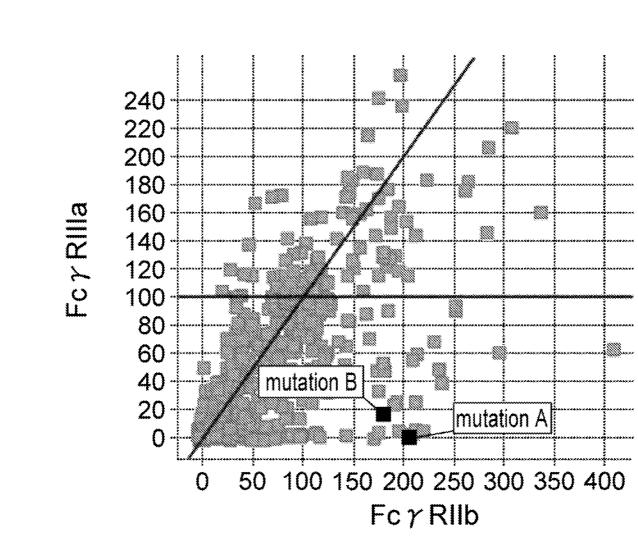
FIG. 2













	1-2
ndex vdfæx	ALGCLVKDYF PEPVTVSBNSGAL TSGVHTF PAVLQSSGLYSLSSVYTVPSSLGTQTYTCMVHRF BNTKVDKRVEPKSCD- ALGCLVKDYF PEPVTVSBNSGAL TSGVHTF PAVLQSSGLYSLSSVYTVPSSNFGTQTYTCMVHRF BNTKVDKRVELKTVG ALGCLVKDYF PEPVTVSBNSGAL TSGVHTF PAVLQSSGLYSLSSVYTVPSSSLGTQTYTCMVHRF BNTKVDKRVELKTVG ALGCLVKDYF PEPVTVSBNSGAL TSGVHTF PAVLQSSGLYSLSSVYTVPSSSLGTKTTTCMVHRF BNTKVDKRVEKTVERKCV- ALGCLVKDYF PEPVTVSBNSGAL TSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTKTTTCMVHRF BNTKVDKRVELKTPLG
x x ya x ya x ya ya y	ALGCLYKDYFFEPYTYSBRSGALTSGYHTFPAVLQSSGLYSLSSWYTYPSSNFGTGTYTCNVDHKPSNTKVDKTVERKCCV- ALGCLYKDYFFEPYTYSBRSGALTSGYHTFPAVLQSSGLYSLSSWYTYPSSSLGTKTYTCNVDHKPSNTKVDKFEKKTPLO ALGCLYKDYFFEPYTYSBRSGALTSGYHTFPAVLQSSGLYSLSSWYTYPSSSLGTKTYTCNVDHKPSNTKVDKFEKTPLO
ndex vdrax	ALGCLVKDYFPEPVTVSBNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTTFTCNVDHKPEMTKVDKKVESKYGF- -3
ndex ndex	-3
ndex za za za za za za za za za za za za za	-3
X S S S S S S S S S S S S S S S S S S S	-00
odex	CFAPELLGGPSVFLFPFKPKFDTLMISKTPEVTCVVVDVSHEDFEVFFMUTVD CCFEPKSCDTPPPCPRCPEFKSCDTPPPCPRCFAFELLGGPSVFLFPFKPKDTLMISKTPEVTCVVVDVSHEDFEVGFMUTVD CCFEPKSCDTPPPCPRCPEFKSCDTPPPCPRCFAFELLGGPSVFLFPFKPKDTLMISKTPEVTCVVVDVSHEDFEVGFMUTVD
x a trainer a trai trai trai trai trai trai trai t	ICPEPRISCOTTOPPECPRICEFRICTION CONTRACTOR AND THAT AND THAT AND
X September Sept	
x approx	
x adex	
	tsvi. Tvy hodbungky kozvenkaldadi i kytiekakoodre dovytiederrde tynovel tolvkofyded lavebeend 15vi. Tvy hodbungky kozvenkcidad i ektiektiektesovytiederrbeerratenvel tolvkofyped lavebeeng
	75VLTVYHODBLMGKEYKCZVSBKGL/APIEKTISKTKGOPREPOVYTLPPSPERHTZMOVSLTCLVKGFYPSDIAVEBESBG
-	F
	GVEVENEMAKTIRPRERQTMSTFRVUSVLIVLEROPULEOPULEVKCKVSUKALPAPIEKTISKTKOOPREFQVITLFPSELENTKNONSLICLVKOFYPSDIAVEBESSO
পণ ১ ১৯	ovevenantikprezofnstyrvvsvltvlhodelngkeykckvsnikglpsslektiskangoprepovytlppsgebatingvsltcivkgfypsdlavebesng
د د د	
The states construction of the second	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
	وQ
1961 QPENNYKTTPPVLDSDGSFFLYSKLTVDKS	of entry y the viewers of the reason of the
	QPENNYKTTPPALDSDG8FFLYSKLTVDKSRUQQANVFSCSVAHEALHNHYTQKSLSLSPGK
1ges Openwykttppmldsdesfflysklydks	opennykttippmi.dsdgfflyski.tvdksrhoognifscsvinheal.hnrftokslsisdgk
1g04 OPENNTRITPPULDSDOSFFLYSRLVDKS	OPERMTTTPPVLDZDGSFTLYDKSRWQEGWVFSCZVRHELLEMNTTQKSLSLSLGK

FIG. 5



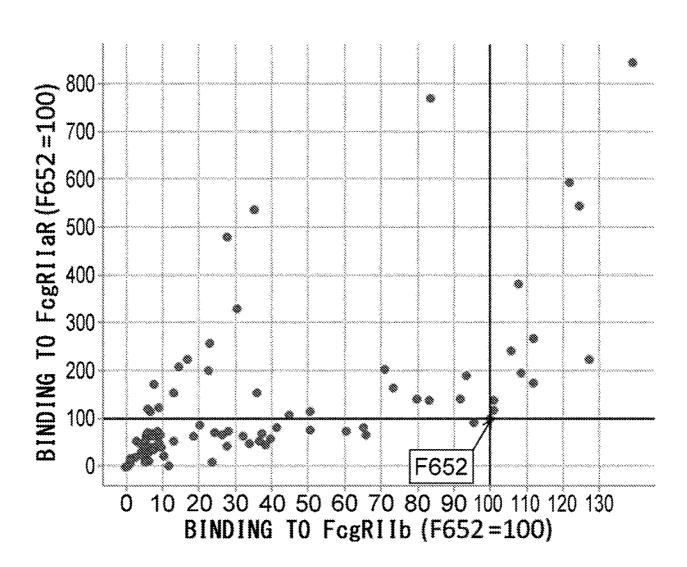


FIG. 6

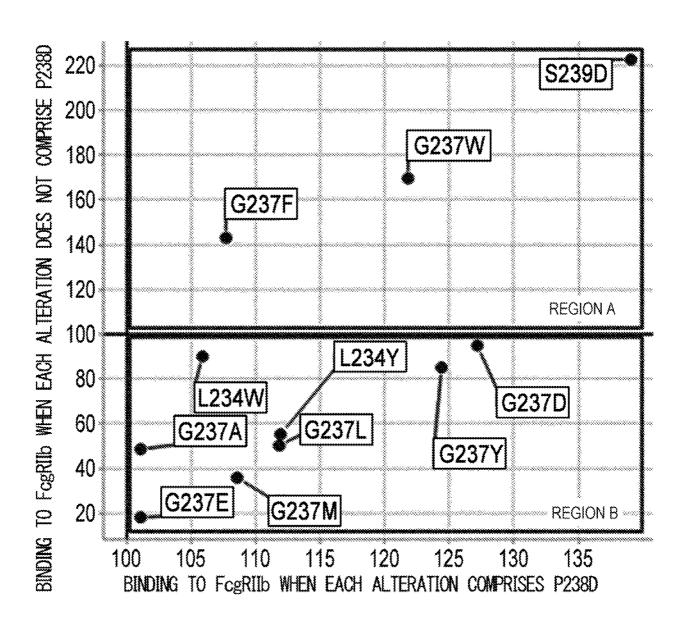
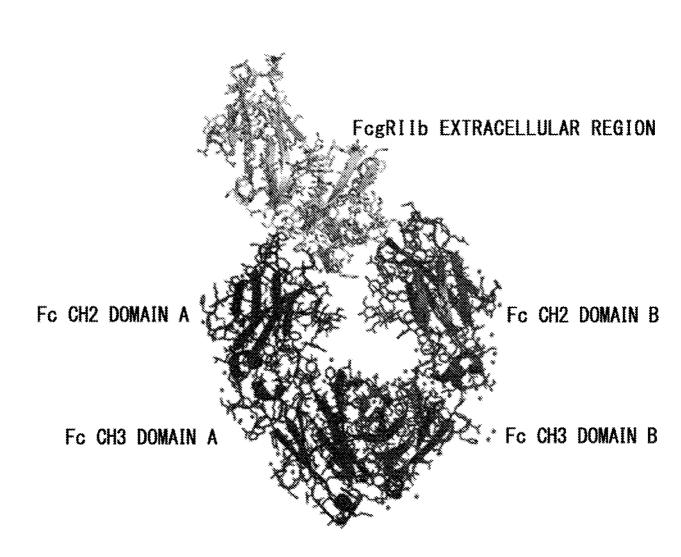
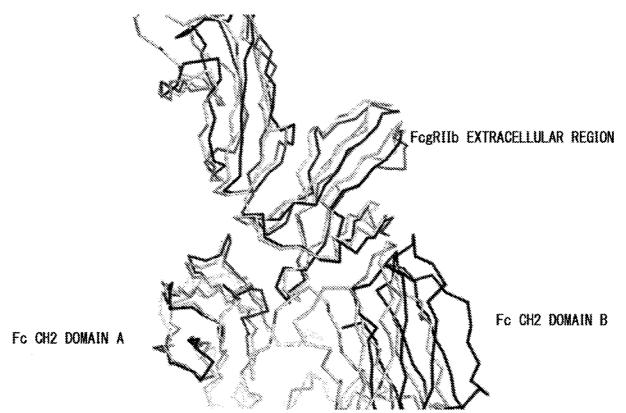
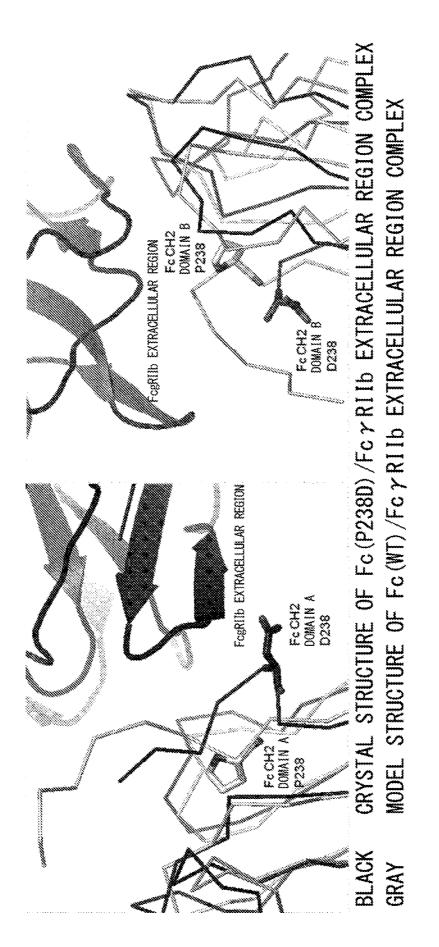


FIG. 7

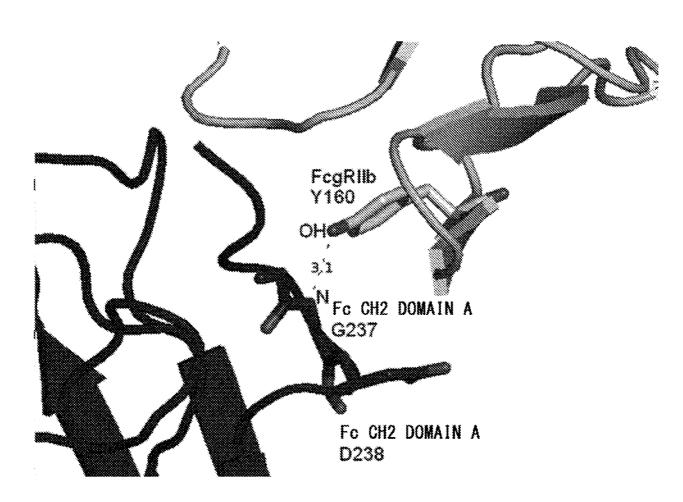


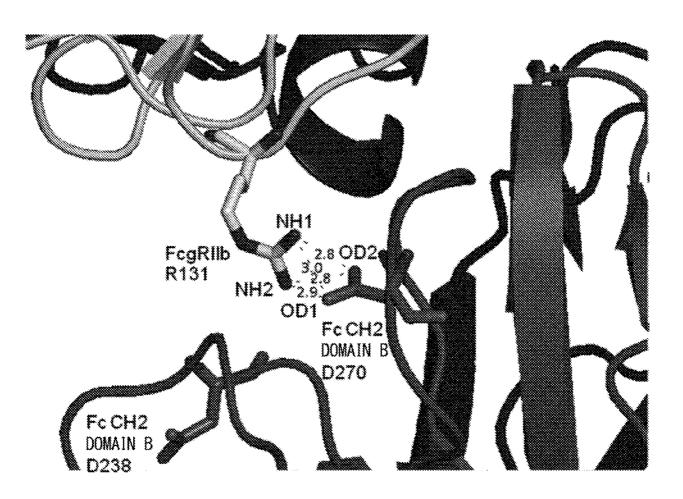


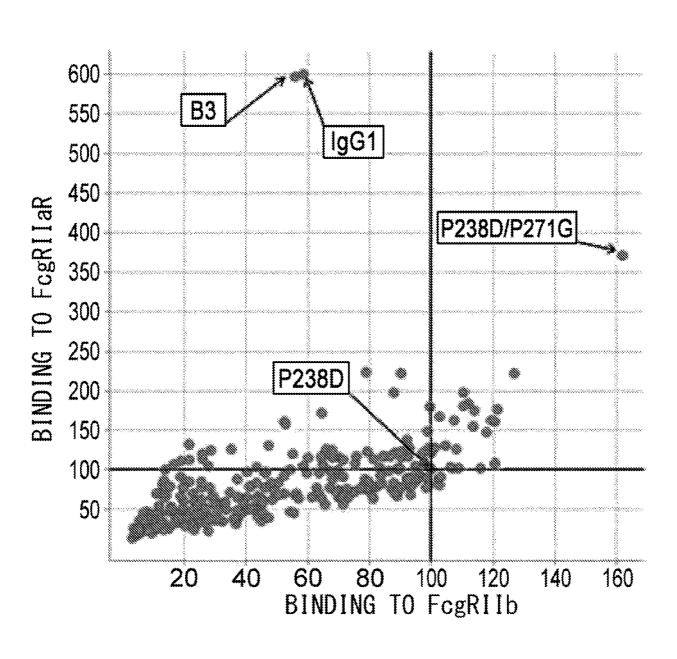
BLACK CRYSTAL STRUCTURE OF Fc(P238D)/FcγRIIb EXTRACELLULAR REGION COMPLEX GRAY MODEL STRUCTURE OF Fc(WT)/FcγRIIb EXTRACELLULAR REGION COMPLEX











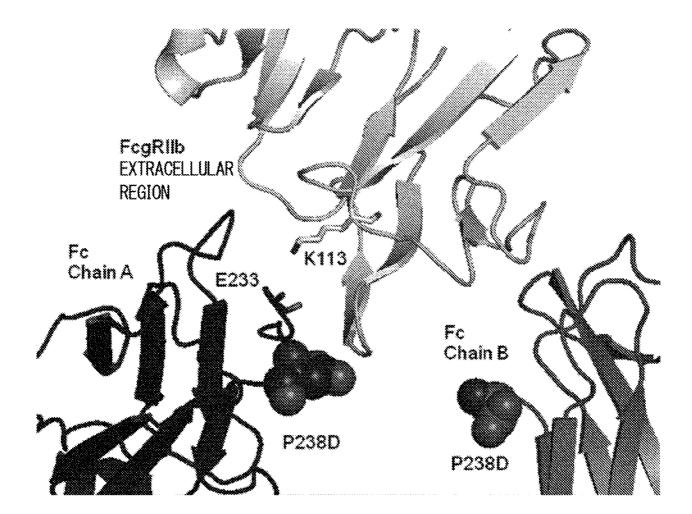
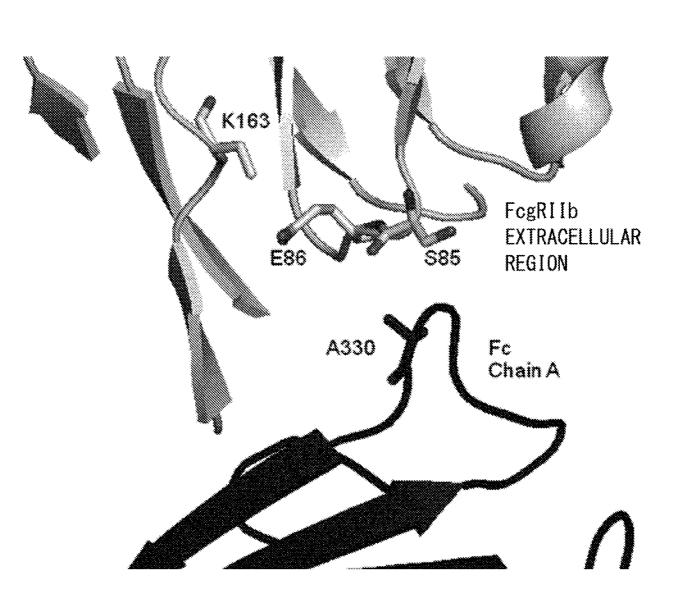
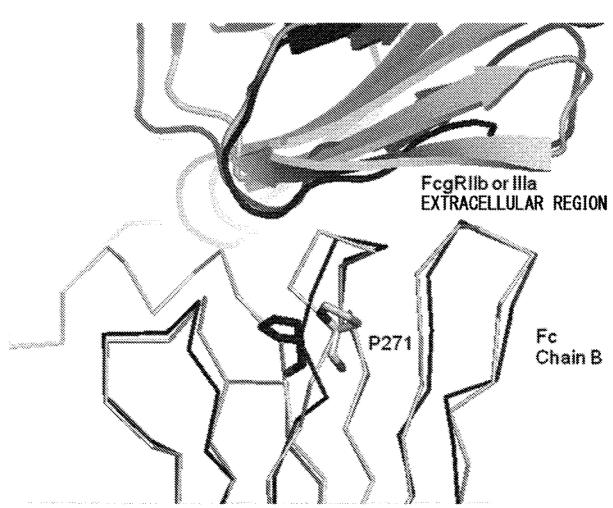


FIG. 14





BLACK CRYSTAL STRUCTURE OF Fc(P238D)/FcyRilb EXTRACELLULAR REGION COMPLEX GRAY CRYSTAL STRUCTURE OF Fc(WT)/FcyRilla EXTRACELLULAR REGION COMPLEX (PDB code: 3SGJ)

P084876D1 Seq Listing SEQUENCE LISTING

- <110> CHUGAI SEI YAKU KABUSHI KI KAI SHA
- <120> Fc-gamma-RIIb-specific Fc antibody
- <130> C1A1102Y1P
- <150> JP 2011-040923 <151> 2011-02-25
- <150> JP 2011-219835 <151> 2011-10-04 <160> 129
- <170> PatentIn version 3.4

<210> 1 <211> 1125 <212> DNA

<213> Homo sapiens <400> 1

60 atgtggttct tgacaactct gctcctttgg gttccagttg atgggcaagt ggacaccaca aaggcagtga tcactttgca gcctccatgg gtcagcgtgt tccaagagga aaccgtaacc 120 180 ttgcactgtg aggtgctcca tctgcctggg agcagctcta cacagtggtt tctcaatggc 240 acagccact c agacct cgac ccccagct ac agaat cacct ct gccagt gt caat gacagt ggt gaat aca ggt gccagag aggt ct ct ca gggcgaagt g accccat aca gct ggaaat c 300 cacagagget ggetactact gcaggtetec ageagagtet teacggaagg agaacetetg 360 gccttgaggt gtcatgcgtg gaaggataag ctggtgtaca atgtgcttta ctatcgaaat 420 ggcaaagcct ttaagttttt ccactggaat tctaacctca ccattctgaa aaccaacata 480 540 agtcacaatg gcacctacca ttgctcaggc atgggaaagc atcgctacac atcagcagga 600 atatctgtca ctgtgaaaga gctatttcca gctccagtgc tgaatgcatc tgtgacatcc 660 ccactcctgg aggggaatct ggtcaccctg agctgtgaaa caaagttgct cttgcagagg cctggtttgc agctttactt ctccttctac atgggcagca agaccctgcg aggcaggaac 720 780 acatectetg aataccaaat actaactget agaagaaga actetgggtt atactggtge 840 gaggetgeca cagaggatgg aaatgteett aagegeagee etgagttgga getteaagtg cttggcctcc agttaccaac tcctgtctgg tttcatgtcc ttttctatct ggcagtggga 900 960 ataatgtttt tagtgaacac tgttctctgg gtgacaatac gtaaagaact gaaaagaaag 1020 aaaaagtggg atttagaaat ctctttggat tctggtcatg agaagaaggt aatttccagc cttcaagaag acagacattt agaagaagag ctgaaatgtc aggaacaaaa agaagaacag 1080 1125 ct gcaggaag gggt gcaccg gaaggagccc caggggggcca cgt ag

01/	~ ^	-					P08	4876	5D1 S	Seq L	isti	ng			
<21(<21 ⁻ <212	1> (2 374 PRT													
<21		-lomo	sapi	ens											
<400	0> 2	2													
Met 1	Tr p	Phe	Leu	Thr 5	Thr	Leu	Leu	Leu	Tr p 10	Val	Pr o	Val	Asp	G y 15	GIn
Val	Asp	Thr	Thr 20	Lys	Al a	Val	lle	Thr 25	Leu	Gn	Pr o	Pr o	Tr p 30	Val	Ser
Val	Phe	G n 35	Glu	Gu	Thr	Val	Thr 40	Leu	His	Cys	Gu	Val 45	Leu	His	Leu
Pr o	G y 50	Ser	Ser	Ser	Thr	G n 55	Tr p	Phe	Leu	Asn	G y 60	Thr	Ala	Thr	Gn
Thr 65	Ser	Thr	Pr o	Ser	Tyr 70	Ar g	lle	Thr	Ser	Ala 75	Ser	Val	Asn	Asp	Ser 80
Яy	Чu	Tyr	Ar g	Cys 85	GIn	Ar g	Gу	Leu	Ser 90	Gу	Ar g	Ser	Asp	Pr o 95	lle
G n	Leu	Gu	e 100	His	Ar g	Gу	Tr p	Leu 105	Leu	Leu	Gn	Val	Ser 110	Ser	Ar g
Val	Phe	Thr 115	Giu	Gу	Gu	Pr o	Leu 120	Al a	Leu	Ar g	Cys	His 125	Al a	Tr p	Lys
Asp	Lys 130	Leu	Val	Tyr	Asn	Val 135	Leu	Tyr	Tyr	Ar g	Asn 140	Gу	Lys	Al a	Phe
Lys 145	Phe	Phe	His	Tr p	Asn 150	Ser	Asn	Leu	Thr	e 155	Leu	Lys	Thr	Asn	lle 160
Ser	His	Asn	Giy	Thr 165	Tyr	His	Cys	Ser	G y 170	Met	Gу	Lys	His	Ar g 175	Tyr
Thr	Ser	Al a	GIy 180	lle	Ser	Val	Thr	Val 185	Lys	Gu	Leu	Phe	Pr o 190	Al a	Pr o
Val	Leu	Asn 195	Al a	Ser	Val	Thr	Ser 200	Pr o	Leu	Leu	Gu	G y 205	Asn	Leu	Val
Thr	Leu 210	Ser	Cys	Gu	Thr	Lys 215	Leu	Leu	Leu	Gn	Ar g 220	Pr o	Яу	Leu	Gin

P084876D1 Seq Listing Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly Arg Asn 225 230 235 240	
Thr Ser Ser Giu Tyr Gin Ile Leu Thr Ala Arg Arg Giu Asp Ser Giy 245 250 255	
Leu Tyr Trp Cys Giu Ala Ala Thr Giu Asp Giy Asn Val Leu Lys Arg 260 265 270	
Ser Pro Giu Leu Giu Leu Gin Val Leu Giy Leu Gin Leu Pro Thr Pro 275 280 285	
Val Trp Phe His Val Leu Phe Tyr Leu Ala Val Giy Ile Met Phe Leu 290 295 300	
Val Asn Thr Val Leu Trp Val Thr Ile Arg Lys Giu Leu Lys Arg Lys 305 310 315 320	
Lys Lys Trp Asp Leu Giulle Ser Leu Asp Ser Giy His Giu Lys Lys 325 330 335	
Vallle Ser Ser Leu Gin Giu Asp Arg His Leu Giu Giu Giu Leu Lys 340 345 350	
Cys Gin Giu Gin Lys Giu Giu Gin Leu Gin Giu Giy Val His Arg Lys 355 360 365	
Giu Pro Gin Giy Ala Thr 370	
<210> 3 <211> 951 <212> DNA <213> Homo sapiens	
<400> 3 atgactatgg agacccaaat gtctcagaat gtatgtccca gaaacctgtg gctgcttcaa	60
ccattgacag ttttgctgct gctggcttct gcagacagtc aagctgctcc cccaaaggct	120
gtgctgaaac ttgagccccc gtggatcaac gtgctccagg aggactctgt gactctgaca	180
tgccaggggg ctcgcagccc tgagagcgac tccattcagt ggttccacaa tgggaatctc	240
attcccaccc acacgcagcc cagctacagg ttcaaggcca acaacaatga cagcggggag	300
tacacgtgcc agactggcca gaccagcctc agcgaccctg tgcatctgac tgtgctttcc	360
gaatggctgg tgctccagac ccctcacctg gagttccagg agggagaaac catcatgctg	420
aggtgccaca gctggaagga caagcctctg gtcaaggtca cattcttcca gaatggaaaa	480
tcccagaaat tctcccattt ggatcccacc ttctccatcc cacaagcaaa ccacagtcac Page 3	540

agt ggt gattaccact gcacaggaaacat aggct acacgct gt t ct cat ccaagcct gt g600accat cact gt ccaagt gcccagcat gggcagct ct t caccaat gggggtcat t gt ggct660gt ggt catt gcgact gct gtagcagccattgt gct gct g t agt ggccttgat ct act gc720aggaaaaaagcggat tt cagccaat t ccactgat cct gt gaaggcca at tt gagcca780cct ggacgt caaat gat t gccat cagaaagagacaact t gaagaaaccaacaat gact atgaaacagct gacggcggct acat gact ct gaaccccagggcacct act ga cgat gat aaa900aacat ct acct gact ct t cc ccaacgaccat gt caaca gt aat aact a951

<210> <211> PRT <212> <213> Homo sapiens <400> Met Thr Met Giu Thr Gin Met Ser Gin Asn Val Cys Pro Arg Asn Leu Trp Leu Leu Gin Pro Leu Thr Val Leu Leu Leu Leu Ala Ser Ala Asp Ser Gin Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Giu Pro Pro Trp lle Asn Val Leu Gin Giu Asp Ser Val Thr Leu Thr Cys Gin Giy Ala Arg Ser Pro Giu Ser Asp Ser IIe Gin Trp Phe His Asn Giy Asn Leu lle Pro Thr His Thr Gin Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser G y G u Tyr Thr Cys G n Thr G y G n Thr Ser Leu Ser Asp Pro Val His Leu Thr Val Leu Ser Giu Trp Leu Val Leu Gin Thr Pro His Leu Giu Phe Gin Giu Giy Giu Thr Ile Met Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu Val Lys Val Thr Phe Phe Gin Asn Giy Lys

P084876D1 Seq Listing Ser Gin Lys Phe Ser His Leu Asp Pro Thr Phe Ser IIe Pro Gin Ala 165 170 175	
Asn His Ser His Ser Giy Asp Tyr His Cys Thr Giy Asn Ile Giy Tyr 180 185 190	
Thr Leu Phe Ser Ser Lys Pro Val Thr IIe Thr Val Gin Val Pro Ser 195 200 205	
Met Gly Ser Ser Ser Pro Met Gly Val IIe Val Ala Val IIe Ala 210 215 220	
Thr Ala Val Ala Ala IIe Val Ala Ala Val Ala Leu IIe Tyr Cys 225 230 235 240	
Arg Lys Lys Arg IIe Ser Ala Asn Ser Thr Asp Pro Val Lys Ala Ala 245 250 255	
Gin Phe Giu Pro Pro Giy Arg Gin Met Ile Ala Ile Arg Lys Arg Gin 260 265 270	
Leu Giu Giu Thr Asn Asn Asp Tyr Giu Thr Ala Asp Giy Giy Tyr Met 275 280 285	
Thr Leu Asn Pro Arg Ala Pro Thr Asp Asp Asp Lys Asn Ile Tyr Leu 290 295 300	
Thr Leu Pro Pro Asn Asp His Val Asn Ser Asn Asn 305 310 315	
<210> 5 <211> 876 <212> DNA <213> Homo sapiens	
<400> 5 atgggaatcc tgtcattctt acctgtcctt gccactgaga gtgactgggc tgactgcaag	60
tcccccagc cttggggtca tatgcttctg tggacagctg tgctattcct ggctcctgtt	120
gctgggacac ctgcagctcc cccaaaggct gtgctgaaac tcgagcccca gtggatcaac	180
gtgctccagg aggactctgt gactctgaca tgccggggga ctcacagccc tgagagcgac	240
tccattcagt ggttccacaa tgggaatctc attcccaccc acacgcagcc cagctacagg	300
ttcaaggcca acaacaatga cagcggggag tacacgtgcc agactggcca gaccagcctc	360
agcgaccctg tgcatctgac tgtgctttct gagtggctgg tgctccagac ccctcacctg	420
gagttccagg agggagaaac catcgtgctg aggtgccaca gctggaagga caagcctctg	480
gtcaaggtca cattcttcca gaatggaaaa tccaagaaat tttcccgttc ggatcccaac Page 5	540

ttctccatcccacaagcaaaccacagtcacagtggtgattaccactgcacaggaaacata600ggctacacgctgtactcatccaagcctgtgaccatcactgtccaagctcccagctcttca660ccgatggggatcattgtggctgtggtcactgggattgctgtagcggccattgttgctgct720gtagtggccttgatctactgcaggaaaaaagcggatttcagccaatcccactaatcctgat780gaggctgacaaagttggggctgagaacacaatcacctattcacttctcatgcacccggat840gctctggaagagcctgatgaccagaaccgtatttag876

<210> 6 291 <211> PRT <212> <213> Homo sapiens <400> 6 Met Giy II e Leu Ser Phe Leu Pro Val Leu Ala Thr Giu Ser Asp Trp 1 5 10 15 1 Ala Asp Cys Lys Ser Pro Gin Pro Trp Giy His Met Leu Leu Trp Thr 20 25 30 Ala Val Leu Phe Leu Ala Pro Val Ala Giy Thr Pro Ala Ala Pro Pro 35 45 40 Lys Ala Val Leu Lys Leu Giu Pro Gin Trp Ile Asn Val Leu Gin Giu 50 55 60 Asp Ser Val Thr Leu Thr Cys Arg G y Thr His Ser Pro G u Ser Asp 65 70 75 80 Ser lle Gin Trp Phe His Asn Giy Asn Leu lle Pro Thr His Thr Gin 85 90 95 Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn Asp Ser G y G u Tyr Thr 10Ŏ 105 110 Cys Gin Thr Giy Gin Thr Ser Leu Ser Asp Pro Val His Leu Thr Val 115 120 125 Leu Ser Gu Trp Leu Val Leu Gin Thr Pro His Leu Giu Phe Gin Giu 130 135 140 Giy Giu Thr Ile Val Leu Arg Cys His Ser Trp Lys Asp Lys Pro Leu 145 150 155 160 160 Val Lys Val Thr Phe Phe Gin Asn Giy Lys Ser Lys Lys Phe Ser Arg 165 170 175 Page 6

Ser Asp Pro Asn Phe Ser IIe Pro Gin Ala Asn His Ser His Ser Giy 180 185 190	
Asp Tyr His Cys Thr Ciy Asn Ile Ciy Tyr Thr Leu Tyr Ser Ser Lys 195 200 205	
Pro Val Thr Ile Thr Val Gin Ala Pro Ser Ser Pro Met Giy Ile 210 215 220	
lle Val Ala Val Val Thr Giy Ile Ala Val Ala Ala Ile Val Ala Ala 225 230 235 240	
Val Val Ala Leu IIe Tyr Cys Arg Lys Lys Arg IIe Ser Ala Asn Pro 245 250 255	
Thr Asn Pro Asp Giu Ala Asp Lys Val Giy Ala Giu Asn Thr Ile Thr 260 265 270	
Tyr Ser Leu Leu Met His Pro Asp Ala Leu Giu Giu Pro Asp Asp Gin 275 280 285	
Asn Arg IIe 290	
<210> 7 <211> 765 <212> DNA <213> Homo sapiens	
<400> 7 atgtggcagc tgctcctccc aactgctctg ctacttctag tttcagctgg catgcggact	60
gaagatetee caaaggetgt ggtgtteetg gageeteaat ggtacagggt getegagaag	120
gacagtgtga ctctgaagtg ccagggagcc tactcccctg aggacaattc cacacagtgg	180
tttcacaatg agagcctcat ctcaagccag gcctcgagct acttcattga cgctgccaca	240
gttgacgaca gtggagagta caggtgccag acaaacctct ccaccctcag tgacccggtg	300
cagctagaag tccatatcgg ctggctgttg ctccaggccc ctcggtgggt gttcaaggag	360
gaagacccta ttcacctgag gtgtcacagc tggaagaaca ctgctctgca taaggtcaca	420
tatttacaga atggcaaagg caggaagtat tttcatcata attctgactt ctacattcca	480
aaagccacac tcaaagacag cggctcctac ttctgcaggg ggcttgttgg gagtaaaaat	540
gtgtcttcag agactgtgaa catcaccatc actcaaggtt tgtcagtgtc aaccatctca	600
tcattctttc cacctgggta ccaagtctct ttctgcttgg tgatggtact cctttttgca	660
gtggacacag gactatattt ctctgtgaag acaaacattc gaagctcaac aagagactgg Page 7	720

aaggaccata aatttaaatg gagaaaggac cctcaagaca aatga 8 <210> <211> <212> 254 PRT <213> Homo sapiens <400> 8 Met Trp Gin Leu Leu Leu Pro Thr Ala Leu Leu Leu Leu Val Ser Ala 15 1 10 Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro 20 25 30 Gin Trp Tyr Arg Val Leu Giu Lys Asp Ser Val Thr Leu Lys Cys Gin 35 40 45 45 Gy Ala Tyr Ser Pro Gu Asp Asn Ser Thr Gin Trp Phe His Asn Gu 50 55 60 Ser Leu IIe Ser Ser Gin Ala Ser Ser Tyr Phe IIe Asp Ala Ala Thr 65 70 75 80 Val Asp Asp Ser G y G u Tyr Arg Cys G n Thr Asn Leu Ser Thr Leu 90 85 95 Ser Asp Pro Val Gin Leu Giu Val His IIe Giy Trp Leu Leu Leu Gin 100 105 110 Ala Pro Arg Trp Val Phe Lys Giu Giu Asp Pro Ile His Leu Arg Cys 115 120 125 His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gin Asn 130 135 140 G y Lys G y Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr IIe Pro 145 150 155 160 Lys Ala Thr Leu Lys Asp Ser Gy Ser Tyr Phe Cys Arg Gy Leu Val 170 165 175 Gy Ser Lys Asn Val Ser Ser Gu Thr Val Asn lle Thr lle Thr Gn 185 180 190 Gy Leu Ser Val Ser Thr IIe Ser Ser Phe Phe Pro Pro Gy Tyr Gn 195 200 205

P084876D1 Seq Listing 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 IIe Arg Ser Ser Thr Arg Asp Trp 225 230 235 240	
Lys Asp His Lys Phe Lys Trp Arg Lys Asp Pro Gin Asp Lys 245 250	
<210> 9 <211> 702 <212> DNA <213> Homo sapiens	
<400> 9	
atgtggcage tgeteetee aactgetetg etaettetag ttteagetgg eatgeggaet	60
gaagatetee caaaggetgt ggtgtteetg gageeteaat ggtacagegt gettgagaag	120
gacagigiga cicigaagig ccagggagcc tactccccig aggacaatic cacacagigg titcacaatg agagccicat cicaagccag gccicgagci acticatiga cgcigccaca	180 240
gt caacgaca gt ggagagt a caggt gccag acaaacct ct ccaccct cag t gacccggt g	300
cagctagaag tocatatogg otggotgttg otcaggood caudedron otdgotgggt gttcaaggag	360
gaagacccta ttcacctgag gtgtcacagc tggaagaaca ctgctctgca taaggtcaca	420
tatttacaga atggcaaaga caggaagtat tttcatcata attctgactt ccacattcca	480
aaagccacac tcaaagatag cggctcctac ttctgcaggg ggcttgttgg gagtaaaaat	540
gtgtcttcag agactgtgaa catcaccatc actcaaggtt tggcagtgtc aaccatctca	600
tcattctctc cacctgggta ccaagtctct ttctgcttgg tgatggtact cctttttgca	660
gtggacacag gactatattt ctctgtgaag acaaacattt ga	702
<210> 10 <211> 233 <212> PRT <213> Homo sapi ens	
<400> 10	
Met Trp Gin Leu Leu Leu Pro Thr Ala Leu Leu Leu Leu Val Ser Ala 1 5 10 15	
Giy Met Arg Thr Giu Asp Leu Pro Lys Ala Val Val Phe Leu Giu Pro 20 25 30	
Gin Trp Tyr Ser Val Leu Giu Lys Asp Ser Val Thr Leu Lys Cys Gin 35 40 45	
Giy Ala Tyr Ser Pro Giu Asp Asn Ser Thr Gin Trp Phe His Asn Giu Page 9	

	50					55	P08	4876	iD1 S	Seq L	isti 60	ng			
Ser 65	Leu	lle	Ser	Ser	GIn 70	Al a	Ser	Ser	Tyr	Phe 75	lle	Asp	Al a	Ala	Thr 80
Val	Asn	Asp	Ser	G y 85	Gu	Tyr	Ar g	Cys	G n 90	Thr	Asn	Leu	Ser	Thr 95	Leu
Ser	Asp	Pr o	Val 100	Gin	Leu	Gu	Val	His 105	lle	Gу	Tr p	Leu	Leu 110	Leu	Gn
Al a	Pr o	Ar g 115	Tr p	Val	Phe	Lys	G u 120	Gu	Asp	Pr o	lle	His 125	Leu	Ar g	Cys
His	Ser 130	Tr p	Lys	Asn	Thr	Al a 135	Leu	Hi s	Lys	Val	Thr 140	Tyr	Leu	Gn	Asn
G y 145	Lys	Asp	Ar g	Lys	Tyr 150	Phe	Hi s	Hi s	Asn	Ser 155	Asp	Phe	His	lle	Pr o 160
Lys	Al a	Thr	Leu	Lys 165	Asp	Ser	Gу	Ser	Tyr 170	Phe	Cys	Ar g	Gу	Leu 175	Val
Gу	Ser	Lys	Asn 180	Val	Ser	Ser	Gu	Thr 185	Val	Asn	lle	Thr	lle 190	Thr	Gin
Gу	Leu	Al a 195	Val	Ser	Thr	lle	Ser 200	Ser	Phe	Ser	Pr o	Pr o 205	Gу	Tyr	Gin
Val	Ser 210	Phe	Cys	Leu	Val	Met 215	Val	Leu	Leu	Phe	Al a 220	Val	Asp	Thr	Gу
Leu 225	Tyr	Phe	Ser	Val	Lys 230	Thr	Asn	lle							
<21 <21 <21 <21	1> 3 2> F	∣1 330 PRT Artif	icia	al											
<22) <22;		an ar	rtifi	ci al	ly s	syntł	nesi z	zed s	seque	ence					
<40		1				,			•						
Al a 1	Ser	Thr	Lys	G y 5	Pr o	Ser	Val	Phe	Pr o 10	Leu	Al a	Pr o	Ser	Ser 15	Lys
Ser	Thr	Ser	GI y 20	Gу	Thr	Ala	Ala	Leu 25	G y Page	-	Leu	Val	Lys 30	Asp	Tyr

Phe Pro	G u 35	Pr o	Val	Thr	Val	Ser 40	Tr p	Asn	Ser	Gу	Ala 45	Leu	Thr	Ser
G y Val 50	Hi s	Thr	Phe	Pr o	Al a 55	Val	Leu	Gn	Ser	Ser 60	Gу	Leu	Tyr	Ser
Leu Ser 65	Ser	Val	Val	Thr 70	Val	Pr o	Ser	Ser	Ser 75	Leu	Яу	Thr	Gn	Thr 80
Tyr I∣e	Cys	Asn	Val 85	Asn	His	Lys	Pr o	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Lys Val	Gu	Pr o 100	Lys	Ser	Cys	Asp	Lys 105	Thr	His	Thr	Cys	Pr o 110	Pr o	Cys
Pro Ala	Pr o 115	Giu	Leu	Leu	Gу	G y 120	Pr o	Ser	Val	Phe	Leu 125	Phe	Pr o	Pr o
Lys Pro 130		Asp	Thr	Leu	Met 135	lle	Ser	Ar g	Thr	Pr o 140	Gu	Val	Thr	Cys
Val Val 145	Val	Asp	Val	Ser 150	Hi s	Gu	Asp	Pr o	G u 155	Val	Lys	Phe	Asn	Tr p 160
Tyr Val	Asp	Giy	Val 165	Gu	Val	His	Asn	Al a 170	Lys	Thr	Lys	Pr o	Ar g 175	Gu
Gu Gn	Tyr	Asn 180	Ser	Thr	Tyr	Ar g	Val 185	Val	Ser	Val	Leu	Thr 190	Val	Leu
His Gin	Asp 195	Tr p	Leu	Asn	Gу	Lys 200	Gu	Tyr	Lys	Cys	Lys 205	Val	Ser	Asn
Lys Ala 210		Pr o	Al a	Pr o	e 215	Gu	Lys	Thr	lle	Ser 220	Lys	Al a	Lys	Gу
Gin Pro 225	Ar g	Giu	Pr o	G n 230	Val	Tyr	Thr	Leu	Pr o 235	Pr o	Ser	Ar g	Asp	G u 240
Leu Thr	Lys	Asn	G n 245	Val	Ser	Leu	Thr	Cys 250	Leu	Val	Lys	Gу	Phe 255	Tyr
Pro Ser	Asp	e 260	Al a	Val	Gu	Tr p	G u 265	Ser	Asn	Gу	Gn	Pr o 270	Gu	Asn
Asn Tyr	Lys	Thr	Thr	Pr o	Pr o	Val	Leu	Asp Page		Asp	Gу	Ser	Phe	Phe

275			P084876 280	SD1 Seq L		ng 285		
Leu Tyr Ser 290	Lys Leu	Thr Val 295	Asp Lys	Ser Arg	Trp 300	Gin Gin	Gу	Asn
Val Phe Ser 305	Cys Ser	Val Met 310	His Giu	Ala Leu 315	His	Asn His	Tyr	Thr 320
Gin Lys Ser	Leu Ser 325	Leu Ser	Pro Giy	Lys 330				
<210> 12 <211> 326 <212> PRT <213> Artif	i ci al							
<220> <223> an ar	tificial	ly syntl	nesi zed :	sequence				
<400> 12								
Ala Ser Thr 1	Lys Giy 5	Pro Ser	Val Phe	Pro Leu 10	Ala	Pro Cys	Ser 15	Ar g
Ser Thr Ser	Glu Ser 20	Thr Ala	Ala Leu 25	Giy Cys	Leu '	Val Lys 30	Asp	Tyr
Phe Pro Giu 35	Pro Val	Thr Val	Ser Trp 40	Asn Ser		Ala Leu 45	Thr	Ser
Giy Val His 50	Thr Phe	Pro Ala 55	Val Leu	Gin Ser	Ser 60	Gy Leu	Tyr	Ser
Leu Ser Ser 65	Val Val	Thr Val 70	Pro Ser	Ser Asn 75	Phe	Giy Thr	Gn	Thr 80
Tyr Thr Cys	Asn Val 85	Asp His	Lys Pro	Ser Asn 90	Thr I	Lys Val	Asp 95	Lys
Thr Val Gu	Arg Lys 100	Cys Cys	Val Giu 105	Cys Pro	Pro	Cys Pro 110	Al a	Pr o
Pro Val Ala 115	Giy Pro	Ser Val	Phe Leu 120	Phe Pro		Lys Pro 125	Lys	Asp
Thr Leu Met 130	lle Ser	Arg Thr 135	Pro Giu	Val Thr	Cys 140	Val Val	Val	Asp
Val Ser His 145	Giu Asp	Pro Giu 150	Val Gin	Phe Asn 155 Page 12	Trp	Tyr Val	Asp	G y 160

Val Giu Val His Asn Ala Lys Thr Lys Pro Arg Giu Giu Gin Phe Asn 165 170 175
Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gin Asp Trp 180 185 190
Leu Asn G y Lys G u Tyr Lys Cys Lys Val Ser Asn Lys G y Leu Pro 195 200 205
Ala Prolle Giu Lys Thr Ile Ser Lys Thr Lys Giy Gin ProArg Giu 210 215 220
Pro Gin Val Tyr Thr Leu Pro Pro Ser Arg Giu Giu Met Thr Lys Asn 225 230 235 240
Gin Val Ser Leu Thr Cys Leu Val Lys Giy Phe Tyr Pro Ser Asp Ile 245 250 255
Ala Val Giu Trp Giu Ser Asn Giy Gin Pro Giu 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 Gin Gin Giy Asn Val Phe Ser Cys 290 295 300
Ser Val Met His Giu Ala Leu His Asn His Tyr Thr Gin Lys Ser Leu 305 310 315 320
Ser Leu Ser Pro G y Lys 325
<210> 13 <211> 377 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 13
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg 1 5 10 15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr 20 25 30

						P08	4876	D1 S	Geq L	.isti	ng			
Phe Pro	G u 1 35	Pr o	Val	Thr	Val	Ser 40	Tr p	Asn	Ser	Gу	Ala 45	Leu	Thr	Ser
Giy Val 50	His⊺	Thr	Phe	Pr o	Ala 55	Val	Leu	Βn	Ser	Ser 60	Gу	Leu	Tyr	Ser
Leu Ser 65	Ser \	Val	Val	Thr 70	Val	Pr o	Ser	Ser	Ser 75	Leu	Gу	Thr	Βn	Thr 80
Tyr Thr	Cys /	Asn	Val 85	Asn	His	Lys	Pr o	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Arg Val		Leu 100	Lys	Thr	Pr o	Leu	G y 105	Asp	Thr	Thr	His	Thr 110	Cys	Pr o
Arg Cys	Pro (115	Giu	Pr o	Lys	Ser	Cys 120	Asp	Thr	Pr o	Pr o	Pr o 125	Cys	Pr o	Ar g
Cys Pro 130	Gul	Pr o	Lys	Ser	Cys 135	Asp	Thr	Pr o	Pr o	Pr o 140	Cys	Pr o	Ar g	Cys
Pro Giu 145	Pro l	Lys	Ser	Cys 150	Asp	Thr	Pr o	Pr o	Pr o 155	Cys	Pr o	Ar g	Cys	Pr o 160
Ala Pro	Gul	Leu	Leu 165	Gу	Gу	Pr o	Ser	Val 170	Phe	Leu	Phe	Pr o	Pr o 175	Lys
Pro Lys		Thr 180	Leu	Met	lle	Ser	Ar g 185	Thr	Pr o	Gu	Val	Thr 190	Cys	Val
Val Val	Asp \ 195	Val	Ser	His	Gu	Asp 200	Pr o	Gu	Val	Βn	Phe 205	Lys	Tr p	Tyr
Val Asp 210	Gу	Val	Gu	Val	His 215	Asn	Al a	Lys	Thr	Lys 220	Pr o	Ar g	Gu	Gu
G n Tyr 225	Asn S	Ser	Thr	Phe 230	Ar g	Val	Val	Ser	Val 235	Leu	Thr	Val	Leu	His 240
Gin Asp	Trp l		Asn 245	Gу	Lys	Gu	Tyr	Lys 250	Cys	Lys	Val	Ser	Asn 255	Lys
Ala Leu		Al a 260	Pr o	lle	Gu	Lys	Thr 265	lle	Ser	Lys	Thr	Lys 270	Gу	Gin
Pro Arg	G u F 275	Pr o	GIn	Val	Tyr	Thr 280		Pr o Page		Ser	Ar g 285	Gu	Gu	Met

290	Asn	Gin	Val	Ser	Leu 295	Thr	Cys	Leu	Val	Lys 300	Gу	Phe	Tyr	Pr o
Ser Asp 305	lle	Al a	Val	G u 310	Tr p	Gu	Ser	Ser	G y 315	Gn	Pr o	Gu	Asn	Asn 320
Tyr Asn	Thr	Thr	Pr o 325	Pr o	Met	Leu	Asp	Ser 330	Asp	Gу	Ser	Phe	Phe 335	Leu
Tyr Ser	Lys	Leu 340	Thr	Val	Asp	Lys	Ser 345	Ar g	Tr p	Gn	Gn	G y 350	Asn	lle
Phe Ser	Cys 355	Ser	Val	Met	His	G u 360	Al a	Leu	His	Asn	Ar g 365	Phe	Thr	Gin
Lys Ser 370	Leu	Ser	Leu	Ser	Pr o 375	Gу	Lys							
<211> <212>	14 327 PRT Artif	icia	al											
<220> <223>	an ar	tifi	ci al	ly s	svnt k	nesi z	red s	seque	ence					
					· •			Joque	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					
<400>	14			,	,			Joque	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					
<400> Al a Ser 1		Lys		-	-			-		Al a	Pr o	Cys	Ser 15	Ar g
Ala Ser 1	Thr		Сі у 5	Pr o	Ser	Val	Phe	Pro 10	Leu					_
Ala Ser 1	Thr Ser	Lys Giu 20	Giy 5	Pr o Thr	Ser Al a	Val Al a	Phe Leu 25	Pro 10 Giy	Leu Cys	Leu	Val	Lys 30	15	Tyr
Al a Ser 1 Ser Thr	Thr Ser G u 35	Lys Giu 20	Giy 5 Ser Val	Pr o Thr Thr	Ser Al a Val	Val Al a Ser 40	Phe Leu 25 Tr p	Pro 10 Gry Asn	Leu Cys Ser	Leu G y	Val Al a 45	Lys 30 Leu	15 Asp	Tyr Ser
Al a Ser 1 Ser Thr Phe Pro G y Val	Thr Ser Giu 35 His	Lys Giu 20 Pro Thr	G y 5 Ser Val Phe	Pr o Thr Thr Pr o	Ser Al a Val Al a	Val Al a Ser 40 Val	Phe Leu 25 Tr p Leu	Pro 10 Gy Asn Gn	Leu Cys Ser Ser	Leu Giy Ser	Val Al a 45 G y	Lys 30 Leu Leu	15 Asp Thr Tyr	Tyr Ser
Al a Ser 1 Ser Thr Phe Pro G y Val 50 Leu Ser 65	Thr Ser Giu 35 His Ser	Lys Giu 20 Pro Thr	Gi y Ser Val Phe Val	Pr o Thr Thr Pr o Thr 70	Ser Al a Val Al a 55	Val Al a Ser 40 Val Pr o	Phe Leu 25 Tr p Leu Ser	Pro 10 Giy Asn Gin Ser	Leu Cys Ser Ser Ser 75	Leu G y Ser 60 Leu	Val Al a 45 G y G y	Lys 30 Leu Leu Thr	15 Asp Thr Tyr	Tyr Ser Ser Thr 80

		P084876D1	Seq Listing	g
G u Phe Leu G y 115	Gy Pro Ser	Val Phe Leu 120		Pro Lys Pro Lys 25
Asp Thr Leu Met 130	lle Ser Arg 135		ı Val Thr C 140	∑ys Val Val Val
Asp Val Ser Gin 145	Giu Asp Pro 150	Gu Val Gr	Phe Asn T 155	rp Tyr Val Asp 160
Giy Val Giu Val	His Asn Ala 165	Lys Thr Lys 170	-	au Gu Gn Phe 175
Asn Ser Thr Tyr 180	Arg Val Val	Ser Val Leu 185	ı Thr Val L	eu His Gin Asp. 190
Trp Leu Asn Giy 195	Lys G u Tyr	Lys Cys Lys 200		sn Lys G y Leu 05
Pro Ser Ser IIe 210	G u Lys Thr 215		AlaLysC 220	aly Gin Pro Arg
Giu Pro Gin Val 225	Tyr Thr Leu 230	Pro Pro Ser	Gin Giu G 235	alu Met Thr Lys 240
Asn Gin Val Ser	Leu Thr Cys 245	Leu Val Lys 250		yr Pro Ser Asp 255
lle Ala Val Giu 260	Trp G u Ser	Asn Giy Gir 265	ı Pro Giu A	sn Asn Tyr Lys 270
Thr Thr Pro Pro 275	Val Leu Asp	Ser Asp Giy 280		Phe Leu Tyr Ser 185
Arg Leu Thr Val 290	Asp Lys Ser 295		IGUGYA 300	sn Val Phe Ser
Cys Ser Val Met 305	His Clu Ala 310	Leu His Asr	His Tyr T 315	hr Gin Lys Ser 320
Leu Ser Leu Ser	Leu G y Lys 325			
<210> 15 <211> 115 <212> PRT <213> Artifici	al			
<220>		De e	- 10	

25 Nov 2016	
2016262766	

<223> an ar	tificia	lly synt			D1 S		isti.	ng			
<400> 15			11001 2		Joque						
Gin Val Gin 1	Leu Val 5	Gin Sei	Gy	Al a	G u 10	Val	Lys	Lys	Pr o	G y 15	Al a
Ser Val Thr	Val Ser 20	Cys Lys	s Ala	Ser 25	Gу	Tyr	Thr	Phe	Thr 30	Asp	Tyr
Giu Met His 35	Trp I∣e	Arg Gi	Pro 40	Pr o	Gу	Gu	Gу	Leu 45	Gu	Tr p	lle
Gy Ala Ile 50	Asp Pro	Lys Thi 55	Gy	Asp	Thr	Al a	Tyr 60	Ser	Gu	Ser	Phe
Gin Asp Arg 65	Val Thr	Leu Thi 70	Ala	Asp	Lys	Ser 75	Thr	Ser	Thr	Al a	Tyr 80
Met Giu Leu	Ser Ser 85	Leu Thi	Ser	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Thr Arg Phe	Tyr Ser 100	Tyr Thi	Tyr	Tr p 105	Gу	Gn	Яу	Thr	Leu 110	Val	Thr
Val Ser Ser 115											
<210> 16 <211> 219 <212> PRT <213> Artif	i ci al										
<220> <223> an ar	tificia	lly synt	hesi z	ed s	seque	ence					
<400> 16											
Asp IIe Val 1	Met Thr 5	Gin Sei	Pro	Leu	Ser 10	Leu	Pr o	Val	Thr	Pr o 15	Gу
Giu Pro Ala	Ser IIe 20	Ser Cys	s Gin	Al a 25	Ser	Gu	Ser	Leu	Val 30	His	Ser
Asn Arg Asn 35	Thr Tyr	Leu His	3 Tr p 40	Tyr	Leu	Gn	Lys	Pr o 45	Gу	Gn	Ser
Pro Gin Leu 50	Leu IIe	Tyr Lys 55	s Val	Ser	Asn	Ar g	Phe 60	Ser	Gу	Val	Pr o
Asp Arg Phe	Ser Gy	Ser Gly	/ Ser	Gу	Thr Page		Phe	Thr	Leu	Lys	lle

65	70	P084876D1 S	Seq Listing 75	ł	80
Ser Arg Val Glu A 8		Val Giy Val 90	Tyr Tyr Cys	Ser G n 7 95	Asn
Thr His Val Pro P 100	Pro Thr Phe	GyGnGy 105	Thr Lys Val	Giulle (110	Gu
Arg Thr Val Ala A 115	Na Pro Ser	Val Phe IIe 120	Phe Pro Pro 125		Gu
Gin Leu Lys Ser G 130	aly Thr Ala 135	Ser Val Val	Cys Leu Leu 140	Asn Asn I	Phe
Tyr Pro Arg Giu A 145	la Lys Val 150	Gin Trp Lys	Val Asp Asn 155		G n 160
Ser G y Asn Ser G 1	ain Giu Ser 65	Val Thr Giu 170	Gin Asp Ser	Lys Asp 3 175	Ser
Thr Tyr Ser Leu S 180	Ser Ser Thr	Leu Thr Leu 185	Ser Lys Ala	Asp Tyr (190	Gu
Lys His Lys Val T 195	⊽yr Ala Cys	G u Val Thr 200	His Gin Giy 205		Ser
Pro Val Thr Lys S 210	Ger Phe Asn 215	Arg Ciy Ciu	Cys		
<210> 17 <211> 328 <212> PRT <213> Artificial					
<220> <223> an artific	ially synth	hesized seque	ence		
<400> 17					
Ala Ser Thr Lys G 1 5	Bly Pro Ser	Val Phe Pro 10	Leu Ala Pro	Ser Ser I 15	Lys
Ser Thr Ser Gly G 20	aly Thr Ala	Ala Leu Giy 25	Cys Leu Val	Lys Asp 30	Tyr
Phe Pro Giu Pro V 35	al Thr Val	Ser Trp Asn 40	Ser Giy Ala 45	Leu Thr S	Ser
Giy Val His Thr P 50	he Pro Ala 55	Val Leu Gin Page	Ser Ser Giy 60 e 18	Leu Tyr S	Ser

	~			
P084876D1	Sea	11	ct.	na
1004070001	ocq		31	нg

Leu S 65	Ser	Ser	Val	Val	Thr 70	Val	Pr o	Ser	Ser	Ser 75	Leu	Яу	Thr	Gn	Thr 80
Tyr I	le	Cys	Asn	Val 85	Asn	His	Lys	Pr o	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Lys \	Val	Gu	Pr o 100	Lys	Ser	Cys	Asp	Lys 105	Thr	His	Thr	Cys	Pr o 110	Pr o	Cys
Pro A	Ala	Pr o 115	Glu	Leu	Leu	Gу	G y 120	Pr o	Ser	Val	Phe	Leu 125	Phe	Pr o	Pr o
Lys f	Pr o 130	Lys	Asp	Thr	Leu	Met 135	lle	Ser	Ar g	Thr	Pr o 140	Gu	Val	Thr	Cys
Val \ 145	Val	Val	Asp	Val	Ser 150	His	Gu	Asp	Pr o	G u 155	Val	Lys	Phe	Asn	Tr p 160
Tyr N	Val	Asp	Giy	Val 165	Gu	Val	His	Asn	Al a 170	Lys	Thr	Lys	Pr o	Ar g 175	Gu
Gu (Βn	Tyr	Asn 180	Ser	Thr	Tyr	Ar g	Val 185	Val	Ser	Val	Leu	Thr 190	Val	Leu
His (Ξn	Asp 195	Tr p	Leu	Asn	Gу	Lys 200	Gu	Tyr	Lys	Cys	Lys 205	Val	Ser	Asn
Lys /	Al a 210	Leu	Pr o	Ala	Pr o	e 215	Gu	Lys	Thr	lle	Ser 220	Lys	Al a	Lys	Gу
Gin F 225	Pro	Ar g	Glu	Pr o	G n 230	Val	Tyr	Thr	Leu	Pr o 235	Pr o	Ser	Ar g	Asp	G u 240
Leu 1	Thr	Lys	Asn	G n 245	Val	Ser	Leu	Thr	Cys 250	Leu	Val	Lys	Яy	Phe 255	Tyr
Pro S	Ser	Asp	e 260	Al a	Val	Gu	Tr p	G u 265	Ser	Asn	Gу	GIn	Pr o 270	Gu	Asn
Asn 1	Tyr	Lys 275	Thr	Thr	Pr o	Pr o	Val 280	Leu	Asp	Ser	Asp	G y 285	Ser	Phe	Phe
Leu 7	Tyr 290	Ser	Lys	Leu	Thr	Val 295	Asp	Lys	Ser	Ar g	Tr p 300	Gn	Gn	Gу	Asn
Val F	Phe	Ser	Cys	Ser	Val	Met	His	Gu	Al a Page		His	Asn	His	Tyr	Thr

305	P084876D1 Seq Listing 310 315	320
Gin Giu Ser Leu Ser 325	Leu Ser Pro	
<210> 18 <211> 443 <212> PRT <213> Artificial		
<220> <223> an artificial	lly synthesized sequence	
<400> 18		
Gin Val Gin Leu Val 1 5	Gin Ser Giy Ala Giu Val Lys Lys Pro G 10 15	
Ser Val Thr Val Ser 20	Cys Lys Ala Ser Gly Tyr Thr Phe Thr As 25 30	p Tyr
Giu Met His Trp IIe 35	Arg Gin Pro Pro Giy Giu Giy Leu Giu Tr 40 45	p IIe
Gly Ala IIe Asp Pro 50	Lys Thr Gly Asp Thr Ala Tyr Ser Glu Se 55 60	r Phe
Gin Asp Arg Val Thr 65	Leu Thr Ala Asp Lys Ser Thr Ser Thr Al 70 75	a Tyr 80
Met Giu Leu Ser Ser 85	Leu Thr Ser Glu Asp Thr Ala Val Tyr Ty 90 95	
Thr Arg Phe Tyr Ser 100	Tyr Thr Tyr Trp Gly Gin Gly Thr Leu Va 105 110	al Thr
Val Ser Ser Ala Ser 115	Thr Lys G y Pro Ser Val Phe Pro Leu Al 120 125	a Pro
Ser Ser Lys Ser Thr 130	Ser Giy Giy Thr Ala Ala Leu Giy Cys Le 135 140	u Val
Lys Asp Tyr Phe Pro 145	Giu Pro Val Thr Val Ser Trp Asn Ser G 150 155	y Ala 160
Leu Thr Ser Gly Val 165	His Thr Phe Pro Ala Val Leu Gin Ser Se 170 17	
Leu Tyr Ser Leu Ser 180	Ser Val Val Thr Val Pro Ser Ser Le 185 190 Page 20	eu Giy

Thr G	31 n	Thr 195	Tyr	lle	Cys	Asn	Val 200	Asn	His	Lys	Pr o	Ser 205	Asn	Thr	Lys
	Asp 210	Lys	Lys	Val	Gu	Pr o 215	Lys	Ser	Cys	Asp	Lys 220	Thr	His	Thr	Cys
Pro F 225	Pr o	Cys	Pr o	Al a	Pr o 230	Gu	Leu	Leu	Gу	G y 235	Pr o	Ser	Val	Phe	Leu 240
Phe F	Pro	Pr o	Lys	Pr o 245	Lys	Asp	Thr	Leu	Met 250	lle	Ser	Ar g	Thr	Pr o 255	Gu
Val T	⁻ hr	Cys	Val 260	Val	Val	Asp	Val	Ser 265	His	Gu	Asp	Pr o	G u 270	Val	Lys
Phe A	\s n	Tr p 275	Tyr	Val	Asp	Gу	Val 280	Gu	Val	His	Asn	Al a 285	Lys	Thr	Lys
Pro A 2	Ar g 290	Gu	Giu	Βn	Tyr	Asn 295	Ser	Thr	Tyr	Ar g	Val 300	Val	Ser	Val	Leu
Thr V 305	/al	Leu	His	Βn	Asp 310	Tr p	Leu	Asn	Gу	Lys 315	Gu	Tyr	Lys	Cys	Lys 320
Val S	Ser	Asn	Lys	Al a 325	Leu	Pr o	Al a	Pr o	e 330	Gи	Lys	Thr	lle	Ser 335	Lys
Ala L	ys	Gу	G n 340	Pr o	Ar g	Gu	Pr o	G n 345	Val	Tyr	Thr	Leu	Pr o 350	Pr o	Ser
Arg A	∖sp	G u 355	Leu	Thr	Lys	Asn	G n 360	Val	Ser	Leu	Thr	Cys 365	Leu	Val	Lys
GyF 3	he 870	Tyr	Pr o	Ser	Asp	e 375	Al a	Val	Gu	Tr p	G u 380	Ser	Asn	Gу	G n
Pro 0 385	Яu	Asn	Asn	Tyr	Lys 390	Thr	Thr	Pr o	Pr o	Val 395	Leu	Asp	Ser	Asp	G y 400
Ser F	he	Phe	Leu	Tyr 405	Ser	Lys	Leu	Thr	Val 410	Asp	Lys	Ser	Ar g	Tr p 415	G n
GnG	Эу	Asn	Val 420	Phe	Ser	Cys	Ser	Val 425	Met	His	Gu	Al a	Leu 430	His	Asn
His T	yr	Thr	Gin	Gu	Ser	Leu	Ser	Leu	Ser	Pro					

435	P084876D1 Seq Listing 440
<210> 19 <211> 119 <212> PRT <213> Artificial	
<220> <223> an artificially synth	hesized sequence
<400> 19	
Gin Val Gin Leu Gin Giu Ser	Giy Pro Giy Leu Val Lys Pro Ser Giu
1 5	10 15
Thr Leu Ser Leu Thr Cys Ala	Val Ser Ciy His Ser Ile Ser His Asp
20	25 30
His Ala Trp Ser Trp Val Arg	Gin Pro Pro Giy Giu Giy Leu Giu Trp
35	40 45
lle Giy Phe Ile Ser Tyr Ser	Giy Ile Thr Asn Tyr Asn Pro Ser Leu
50 55	60
Gin Giy Arg Val Thr Ile Ser	Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70	75 80
Leu Gin Met Asn Ser Leu Arg	Ala Giu Asp Thr Ala Val Tyr Tyr Cys
85	90 95
Ala Arg Ser Leu Ala Arg Thr	Thr Ala Met Asp Tyr Trp Gly Glu Gly
100	105 110
Thr Leu Val Thr Val Ser Ser 115	
<210> 20 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synth	hesized sequence
<400> 20	
Gin Val Gin Leu Gin Giu Ser	Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5	10 15
Thr Leu Ser Leu Thr Cys Ala	Val Ser Gly His Ser Ile Ser His Asp
20	25 30

His	Al a	Tr p 35	Ser	Tr p	Val	Ar g				Seq L Giy			Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Яу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Яу	Pr o 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn

P084876D1 Seq Listing	
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg Val 290 295 300	
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320	
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335	
Thr lle Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350	
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val Ser Leu Thr 355 360 365	
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val Glu Trp Glu 370 375 380	
Ser Asn G y G n Pro G u Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	
Ala Leu His Asn His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 21 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 21	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15	
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30	
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45	

_	∃ly Ph i0	ne II e	Ser	Tyr	Ser 55				Beq L Asn			Pr o	Ser	Leu
Gin G 65	∃iy Ar	g Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G	∃in Ma	et Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala A	∧rg Se	er Leu 100		Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	Сіу 110	Gu	Gу
Thr L	.eu Va 11		Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
	.eu Al 30	a Pro	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y C 145	ys L€	eu Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn S	Ser G	y Ala	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n S	Ser Se	er Giy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser S	Ser Le 19	eu Giy 95	Thr	G n	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
	asn Th 10	nr Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr H 225	lis Th	nr Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser V	/al Pł	ne Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg T	ħr Pr	o Giu 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro G	∃u Va 27	al Lys 75	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn
	.ys Th 190	nr Lys	Pr o	Ar g	G u 295	Gu	Βn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val

	F	2084876D1 S	eq Listi	ng	
Val Ser Val Leu Th 305	r Val Leu Hi 310	s Gin Asp	Trp Leu 315	Asn Giy	Lys Gu 320
Tyr Lys Cys Lys Va 32		ys Ala Leu 330	Pro Ala		Giu Lys 335
Thr IIe Ser Lys Al 340	a Lys Gly G	n Pro Arg 345	Giu Pro	Gin Val 350	Tyr Thr
Leu Pro Pro Ser Ar 355		eu Thr Lys 60		Val Ser 365	Leu Thr
Cys Leu Val Lys G 370	y Phe Tyr Pr 375	o Ser Asp	lle Ala 380	Val Gu	Trp Gu
Ser Asn Ciy Cin Pr 385	o Giu Asn As 390	sn Tyr Lys	Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp G y Se 40		eu Tyr Ser 410	Lys Leu	Thr Val	Asp Lys 415
Ser Arg Trp Gin G 420	n Giy Asn Va	al Phe Ser 425	Cys Ser	Val Met 430	His Giu
Ala Leu His Asn Hi 435		n Lys Ser 40	Leu Ser	Leu Ser 445	Pr o
<210> 22 <211> 214 <212> PRT <213> Artificial					
<220> <223> an artifici	ally synthes	sized seque	ence		
<400> 22					
Asplle Gin Met Th 1 5	r Gin Ser Pr	o Ser Ser 10	Leu Ser	Ala Ser	Val Giy 15
Asp Arg Val Thr II 20	e Thr Cys Ar	rg Ala Ser 25	Gin Asp	IIe Ser 30	Ser Tyr
Leu Asn Trp Tyr G 35	n Gin Lys Pr 40		Ala Pro	Lys Leu 45	Leu IIe
Tyr Tyr Thr Ser Ar 50	g Leu His Se 55	er Giy Val	Pro Ser 60	Arg Phe	Ser Giy

P084876D1 Seq Listing Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro 65 70 75 80
Giu Aspille Ala Thr Tyr Tyr Cys Gin Gin Giy Asn Thr Leu Pro Tyr 85 90 95
Thr Phe Giy Gin Giy Thr Lys Val Giu IIe Lys Arg Thr Val Ala Ala 100 105 110
Pro Ser Val Phe IIe Phe Pro Pro Ser Asp Giu Gin Leu Lys Ser Giy 115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Giu Ala 130 135 140
Lys Val Gin Trp Lys Val Asp Asn Ala Leu Gin Ser Giy Asn Ser Gin 145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr 180 185 190
Ala Cys Giu Val Thr His Gin Giy Leu Ser Ser Pro Val Thr Lys Ser 195 200 205
Phe Asn Arg Giy Giu Cys 210
<210> 23 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 23
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Phe Ile Ser Tyr Ser Ciy Ile Thr Asn Tyr Asn Pro Ser Leu Page 27

	50					55	P08	4876	iD1 S	Seq L	isti 60	ng			
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gin	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Pr o 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	G n	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val

P084876D1 Seq Listing Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Gig 305 310 315	y Lys G u 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Giu Pro Ala Pro II 325 330	e G u Lys 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val 340 345 35	
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Sel 355 360 365	r Leu Thr
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val G 370 375 380	u Trp G u
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro 385 390 395	o Val Leu 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 405 410	I Asp Lys 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Me 420 425 431	tHisGiu 0
Ala Leu His Asn His Tyr Thr Gin Lys Ser Leu Ser Leu Ser 435 440 445	r Pro
<210> 24 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 24	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro 1 5 10	o Ser Giu 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser 20 25 30	r His Asp
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Lei 35 40 45	u G u Trp
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pr 50 55 60	o Ser Leu
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thi Page 29	r Leu Tyr

65	P0- 70	84876D1 Seq L 75	⊥isting	80
Leu Gin Met Asn Ser 85	Leu Arg Ala	GuAspThr 90		Tyr Cys 95
Ala Arg Ser Leu Ala 100	Arg Thr Thr	Ala Met Asp 105	Tyr Trp Giy 110	Gu Gy
Thr Leu Val Thr Val 115	Ser Ser Ala 120		Giy Pro Ser 125	Val Phe
Pro Leu Ala Pro Ser 130	Ser Lys Ser 135	Thr Ser Giy	Giy Thr Ala 140	Ala Leu
Giy Cys Leu Val Lys 145	Asp Tyr Phe 150	Pro Giu Pro 155	Val Thr Val	Ser Trp 160
Asn Ser Giy Ala Leu 165		Val His Thr 170	Phe Pro Ala	Val Leu 175
Gin Ser Ser Giy Leu 180	Tyr Ser Leu	Ser Ser Val 185	Val Thr Val 190	Pro Ser
Ser Ser Leu Giy Thr 195	Gin Thr Tyr 200		Val Asn His 205	Lys Pro
Ser Asn Thr Lys Val 210	Asp Lys Lys 215	Val GuPro	Lys Ser Cys 220	Asp Lys
Thr His Thr Cys Pro 225	Pro Cys Pro 230	Ala Pro Giu 235	Leu Leu Gy	Giy Pro 240
Ser Val Phe Leu Phe 245		Pro Lys Asp 250	Thr Leu Met	lle Ser 255
Arg Thr Pro Giu Val 260	Thr Cys Val	Val Val Asp 265	Val Giu His 270	Gu Asp
Pro Giu Val Lys Phe 275	Asn Trp Tyr 280		Val Giu Val 285	His Asn
Ala Lys Thr Lys Pro 290	Arg Giu Giu 295	Gin Tyr Asn	Ser Thr Tyr 300	Arg Val
Val Ser Val Leu Thr 305	Val Leu His 310	Gin Asp Trp 315	Leu Asn Gy	Lys Giu 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Phe Pro Ala Pro Ile Giu Lys 325 330 335	
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr 340 345 350	
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365	
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380	
Ser Asn Gly Gin Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	
Ala Leu His Asn His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 25 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 25	
<400> 25 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser IIe Ser His Asp	I
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 Thr Leu Ser Leu Thr Cys Alia Val Ser Giy His Ser II e Ser His Asp His Alia Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp	•
Gin ValGin LeuGinGiuSerGiyProGiyLeuValLysProSerGiuThrLeuSerLeuThrOysAlaValSerGiyHisSerIIeSerHisAspHisAlaTrpSerTrpValArgGinProProGiyGiuGiyLeuGiuTrpIIeGiyPheIIeSerTyrSerGiyIIeThrAsnTyrAsnProSerLeu	•

	85	P084876D1 Se 90	eq Listing	95
Ala Arg Ser Leu 100		Thr Ala Met A 105	Asp Tyr Trp G y 110	GuGy
Thr Leu Val Thr 115	Val Ser Ser	Ala Ser Thr L 120	Lys Giy Pro Ser 125	Val Phe
Pro Leu Ala Pro 130	Ser Ser Lys 135		Giy Giy Thr Ala 140	Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr 150		Pro Val Thr Val 155	Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser 165	Giy Val His 1 170	Thr Phe Pro Ala	Val Leu 175
Gin Ser Ser Giy 180		Leu Ser Ser V 185	Val Val Thr Val 190	Pro Ser
Ser Ser Leu Giy 195	Thr G n Thr	Tyr lle Cys A 200	Asn Val Asn His 205	Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys 215		Pro Lys Ser Cys 220	Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230		G u Leu Leu G y 235	Gy Asp 240
Ser Val Phe Leu	Phe Pro Pro 245	Lys Pro Lys A 250	Asp Thr Leu Met	lle Ser 255
Arg Thr Pro Giu 260	Val Thr Cys	Val Val Val A 265	Asp Val Ser His 270	Gu Asp
Pro Giu Val Lys 275	Phe Asn Trp	Tyr Val Asp (280	Giy Val Giu Val 285	His Asn
Ala Lys Thr Lys 290	Pro Arg Giu 295		Asn Ser Thr Tyr 300	Arg Val
Val Ser Val Leu 305	Thr Val Leu 310		Trp Leu Asn Gy 315	Lys Giu 320
Tyr Lys Cys Lys	Val Ser Asn 325	Lys Ala Giu F 330	Pro Ala Pro Ile	G u Lys 335

Thr IIe Ser	Lys 340	Al a	Lys	Яу			D1 S Arg				Val 350	Tyr	Thr
Leu Pro Pro 355		Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Βn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn Gy 385	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	G n 420	G n	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His 435	Asn	His	Tyr	Thr	G n 440	Lys	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 26 <211> 447 <212> PRT <213> Arti	ficia	al											
<220> <223> an a	rtifi	ci al	ly s	synt h	nesi z	zed s	seque	ence					
	rtifi	ci al	ly s	synt f	nesi z	zed s	seque	ence					
<223> an a			-	-					Val	Lys	Pr o	Ser 15	Gu
<223> an a <400> 26 G n Val G n	Leu	Gin 5	Gu	Ser	Gу	Pr o	G y 10	Leu		-		15	
<223> an a <400> 26 Gin Val Gin 1	Leu Leu 20	G n 5 Thr	G u Cys	Ser Al a	G y Val	Pr o Ser 25	G y 10 G y	Leu His	Ser	lle	Ser 30	15 His	Asp
<223> an a <400> 26 Gin Val Gin 1 Thr Leu Ser His Ala Trp	Leu 20 Ser	Gn 5 Thr Trp	G u Cys Val	Ser Al a Ar g	G y Val G n 40	Pr o Ser 25 Pr o	Giy 10 Giy Pro	Leu His Giy	Ser G u	IIe Gy 45	Ser 30 Leu	15 His Giu	Asp Tr p
<223> an a <400> 26 G n Val G n 1 Thr Leu Ser His Al a Trp 35	Leu 20 Ser II e	G n 5 Thr Tr p Ser	G u Cys Val Tyr	Ser Al a Ar g Ser 55	G y Val G n 40 G y	Pr o Ser 25 Pr o I I e	Giy 10 Giy Pro Thr	Leu His Giy Asn	Ser G u Tyr 60	IIe Gy 45 Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu
<223> an a <400> 26 G n Val G n 1 Thr Leu Ser His Al a Trp 35 II e G y Phe 50 G n G y Arg	Leu 20 Ser II e Val	Gin Thr Trp Ser Thr	G u Cys Val Tyr I I e 70	Ser Al a Ar g Ser 55 Ser	G y Val G n G y Ar g	Pro Ser 25 Pro IIe Asp	Giy 10 Giy Pro Thr Asn	Leu His Gy Asn Ser 75	Ser G u Tyr 60 Lys	IIe Gy 45 Asn Asn	Ser 30 Leu Pr o Thr	15 His Giu Ser	Asp Trp Leu Tyr 80

	100	P08	34876D1 105	Seq Listi	ng	110		
Thr Leu Val 115	Thr Val Ser	Ser Ala 120		Lys Gy	Pr o 125	Ser V	Val	Phe
Pro Leu Ala 130	Pro Ser Ser	Lys Ser 135	Thr Ser	G y G y 140	Thr	Ala	Ala	Leu
G y Cys Leu 145	Val Lys Asp 150		Pro Giu	Pro Val 155	Thr	Val S	Ser	Tr p 160
Asn Ser Gy	Ala Leu Thr 165	Ser Giy	Val His 170		Pr o		Val 175	Leu
Gin Ser Ser	G y Leu Tyr 180	Ser Leu	Ser Ser 185	Val Val	Thr	Val I 190	Pro	Ser
Ser Ser Leu 195	Gly Thr Clr	n Thr Tyr 200	lle Cys	Asn Val	Asn 205	Hisl	Lys	Pr o
Ser Asn Thr 210	Lys Val Asp	D Lys Lys 215	Val Gu	Pro Lys 220	Ser	Cys /	Asp	Lys
Thr His Thr 225	Cys Pro Pro 230		Ala Pro	G u Leu 235	Leu	Gy(Gу	Asp 240
Ser Val Phe	Leu Phe Pro 245) Pro Lys	Pro Lys 250		Leu		e 255	Ser
Arg Thr Pro	G u Val Thr 260	Cys Val	Val Val 265	Asp Val	Gu	His (270	Giu	Asp
Pro Giu Val 275	Lys Phe Asr	n Trp Tyr 280		Gy Val	G u 285	Val I	His	Asn
Ala Lys Thr 290	Lys Pro Arg	g G u G u 295	Gin Tyr	Asn Ser 300	Thr	Tyr /	Ar g	Val
Val Ser Val 305	Leu Thr Val 31(Gin Asp	Trp Leu 315	Asn	Gyl	Lys	G u 320
Tyr Lys Cys	Lys Val Ser 325	Asn Lys	Ala Phe 330		Pr o		G u 335	Lys
Thr IIe Ser	Lys Ala Lys 340	Gy Gin	Pro Arg 345	Giu Pro	Gn	Val ⁻ 350	Tyr	Thr

Leu Pro Pro 355	Ser A	Arg Asp	Gu	P08 Leu 360	4876 Thr	D1 S Lys	eq L Asn	isti Gin	ng Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys G	∃y Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G y 385	Gin P	Pro Giu 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp		Ser Phe 05	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	Gin C 420	3in Giy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His 435	Asn H	his Tyr	Thr	G n 440	Lys	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 27 <211> 447 <212> PRT <213> Arti	ficial											
<220> <223> an ai	rtific	ially :	syntł	nesi z	zed s	seque	ence					
<400> 27		-	-									
Gin Val Gin 1	Leu G 5	aln Glu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
	5	•		-					-		15	
1	5 Leu T 20	hr Cys	Ala	Val	Ser 25	10 G y	His	Ser	lle	Ser 30	15 His	Asp
1 Thr Leu Ser His Ala Trp	5 Leu T 20 Ser T	[;] ⁻hr Cys ⁻rp Val	Al a Ar g	Val G n 40	Ser 25 Pr o	10 G y Pr o	His Gy	Ser Gi u	IIe Gy 45	Ser 30 Leu	15 His Gu	Asp Tr p
1 Thr Leu Ser His Ala Trp 35	5 Leu T 20 Ser T IIe S	; Thr Cys Trp Val Ger Tyr	Al a Ar g Ser 55	Val G n 40 G y	Ser 25 Pr o	10 G y Pr o Thr	His Giy Asn	Ser G u Tyr 60	IIe Gy 45 Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu
1 Thr Leu Ser His Ala Trp 35 Ile Giy Phe 50 Arg	5 Leu T 20 Ser T IIe S Val T Asn S	Frp Val Frp Val Ser Tyr Frr IIe 70	Al a Ar g Ser 55 Ser	Val G n 40 G y Ar g	Ser 25 Pr o I I e Asp	10 G y Pr o Thr Asn	His Gy Asn Ser 75	Ser G u Tyr 60 Lys	IIe Gy 45 Asn Asn	Ser 30 Leu Pr o Thr	15 His Giu Ser	Asp Trp Leu Tyr 80
1 Thr Leu Ser His Ala Trp 35 Ile Giy Phe Gin Giy Arg 65	5 Leu T 20 Ser T IIe S Val T Asn S 8	Frp Val Frp Val Ser Tyr Frr IIe 70 Ser Leu	Al a Ar g Ser 55 Ser Ar g	Val G n 40 G y Ar g Al a	Ser 25 Pro I I e Asp Gi u	10 Giy Pro Thr Asn Asp 90	His Giy Asn Ser 75 Thr	Ser Giu Tyr 60 Lys Ala	II e Giy 45 Asn Asn Val	Ser 30 Leu Pr o Thr Tyr	15 His Giu Ser Leu Tyr 95	Asp Trp Leu Tyr 80 Cys

1	115			P08 120	84876	5D1 S	Seq L	isti.	ng 125			
Pro Leu A 130	Ala Pro	Ser Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Giy Cys L 145	Leu Val	Lys Asp 150		Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser (Giy Ala	Leu Thi 165	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser S	Ser Giy 180	Leu Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser L 1	Leu Giy 195	Thr Gi	1 Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 1 210	Thr Lys	Val Asp	215 Lys	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His T 225	Thr Cys	Pro Pro 230		Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Pr o 240
Ser Val F	Phe Leu	Phe Pro 245) Pro	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Arg Thr F	Pro Giu 260	Val Thi	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
ProGiu \ 2	Val Lys 275	Phe Ası	n Trp	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys T 290	Thr Lys	Pro Arę	g G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser \ 305	Val Leu	Thr Val 310		His	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys (Cys Lys	Val Sei 325	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr lle S	Ser Lys 340	Ala Ly:	Gy	G n	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu Pro F	Pro Ser 355	Arg Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr

Cys Leu Val Ly 370	s G y Phe		34876D1 S Ser Asp			Trp Gu
Ser Asn Cly Cl 385	n Pro Giu 390	Asn Asn	Tyr Lys	Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp G	y Ser Phe 405	Phe Leu	Tyr Ser 410	Lys Leu	Thr Val	Asp Lys 415
Ser Arg Trp Gi 42		Asn Val	Phe Ser 425	Cys Ser	Val Met 430	His Giu
Ala Leu His Ty 435	r His Tyr	Thr Gn 440	Lys Ser	Leu Ser	Leu Ser 445	Pr o
<210> 28 <211> 447 <212> PRT <213> Artific	i al					
<220> <223> an arti	ficiallys	synt hesi :	zed sequ	ence		
<400> 28						
Gin Val Gin Le 1	u Gin Giu 5	Ser Giy	ProGy 10	Leu Val	Lys Pro	Ser Glu 15
Thr Leu Ser Le 20	u Thr Cys	Ala Val	Ser Giy 25	His Ser	lle Ser 30	His Asp
His Ala Trp Se 35	r Trp Val	Arg Gin 40	Pro Pro	G y G u	G y Leu 45	Gu Trp
lle Giy Phe II 50	e Ser Tyr	Ser Giy 55	lle Thr	Asn Tyr 60	Asn Pro	Ser Leu
Gin Giy Arg Va 65	Thr IIe 70	Ser Arg	Asp Asn	Ser Lys 75	Asn Thr	Leu Tyr 80
Leu Gin Met As	n Ser Leu 85	Arg Ala	GuAsp 90	Thr Ala	Val Tyr	Tyr Cys 95
Ala Arg Ser Le 10		Thr Thr	Ala Met 105	Asp Tyr	Trp Gy 110	
Thr Leu Val Th 115	r Val Ser	Ser Ala 120	Ser Thr	Lys Gy	Pro Ser 125	Val Phe
Pro Leu Ala Pr	o Ser Ser	Lys Ser	Thr Ser Page		Thr Ala	Ala Leu

130		P08 135	34876D1		istir 140	ıg			
G y Cys Leu 145	Val Lys Asp 150	Tyr Phe	Pro Gi	u Pro 155	Val -	Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu Thr 165	Ser Giy	Val His 170		Phe I	Pro	Ala	Val 175	Leu
Gin Ser Ser	G y Leu Tyr 180	Ser Leu	Ser Sei 185	r Val	Val ⁻	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Gly Thr Cln	Thr Tyr 200	lle Cys	s Asn		Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val Asp	Lys Lys 215	Val Gi		Lys \$ 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro Pro 230	Cys Pro	Ala Pro	o Gu 235	Leu I	Leu	Gу	Gу	Asp 240
Ser Val Phe	Leu Phe Pro 245	Pro Lys	Pro Lys 250		Thr I	Leu	Tyr	e 255	Ser
Arg Thr Pro	Glu Val Thr 260	Cys Val	Val Val 265	Asp	Val S		His 270	Gu	Asp
Pro Giu Val 275	Lys Phe Asn	Trp Tyr 280	Val As _l	рGу		G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro Arg	GuGu 295	Gin Tyr		Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr Val 310	Leu His	Gin Asj	p Trp 315	Leu /	Asn	Gу	Lys	G u 320
Tyr Lys Cys	Lys Val Ser 325	Asn Lys	Ala Lei 330		Alal	Pr o	lle	G u 335	Lys
Thr IIe Ser	Lys Ala Lys 340	Gy Gn	Pro Are 345	gGu	Pro (Val 350	Tyr	Thr
Leu Pro Pro 355	Ser Arg Asp	G u Leu 360	Thr Lys	s Asn		Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys G y Phe	Tyr Pro 375	Ser Ası		Ala ' 380	Val	Gu	Tr p	Gu

Ser Asn G 385	/Gin Pro	9 Giu Asn 390		6D1 Seq l Lys Thr 395	Thr Pro	Pro Val	Leu 400
Asp Ser Asj	o Giy Ser 405		e Leu Tyr	Ser Lys 410	Leu Thr	Val Asp 415	
Ser Arg Tri	o Gin Gir 420	ı Giy Asn	Val Phe 425	Ser Cys	Ser Val	Met His 430	Gu
Ala Leu His 43		Tyr Thr	GnLys 440	Ser Leu	Ser Leu 445)
<210> 29 <211> 447 <212> PRT <213> Arti	ficial						
<220> <223> an a	artificia	ully synt	hesi zed	sequence			
<400> 29							
Gin Val Gi 1	n Leu Gir 5	ı Giu Ser	Gly Pro	G y Leu 10	Val Lys	Pro Ser 15	Gu
Thr Leu Sei	Leu Thr 20	Cys Ala	Val Ser 25	Giy His	Ser IIe	Ser His 30	Asp
His Ala Tr _l 35	o Ser Trp	o Val Arg	Gin Pro 40	Pro Giy	GuGy 45	Leu Gι	ı Trp
lle Giy Pho 50	elle Ser	Tyr Ser 55	Gly IIe	Thr Asn	Tyr Asn 60	Pro Ser	Leu
Gin Giy Arg 65	g Val Thr	lle Ser 70	Arg Asp	Asn Ser 75	Lys Asn	Thr Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu Arg	Ala Giu	Asp Thr 90	Ala Val	Tyr Tyr 95	Cys
Ala Arg Sei	Leu Ala 100	ı Arg Thr	Thr Ala 105		Tyr Trp	Gу Gι 110	ЧGУ
Thr Leu Val		Ser Ser	Ala Ser 120	Thr Lys	Giy Pro 125		Phe
Pro Leu Ala 130	a Pro Ser	Ser Lys 135		Ser Giy	Giy Thr 140	Ala Ala	. Leu
Giy Cys Lei	u Val Lys	Asp Tyr	Phe Pro	G u Pro Page 39	Val Thr	Val Ser	Tr p

145	P0 150	084876D1 Seq 155		160
Asn Ser Giy Ala Leu 165		y Val His Thr 170	Phe Pro Ala	Val Leu 175
Gin Ser Ser Giy Leu 180	Tyr Ser Le	u Ser Ser Val 185	Val Thr Val 190	Pro Ser
Ser Ser Leu Gly Thr 195	Gin Thr Ty 20		Val Asn His 205	Lys Pro
Ser Asn Thr Lys Val 210	Asp Lys Ly 215	s Val Giu Pro	Lys Ser Cys 220	Asp Lys
Thr His Thr Cys Pro 225	Pro Cys Pr 230	o Ala Pro Giu 235		Gy Asp 240
Ser Val Phe Leu Phe 245		s Pro Lys Asp 250	Thr Leu Tyr	IIe Ser 255
Arg Thr Pro Giu Val 260	Thr Cys Va	l Val Val Asp 265	Val Ser His 270	Gu Asp
Pro Giu Val Lys Phe 275	Asn Trp Ty 28		Val Giu Val 285	His Asn
Ala Lys Thr Lys Pro 290	Arg Clu Cl 295	u Gin Tyr Asn	Ser Thr Tyr 300	Arg Val
Val Ser Val Leu Thr 305	Val Leu Hi 310	s Gin Asp Trp 315	Leu Asn G y	Lys Giu 320
Tyr Lys Cys Lys Val 325	Ser Asn Ly	s Ala Leu Pro 330	Ala Pro Ile	G u Lys 335
Thr IIe Ser Lys Ala 340	Lys G y G	n Pro Arg Giu 345	Pro Gin Val 350	Tyr Thr
Leu Pro Pro Ser Arg 355	Asp G u Le 36		Gin Val Ser 365	Leu Thr
Cys Leu Val Lys Gy 370	Phe Tyr Pr 375	o Ser Asp Ile	Ala Val Giu 380	Trp Giu
Ser Asn Gly Gin Pro 385	Giu Asn As 390	n Tyr Lys Thr 395		Val Leu 400

P084876D1 Seq Listing Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Tyr His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro 435 440 445
<210> 30 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 30
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Page 41

		165		P08	4876	D1 S 170	Seq L	isti.	ng		175	
Gin Ser S	Ser Giy 180	Leu Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser L 1	∟eu Giy I95	Thr Gr	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	Hi s	Lys	Pr o
Ser Asn T 210	Thr Lys	Val Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His T 225	Thr Cys	Pro Pro 230		Pr o	Al a	Pr o	G u 235	Tyr	Leu	Яу	Яу	Asp 240
Ser Val F	Phe Leu	Phe Pro 245	Pro	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Arg Thr F	Pro Giu 260	Val Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu V 2	/al Lys 275	Phe Asr	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys T 290	Thr Lys	Pro Arg	G u 295	Gu	GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser V 305	/al Leu	Thr Val 310		His	GIn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys C	Cys Lys	Val Ser 325	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr Ile S	Ser Lys 340	Ala Lys	Gу	Gin	Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr
Leu Pro P 3	Pro Ser 355	Arg Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu V 370	/al Lys	Giy Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G 385	Jiy Gin	Pro Giu 390		Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser A	Asp Giy	Ser Phe 405	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys

Ser Arg Trp Gi 42			'6D1 Seq List e Ser Cys Ser 5	
Ala Leu His Ty 435	r His Tyr	Thr G n Ly: 440	s Ser Leu Ser	Leu Ser Pro 445
<210> 31 <211> 447 <212> PRT <213> Artific	i al			
<220> <223> an arti	ficially s	synt hesi zed	sequence	
<400> 31				
Gin Val Gin Le 1	u Gin Giu 5	Ser G y Pro	o G y Leu Val 10	Lys Pro Ser Giu 15
Thr Leu Ser Le 20	u Thr Cys	Ala Val Sei 25	Giy His Ser	lle Ser His Asp 30
His Ala Trp Se 35	r Trp Val	Arg Gin Pro 40	p Pro Gy Gu	Gy Leu Gu Trp 45
lle Giy Phe II 50	e Ser Tyr	Ser Giy II 55	e Thr Asn Tyr 60	Asn Pro Ser Leu
Gin Giy Arg Va 65	I Thr IIe 70	Ser Arg As	o Asn Ser Lys 75	s Asn Thr Leu Tyr 80
Leu Gin Met As	n Ser Leu 85	Arg Ala G	u Asp Thr Ala 90	a Val Tyr Tyr Cys 95
Ala Arg Ser Le 10		Thr Thr Al a 10		Trp Gly Glu Gly 110
Thr Leu Val Th 115	r Val Ser	Ser Ala Sei 120	Thr Lys Giy	v Pro Ser Val Phe 125
Pro Leu Ala Pr 130	o Ser Ser	Lys Ser Thi 135	Ser Giy Giy 140	7 Thr Ala Ala Leu)
Gry Cys Leu Va 145	I Lys Asp 150	Tyr Phe Pr	o Giu Pro Val 155	Thr Val Ser Trp 160
Asn Ser Giy Al	a Leu Thr 165	Ser G y Va	His Thr Phe 170	e Pro Ala Val Leu 175
Gin Ser Ser G	y Leu Tyr	Ser Leu Se	⁻ Ser Val Val Page 43	Thr Val Pro Ser

	180		P08	4876 185	D1 S	Seq L	isti.	ng	190		
Ser Ser Leu 195	Giy Thr	G n Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr I 210	Lys Val	Asp Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 0 225	Cys Pro	Pro Cys 230	Pr o	Al a	Pr o	G u 235	Leu	Leu	Яу	Al a	Asp 240
Ser Val Phe I	Leu Phe 245	Pro Pro	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu Val 275	Lys Phe	Asn Trp	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr 1 290	Lys Pro	Arg Giu 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val I 305	Leu Thr	Val Leu 310	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys I	Lys Val 325	Ser Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr IIe Ser I	Lys Ala 340	Lys Gy	Gn	Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr
Leu Pro Pro 3 355	Ser Arg	Asp G u	Leu 360	Thr	Lys	Asn	Gη	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys Giy	Phe Tyr 375		Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G y 385	Gin Pro	Giu Asn 390	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy Ser 405	Phe Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	Gin Gin 420	Giy Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu

P084876D1 Seq Listing Ala Leu His Tyr His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro 435 440 445 <210> 32 <211> <212> 447 PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> 32 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45 Ile Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 60 Gin Giy Arg Val Thr IIe Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 65 80 70 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 90 95 85 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp G y G u G y 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 125 115 120 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu 130 135 140 G y Cys Leu Val Lys Asp Tyr Phe Pro G u Pro Val Thr Val Ser Trp 145 150 155 160 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 165 170 175 Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190 Ser Ser Leu Giy Thr Gin Thr Tyr Ile Cys Asn Val Asn His Lys Pro Page 45

195		P084876D1 200	Seq Listi	ng 205	
Ser Asn Thr Lys 210	Val Asp Lys 215		u Pro Lys 220	Ser Cys	Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230	Pro Ala Pr	ro G u Leu 235	Leu Gy	Asp Asp 240
Ser Val Phe Leu	Phe Pro Pro 245		ys Asp Thr 50	Leu Tyr	IIe Ser 255
Arg Thr Pro Giu 260	Val Thr Cys	Val Val Va 265	al Asp Val	Ser His 270	Gu Asp
Pro Giu Val Lys 275	Phe Asn Trp	Tyr Val As 280	sp G y Val	G u Val 285	His Asn
Ala Lys Thr Lys 290	Pro Arg Giu 295		yr Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val Leu 305	Thr Val Leu 310	His Gin As	sp Trp Leu 315	Asn Giy	Lys Giu 320
Tyr Lys Cys Lys	Val Ser Asn 325		eu Pro Ala 30	Pro Ile	G u Lys 335
Thr IIe Ser Lys 340	Ala Lys Giy	Gin Pro Ar 345	rg Giu Pro	G n Val 350	Tyr Thr
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Ly 360	ys Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val Lys 370	G y Phe Tyr 375	Pro Ser As	splle Ala 380	Val Gu	Trp Gu
Ser Asn Giy Gin 385	Pro Giu Asn 390	Asn Tyr Ly	ys Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp Giy	Ser Phe Phe 405		er Lys Leu 10	Thr Val	Asp Lys 415
Ser Arg Trp Gin 420	Gin Giy Asn	Val Phe Se 425	er Cys Ser	Val Met 430	His Giu
Ala Leu His Tyr 435	His Tyr Thr	Gin Lys Se 440	er Leu Ser	Leu Ser 445	Pr o

						P08	4876	D1 S	Seq L	isti	ng			
<210> <211> <212> <213>	33 447 PRT Arti	ficia	al											
<220> <223>	an a	rtifi	i ci al	ly s	synt l	nesi z	zed s	seque	ence					
<400>	33													
Gin Va 1	l Gin	Leu	G n 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Le	u Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Al	a Trp 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle G 50	y Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin G 65	y Arg	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G	n Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Ar	g Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Le	u Val 115		Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Le 13		Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y Cy 145	s Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Se	r Giy	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Se	r Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Se	r Leu 195	Gу	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser As	n Thr	Lys	Val	Asp	Lys	Lys	Val	Gu	Pr o	Lys	Ser	Cys	Asp	Lys

210		P08 215	34876D1	Seq Listi 220	ng	
Thr His Thr 0 225	Cys Pro Pro 230	Cys Pro	Ala Pro	G u Leu 235	Leu Gy	Giu Asp 240
Ser Val Phe I	Leu Phe Pro 245	Pro Lys	ProLys 250	Asp Thr	Leu Tyr	IIe Ser 255
Arg Thr Pro	Giu Val Thr 260	Cys Val	Val Val 265	Asp Val	Ser His 270	Gu Asp
Pro Giu Val I 275	Lys Phe Asn	Trp Tyr 280	Val Asp	Giy Val	G u Val 285	His Asn
Ala Lys Thr 1 290	Lys Pro Arg	GuGu 295	Gin Tyr	Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val I 305	Leu Thr Val 310	Leu His	Gin Asp	Trp Leu 315	Asn Giy	Lys Gu 320
Tyr Lys Cys I	Lys Val Ser 325	Asn Lys	Ala Leu 330	Pro Ala	Pro IIe	G u Lys 335
	Lys Ala Lys 340	Gy Gn	Pro Arg 345	Giu Pro	G n Val 350	
Leu Pro Pro 3 355	Ser Arg Asp	G u Leu 360	Thr Lys	Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val 370	Lys G y Phe	Tyr Pro 375	Ser Asp	lle Ala 380	Val Giu	Trp Gu
Ser Asn G y 385	Gin Pro Ciu 390	Asn Asn	Tyr Lys	Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp	Giy Ser Phe 405	Phe Leu	Tyr Ser 410	Lys Leu	Thr Val	Asp Lys 415
Ser Arg Trp	Gin Gin Giy 420	Asn Val	Phe Ser 425	Cys Ser	Val Met 430	His Giu
Ala Leu His 435	Tyr His Tyr	Thr G n 440	Lys Ser	Leu Ser	Leu Ser 445	Pr o
<210> 34 <211> 447 <212> PRT <213> Artifi	i ci al		Page	. 49		

P084876D1 Seq Listing												
<220> <223> ar	n artif	icially	synt	hesi:	zed :	seque	ence					
<400> 34	4											
Gin Val (1	Gin Leu	GnG 5	u Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu S	Ser Leu 20	Thr Cy	s Ala	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala 1 3	Trp Ser 35	Trp Va	l Arg	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle Gly F 50	Phe IIe	Ser Ty	r Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy A 65	Arg Val	Thr II 7(Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin M	Met Asn	Ser Le 85	u Arg	Al a	Gu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Ala Arg S	Ser Leu 100	Ala Ar	g Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu V	Val Thr 115	Val Se	r Ser	Al a 120	Ser	Thr	Lys	Яу	Pr o 125	Ser	Val	Phe
Pro Leu A 130	Ala Pro	Ser Se	r Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Ala	Leu
Giy Cys l 145	Leu Val	Lys As 15		Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser (Giy Ala	Leu Tr 165	r Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser S	Ser Giy 180	Leu Ty	r Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser L	Leu Giy 195	Thr G	n Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr Lys	Val As	p Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His T	Thr Cys	Pro Pr	o Cys	Pr o	Al a	Pr o Page		Leu	Leu	Gу	Phe	Asp

225	230	P084876D1 Sec 23	η Listing 35	240
Ser Val Phe Leu Phe 245		_ys Pro Lys As 250	sp Thr Leu Tyr	IIe Ser 255
Arg Thr Pro Giu Val 260	Thr Cys V	Val Val Val As 265	sp Val Ser His 270	Giu Asp
Pro Giu Val Lys Phe 275		Tyr Val Asp G 280	y Val Giu Val 285	His Asn
Ala Lys Thr Lys Pro 290	Arg Clu C 295	Giu Gin Tyr As	sn Ser Thr Tyr 300	Arg Val
Val Ser Val Leu Thr 305	Val Leu H 310		rp Leu Asn Giy 15	Lys Giu 320
Tyr Lys Cys Lys Val 325		_ys Ala Leu Pr 330	ro Ala Pro Ile	GuLys 335
Thr IIe Ser Lys Ala 340	ıLys Giy G	Gin Pro Arg Gi 345	u Pro Gin Val 350	Tyr Thr
Leu Pro Pro Ser Arg 355		Leu Thr Lys As 360	sn G n Val Ser 365	Leu Thr
Cys Leu Val Lys Gy 370	Phe Tyr F 375	Pro Ser Asp II	e Ala Val Giu 380	Trp G u
Ser Asn Ciy Cin Pro 385	9 Giu Asn A 390		nr Thr Pro Pro 95	Val Leu 400
Asp Ser Asp G y Ser 405		Leu Tyr Ser Ly 410	ys Leu Thr Val	Asp Lys 415
Ser Arg Trp Gin Gir 420	ı Giy Asn V	Val Phe Ser O 425	ys Ser Val Met 430	His Giu
Ala Leu His Tyr His 435		3 n Lys Ser Lo 440	eu Ser Leu Ser 445	Pr o
<210> 35 <211> 447 <212> PRT <213> Artificial				
<220> <223> an artificia	llly synthe	esized sequend	ce	

<400> 35		P08	34876D1 \$	Seq Listi	ng		
Gin Val Gin Le 1	u Gin Giu 5	Ser Giy	Pro Giy 10	Leu Val	Lys Pro	Ser 15	Gu
Thr Leu Ser Le 20	u Thr Cys	Ala Val	Ser Giy 25	His Ser	lle Ser 30	Hi s	Asp
His Ala Trp Se 35	r Trp Val	Arg Gin 40	Pro Pro	G y G u	G y Leu 45	Gu	Tr p
lle Giy Phe II 50	e Ser Tyr	Ser Giy 55	lle Thr	Asn Tyr 60	Asn Pro	Ser	Leu
Gin Giy Arg Va 65	Thr IIe 70	Ser Arg	Asp Asn	Ser Lys 75	Asn Thr	Leu	Tyr 80
Leu Gin Met As	n Ser Leu 85	Arg Ala	Giu Asp 90	Thr Ala	Val Tyr	Tyr 95	Cys
Ala Arg Ser Le 10		Thr Thr	Ala Met 105	Asp Tyr	Trp Giy 110		Gу
Thr Leu Val Tr 115	r Val Ser	Ser Ala 120	Ser Thr	Lys Gy	Pro Ser 125	Val	Phe
Pro Leu Ala Pr 130	o Ser Ser	Lys Ser 135	Thr Ser	G y G y 140	Thr Ala	Al a	Leu
G y Cys Leu Va 145	Lys Asp 150	Tyr Phe	Pro Giu	Pro Val 155	Thr Val	Ser	Tr p 160
Asn Ser Giy Al	a Leu Thr 165	Ser Giy	Val His 170	Thr Phe	Pro Ala	Val 175	Leu
Gin Ser Ser Gi 18		Ser Leu	Ser Ser 185	Val Val	Thr Val 190		Ser
Ser Ser Leu G 195	y Thr Gin	Thr Tyr 200	lle Cys	Asn Val	Asn His 205	Lys	Pr o
Ser Asn Thr Ly 210	s Val Asp	Lys Lys 215	Val Giu	Pro Lys 220	Ser Cys	Asp	Lys
Thr His Thr Cy 225	s Pro Pro 230	Cys Pro	Ala Pro	G u Leu 235	Leu Gy	Leu	Asp 240
Ser Val Phe Le	u Phe Pro	Pro Lys	Pro Lys Page	•	Leu Tyr	lle	Ser

	245	P084876D1 \$ 250	Seq Listinų	g	255
Arg Thr Pro Giu 260	Val Thr Cys	Val Val Val 265	Asp Val S	er His 270	Giu Asp
Pro Giu Val Lys 275	Phe Asn Trp	Tyr Val Asp 280		lu Val 85	His Asn
Ala Lys Thr Lys 290	Pro Arg Giu 295	Giu Gin Tyr	Asn Ser T 300	hr Tyr	Arg Val
Val Ser Val Leu 305	Thr Val Leu 310	His Gin Asp	Trp Leu A 315	sn Giy	Lys Giu 320
Tyr Lys Cys Lys	Val Ser Asn 325	Lys Ala Leu 330	Pro Ala P	ro IIe	G u Lys 335
Thr IIe Ser Lys 340	Ala Lys Giy	Gin Pro Arg 345	Giu Pro G	in Val 350	Tyr Thr
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360		al Ser 65	Leu Thr
Cys Leu Val Lys 370	G y Phe Tyr 375	Pro Ser Asp	lle Ala V 380	al Gu	Trp Giu
Ser Asn Giy Gin 385	Pro Giu Asn 390	Asn Tyr Lys	Thr Thr P 395	ro Pro	Val Leu 400
Asp Ser Asp Giy	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu T	hr Val	Asp Lys 415
Ser Arg Trp Gin 420	Gin Giy Asn	Val Phe Ser 425	Cys Ser V	al Met 430	His Giu
Ala Leu His Tyr 435	His Tyr Thr	G n Lys Ser 440		eu Ser 45	Pr o
<210> 36 <211> 447 <212> PRT <213> Artifici	al				
	icially syntl	hesized sequ	ence		
<400> 36 Gin Val Gin Leu 1	Gin Giu Ser 5	Giy Pro Giy 10 Page	Leu Val L 9 52	ys Pro	Ser Giu 15

Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	Hi s	Asp
His	Ala	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Ala	Val 175	Leu
Gn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Met	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Ar g	Thr	Pr o	Giu	Val	Thr	Cys	Val	Val	Val Page	-	Val	Ser	His	Gu	Asp

P084876D1 Seq Listing

	260	P084876 265	6D1 Seq Listi	ng 270
Pro Giu Val 275	Lys Phe Asn	Trp Tyr Val 280	Asp G y Val	Giu Val His Asn 285
Ala Lys Thr 290	Lys Pro Arg	GuGuGn 295	Tyr Asn Ser 300	Thr Tyr Arg Val
Val Ser Val 305	Leu Thr Val 310	Leu His Gin	Asp Trp Leu 315	Asn Ciy Lys Ciu 320
Tyr Lys Cys	Lys Val Ser 325	Asn Lys Ala	Leu Pro Ala 330	Prolle Gu Lys 335
	Lys Ala Lys 340	Giy Gin Pro 345	Arg Ciu Pro	Gin Val Tyr Thr 350
Leu Pro Pro 355	Ser Arg Asp	G u Leu Thr 360	Lys Asn Gin	Val Ser Leu Thr 365
Cys Leu Val 370	Lys Gy Phe	Tyr Pro Ser 375	Asp IIe Ala 380	Val Giu Trp Giu
Ser Asn G y 385	Gin Pro Giu 390	Asn Asn Tyr	Lys Thr Thr 395	Pro Pro Val Leu 400
Asp Ser Asp	G y Ser Phe 405	Phe Leu Tyr	Ser Lys Leu 410	Thr Val Asp Lys 415
Ser Arg Trp	GnGnGy 420	Asn Val Phe 425	Ser Cys Ser	Val Met His Giu 430
Ala Leu His 435	Tyr His Tyr	Thr G n Lys 440	Ser Leu Ser	Leu Ser Pro 445
<210> 37 <211> 447 <212> PRT <213> Artif	i ci al			
<220> <223> an ar	tificially s	synt hesi zed s	sequence	
<400> 37				
Gin Val Gin 1	Leu G n G u 5	Ser Giy Pro	G y Leu Val 10	Lys Pro Ser Giu 15
Thr Leu Ser	Leu Thr Cys 20	Ala Val Ser 25	Giy His Ser Page 54	lle Ser His Asp 30

His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
e	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gin	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Яу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Яу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Яу	Tr p	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val	Lys	Phe	Asn	Tr p	Tyr	Val	Asp Page	-	Val	Gu	Val	Hi s	Asn

275			P084876 280	iD1 Seq L	isti.	ng 285			
Ala Lys Thr 290	Lys Pro A	Arg Giu 295	Gu Gn	Tyr Asn	Ser 300	Thr ⁻	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr \	Val Leu 310	His Gin	Asp Trp 315	Leu	Asn (Gу	Lys	G u 320
Tyr Lys Cys	Lys Val S 325	Ser Asn	Lys Ala	Leu Pro 330	Al a	Pro I	lle	G u 335	Lys
Thr IIe Ser	Lys Ala L 340	Lys Gy	Gin Pro 345	Arg Giu	Pr o		Val 350	Tyr	Thr
Leu Pro Pro 355	Ser Arg A		Leu Thr 360	Lys Asn	Βn	Val 3 365	Ser	Leu	Thr
Cys Leu Val 370	Lys Giy F	Phe Tyr 375	Pro Ser	Asp IIe	Al a 380	Val (Gu	Tr p	Gu
Ser Asn Giy 385		Giu Asn 390	Asn Tyr	Lys Thr 395	Thr	Pro I	Pr o	Val	Leu 400
Asp Ser Asp	Gly Ser F 405	Phe Phe	Leu Tyr	Ser Lys 410	Leu	Thr V	Val	Asp 415	Lys
Ser Arg Trp	Gin Gin (420	Giy Asn	Val Phe 425	Ser Cys	Ser		Met 430	His	Gu
Ala Leu His 435	Tyr His ⊺		G n Lys 440	Ser Leu	Ser	Leu \$ 445	Ser	Pr o	
<210> 38 <211> 447 <212> PRT <213> Artif	i ci al								
<220> <223> an ar	tificiall	ly synth	iesized s	sequence					
<400> 38									
Gin Val Gin 1	Leu Gin (5	Giu Ser	Giy Pro	Gy Leu 10	Val	Lys I	Pr o	Ser 15	Gu
Thr Leu Ser	Leu Thr (20	Cys Ala	Val Ser 25	Giy His	Ser		Ser 30	His	Asp
His Ala Trp 35	Ser Trp \	Val Arg	Gin Pro 40	Pro Giy Page 56	Gu	G y I 45	Leu	Gu	Tr p

lle Giy 50	Phe II	e Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy 65	Arg Va	l Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G n	Met As	n Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	Ser Le 10		Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val Th 115	r Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Ala Pr	o Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Ala	Al a	Leu
G y Cys 145	Leu Va	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gy Al	a Leu 165		Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser G 18	y Leu 0	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu G 195	y Thr	G n	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr Ly	s Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr Cy	s Pro	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Tyr	Asp 240
Ser Val	Phe Le	u Phe 245		Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Arg Thr	Pro Gi 26		Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val Ly 275	s Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn

P084876D1 Seq Listing 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Aspille Ala Val Glu Trp Glu 370 375 380
Ser Asn G y G n Pro G u Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Tyr His Tyr Thr Gin Lys Ser Leu Ser Leu Ser Pro 435 440 445
<210> 39 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 39
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Gly Phe Ile Ser Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60 Page 58

P084876D1	Seq	Listing

Gin Giy 65	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Asp Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Tyr	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser	Val	Leu	Thr	Val	Leu	His	G n	Asp Page	-	Leu	Asn	Gу	Lys	Gu

305	P08 310	34876D1 Seq Listing 315	320
Tyr Lys Cys Lys Val 325		Ala Leu Pro Ala Pro Ile Giu 330 335	Lys
Thr IIe Ser Lys Ala 340	Lys Gly Gin	Pro Arg Giu Pro Gin Val Tyr 345 350	Thr
Leu Pro Pro Ser Arg 355	Asp G u Leu 360	Thr Lys Asn G n Val Ser Leu 365	Thr
Cys Leu Val Lys Gy 370	Phe Tyr Pro 375	Ser Asp IIe Ala Val Giu Trp 380	Gu
Ser Asn Giy Gin Pro 385	G u Asn Asn 390	Tyr Lys Thr Thr Pro Pro Val 395	Leu 400
Asp Ser Asp Gry Ser 405		Tyr Ser Lys Leu Thr Val Asp 410 415	Lys
Ser Arg Trp Gin Gin 420	Gy Asn Val	Phe Ser Cys Ser Val Met His 425 430	Gu
Ala Leu His Tyr His 435	Tyr Thr Gin 440	Lys Ser Leu Ser Leu Ser Pro 445	
<210> 40 <211> 447 <212> PRT <213> Artificial			
<220> <223> an artificia	lly synthesi	zed sequence	
<400> 40			
Gin Val Gin Leu Gin 1 5	GuSerGy	Pro Giy Leu Val Lys Pro Ser 10 15	Gu
Thr Leu Ser Leu Thr 20	Cys Ala Val	Ser Gly His Ser IIe Ser His 25 30	Asp
His Ala Trp Ser Trp 35	Val Arg Gin 40	Pro Pro Gy Gu Gy Leu Gu 45	Tr p
lle Giy Phe Ile Ser 50	Tyr Ser Giy 55	lle Thr Asn Tyr Asn Pro Ser 60	Leu
Gin Giy Arg Val Thr 65	lle Ser Arg 70	Asp Asn Ser Lys Asn Thr Leu 75 Page 60	Tyr 80

P084876D1 Seq Listing

Leu Gin	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gly Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Gη	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Pr o 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	G n	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val	Ser	Asn	Lys		Leu Page		Al a	Pr o	lle	Gu	Lys

	325	P084876D1 S 330	Seq Listing	335
Thr IIe Ser Lys 340		Gin Pro Arg 345		Val Tyr Thr 350
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360	Asn G n Val 365	Ser Leu Thr
Cys Leu Val Lys 370	GyPheTyr 375	Pro Ser Asp	lle Ala Val 380	Gu Trp Gu
Ser Asn Gly Glr 385	Pro Giu Asn 390	Asn Tyr Lys	Thr Thr Pro 395	Pro Val Leu 400
Asp Ser Asp G y	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu Thr	Val Asp Lys 415
Ser Arg Trp Gir 420		Val Phe Ser 425		Met His Giu 430
Ala Leu His Asr 435	ı His Tyr Thr	Gin Giu Ser 440	Leu Ser Leu 445	Ser Pro
<210> 41 <211> 447 <212> PRT <213> Artifici	al			
<220> <223> an artif	icially synt	hesized seque	ence	
<400> 41				
Gin Val Gin Leu 1	IGNGUSer 5	Giy Pro Giy 10	Leu Val Lys	Pro Ser Giu 15
Thr Leu Ser Leu 20	IThr Cys Ala	Val Ser Gy 25		Ser His Asp 30
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40	GyGuGy 45	Leu G u Trp
lle Giy Phe Ile 50	e Ser Tyr Ser 55	Gly II e Thr	Asn Tyr Asn 60	Pro Ser Leu
GnGyArgVal 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys Asn 75	Thr Leu Tyr 80
Leu Gin Met Asr	i Ser Leu Arg 85	Ala Gu Asp 90 Page		Tyr Tyr Cys 95

Ala Arg	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser	Giy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Βn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
290		Lys Leu			295					300				
290 Val Ser	Val	Leu	Thr	Val 310	295 Leu	His	G n	Asp	Tr p 315	300 Leu	Asn	Gу	Lys	G u 320

P084876D1 Seq Listing

	340			P08	4876 345	D1 S	Seq L	isti	ng	350		
Leu Pro Pro 355	Ser Arç	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys G y	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn Giy 385	Gin Pro	9 G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy Ser 405		Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	Gin Gir 420	Gy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His 435	Asn His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 42 <211> 447 <212> PRT <213> Artif	i ci al											
<220> <223> an ar	tificia	ully s	synt h	nesi z	zed s	seque	ence					
<400> 42												
Gin Val Gin 1	Leu Gr 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu Ser	Leu Thr 20	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala Trp 35	Ser Trp	o Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
	lle Ser	Tvr	Ser	Gу	lle	Thr	Asn	Tyr	Asn	Pr o	Ser	Leu
lle Giy Phe 50		.,.	55					60				
= ~ '		-	55	_	Asp	Asn	_	60	Asn	Thr		
50 Gin Giy Arg	Val Thr	II e 70	55 Ser	Ar g			Ser 75	60 Lys		Thr Tyr		Tyr 80

Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	Hi s	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gin	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	Gη	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu	Pr o	Pr o	Ser	Ar g	Asp	Gu	Leu	Thr	Lys Page		Gin	Val	Ser	Leu	Thr

355		P084876D1 S 360		g 865	
Cys Leu Val Lys 370	G y Phe Tyr 375	Pro Ser Asp	lle Ala V 380	/al Gu Trp (Gu
Ser Asn Ciy Cin 385	Pro Giu Asn 390	Asn Tyr Lys	Thr Thr F 395		Leu 400
Asp Ser Asp Giy	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu T	Thr Val Asp I 415	Lys
Ser Arg Trp Gin 420	Gn Gy Asn	Val Phe Ser 425	Cys Ser V	/al Met His (430	Gu
Ala Leu His Asn 435	His Tyr Thr	GnGuSer 440		₋eu Ser Pro I45	
<210> 43 <211> 447 <212> PRT <213> Artificia	al				
<220> <223> an artifi	cially synt	hesized sequ	ence		
<400> 43					
Gn Val Gn Leu 1	GnGuSer 5	GyProGy 10	Leu Val L	ys Pro Ser (15	Gu
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser G y 25	His Ser I	le Ser His / 30	Asp
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40		Giy Leu Giu ⁻ I5	Tr p
lle Giy Phe lle 50	Ser Tyr Ser 55	Gylle Thr	Asn Tyr A 60	Asn Pro Ser I	Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys A 75		Tyr 80
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu Asp 90	Thr Ala V	/al Tyr Tyr (95	Cys
Ala Arg Ser Leu 100	Ala Arg Thr	Thr Ala Met 105	Asp Tyr T	FrpGyGu(110	Gу
Thr Leu Val Thr 115	Val Ser Ser	Al a Ser Thr 120 Page	1	Pro Ser Val I 25	Phe

Pro Leu 130	Ala	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu '	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser		GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Gу	Thr	G n	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	Hi s	Lys	Pr o
Ser Asn 210		Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Яу	Яу	Asp 240
Ser Val	Phe I	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr		GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Al a	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Ala Lys 290		Lys	Pr o	Ar g	G u 295	Gu	GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val I	Leu	Thr	Val 310	Leu	His	GIn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr IIe		Lys 340	Ala	Lys	Gу	Βn	Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr
Leu Pro	Pr o 3 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Βn	Val 365	Ser	Leu	Thr
Cys Leu	Vall	Lys	Gу	Phe	Tyr	Pr o	Ser	Asp Page		Al a	Val	Gu	Tr p	Gu

370		P084 375	4876D1 Se	q Listing 380	
Ser Asn G y 385	Gin Pro Giu 390			Thr Thr Pr 395	o Pro Val Leu 400
Asp Ser Asp	Giy Ser Phe 405	Phe Leu	Tyr Ser L 410	ys Leu Th.	r Val Asp Lys 415
Ser Arg Trp	Gin Gin Giy 420		Phe Ser C 425	Cys Ser Va	l Met His Giu 430
Ala Leu His 435	Asn His Tyr	Thr G n 440	Giu Ser L	eu Ser Le. 44	
<210> 44 <211> 447 <212> PRT <213> Arti	ficial				
<220> <223> an a	rtificially	synt hesi z	ed sequen	ice	
<400> 44					
Gin Val Gin 1	Leu G n G u 5	Ser Giy	ProGiyL 10	.eu Val Ly	s Pro Ser Giu 15
Thr Leu Ser	Leu Thr Cys 20		Ser Giy H 25	His Ser II	e Ser His Asp 30
His Ala Trp 35	Ser Trp Val	Arg Gin 40	Pro Pro O	Aggau Gi 45	y Leu G u Trp
lle Gy Phe 50	lle Ser Tyr	Ser Gy 55	lle Thr A	Asn Tyr As 60	n Pro Ser Leu
Gin Giy Arg 65	Val Thr Ile 70	Ser Arg		Ser Lys As 75	n Thr Leu Tyr 80
Leu Gin Met	Asn Ser Leu 85	Arg Ala	GuAspT 90	「hr Ala Va	l Tyr Tyr Cys 95
Ala Arg Ser	Leu Ala Arg 100	Thr Thr	Ala Met A 105	Asp Tyr Tr	p G y G u G y 110
Thr Leu Val 115	Thr Val Ser	Ser Ala 120	Ser Thr L	_ys Giy Pr 12	
Pro Leu Ala 130	Pro Ser Ser	Lys Ser 135	Thr Ser G Page	140	r Ala Ala Leu

P084876D1	Seq	Listing

Giy Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n Ser	Ser	Giy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Gу	Thr	G n	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	G n	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Βn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	Βn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr Ile	Ser	Lys 340	Al a	Lys	Gу	G n	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr
Leu Pro	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	G n	Val 365	Ser	Leu	Thr
Cys Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn	Gу	Gin	Pr o	Gu	Asn	Asn	Tyr	Lys Page		Thr	Pr o	Pr o	Val	Leu

385	390	P0848	876D1 Seq L 395	isting		400
Asp Ser Asp Giy	Ser Phe 405	Phe Leu T	yr Ser Lys 410	Leu Thr	Val Asp 415	Lys
Ser Arg Trp Gin 420	GnGy		Phe Ser Cys 25	Ser Val	Met His 430	Gu
Ala Leu His Asn 435	His Tyr	Thr G n G 440	Blu Ser Leu	Ser Leu 445	Ser Pro	
<210> 45 <211> 447 <212> PRT <213> Artifici	al					
<220> <223> an artif	icially s	ynt hesi ze	ed sequence			
<400> 45						
Gin Val Gin Leu 1	Gin Giu 5	Ser G y P	Pro Gly Leu 10	Val Lys	Pro Ser 15	Gu
Thr Leu Ser Leu 20	Thr Cys		Ser Gly His 25	Ser IIe	Ser His 30	Asp
His Ala Trp Ser 35	Trp Val	Arg Gin P 40	Pro Pro Giy	GuGy 45	Leu Gu	Tr p
lle Giy Phe lle 50		Ser Giy I 55	le Thr Asn	Tyr Asn 60	Pro Ser	Leu
Gin Giy Arg Val 65	Thr IIe 70	Ser Arg A	Asp Asn Ser 75	Lys Asn	Thr Leu	Tyr 80
Leu Gin Met Asn	Ser Leu 85	Arg Ala G	Elu Asp Thr 90	Ala Val	Tyr Tyr 95	Cys
Ala Arg Ser Leu 100	-		Ala Met Asp 05	Tyr Trp	Gy Gu 110	Gу
Thr Leu Val Thr 115	Val Ser	Ser Ala S 120	Ser Thr Lys	Giy Pro 125	Ser Val	Phe
Pro Leu Ala Pro 130		Lys Ser T 135	⁻hr Ser Ciy	G y Thr 140	Ala Ala	Leu
G y Cys Leu Val 145	Lys Asp 150	Tyr Phe P	Pro G u Pro 155 Page 70	Val Thr	Val Ser	Tr p 160

Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n Ser	Ser	Giy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Gη	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Val	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	G n	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr Ile	Ser	Lys 340	Al a	Lys	Gу	G n	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr
Leu Pro	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	G n	Val 365	Ser	Leu	Thr
Cys Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn 385	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser	Asp	Giy	Ser	Phe	Phe	Leu	Tyr	Ser Page		Leu	Thr	Val	Asp	Lys

	405	P084876D1 Seq L 410	isting.	415
Ser Arg Trp Gir 420		Val Phe Ser Cys 425	Ser Val Met 430	His Giu
Ala Leu His Asr 435	n His Tyr Thr	Gin Giu Ser Leu 440	Ser Leu Ser 445	Pr o
<210> 46 <211> 447 <212> PRT <213> Artifici	al			
<220> <223> an artif	icially synt	hesized sequence		
<400> 46				
Gin Val Gin Leu 1	ı Gin Giu Ser 5	Gly Pro Gly Leu 10	Val Lys Pro	Ser Giu 15
Thr Leu Ser Leu 20	ı Thr Cys Ala	Val Ser Giy His 25	Ser IIe Ser 30	His Asp
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro Giy 40	Glu Gly Leu 45	Gu Trp
lle Giy Phe Ile 50	e Ser Tyr Ser 55	Giyille Thr Asn	Tyr Asn Pro 60	Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn Ser 75	Lys Asn Thr	Leu Tyr 80
Leu Gin Met Asr	n Ser Leu Arg 85	Ala Giu Asp Thr 90	Ala Val Tyr	Tyr Cys 95
Ala Arg Ser Leu 100		Thr Ala Met Asp 105	Tyr Trp Giy 110	GuGy
Thr Leu Val Thr 115	Val Ser Ser	Ala Ser Thr Lys 120	Gly Pro Ser 125	Val Phe
Pro Leu Ala Pro 130	o Ser Ser Lys 135	Ser Thr Ser G y	Gly Thr Ala 140	Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr 150	Phe Pro Giu Pro 155	Val Thr Val	Ser Trp 160
Asn Ser Ciy Ala	a Leu Thr Ser 165	Giy Val His Thr 170 Page 72	Phe Pro Ala	Val Leu 175

Gin Se	^r Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Se	r Leu 195		Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser As 21	n Thr D	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr Hi 225	s Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Va	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Th	r Pro	G u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
Pro Gi	u Val 275		Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Ly 29		Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Se 305	^r Val	Leu	Thr	Val 310	Leu	Hi s	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Ly	s Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr II	e Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu Pr	o Pro 355		Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Le 37	-	Lys	Яу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser As 385	пGу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Se	^r Asp	Gу	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Ar	g Trp	GIn	Gn	Яу	Asn	Val	Phe	Ser Page	-	Ser	Val	Met	His	Gu

	420	P084876 425	SD1 Seq Listi	ng 430
Ala Leu His 435	Asn His Tyr	Thr Gn Gu 440	Ser Leu Ser	Leu Ser Pro 445
<210> 47 <211> 447 <212> PRT <213> Artif	i ci al			
<220> <223> an ar	tificially s	synt hesi zed	sequence	
<400> 47				
Gin Val Gin 1	Leu Gin Giu 5	Ser Cly Pro	G y Leu Val 10	Lys Pro Ser Giu 15
Thr Leu Ser	Leu Thr Cys 20	Ala Val Ser 25	Giy His Ser	lle Ser His Asp 30
His Ala Trp 35	Ser Trp Val	Arg Gin Pro 40	Pro Gly Glu	GyLeuGuTrp 45
lle Gly Phe 50	lle Ser Tyr	Ser Ciylle 55	Thr Asn Tyr 60	Asn Pro Ser Leu
Gin Giy Arg 65	Val Thr IIe 70	Ser Arg Asp	Asn Ser Lys 75	Asn Thr Leu Tyr 80
Leu Gin Met	Asn Ser Leu 85	Arg Ala Giu	Asp Thr Ala 90	Val Tyr Tyr Cys 95
Ala Arg Ser	Leu Ala Arg 100	Thr Thr Ala 105	Met Asp Tyr	Trp Gly Glu Gly 110
Thr Leu Val 115	Thr Val Ser	Ser Ala Ser 120	Thr Lys Gy	Pro Ser Val Phe 125
Pro Leu Ala 130	Pro Ser Ser	Lys Ser Thr 135	Ser Gy Gy 140	Thr Ala Ala Leu
G y Cys Leu 145	Val Lys Asp 150	Tyr Phe Pro	Giu Pro Val 155	Thr Val Ser Trp 160
Asn Ser Giy	Ala Leu Thr 165	Ser G y Val	His Thr Phe 170	Pro Ala Val Leu 175
Gin Ser Ser	Giy Leu Tyr 180	Ser Leu Ser 185	Ser Val Val Page 74	Thr Val Pro Ser 190

Ser	Ser	Leu 195	Giy	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Яу	Яу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	G u 270	Gu	Asp
Pro	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Βn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gη	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gη	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser	Ar g	Tr p	GIn 420	Gn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala	Leu	His	Asn	His	Tyr	Thr	Gn	Gu	Ser Page		Ser	Leu	Ser	Pr o	

435		P084876D1 S 440		ng 445	
<210> 48 <211> 447 <212> PRT <213> Artifici	al				
<220> <223> an artif	icially syntl	hesized seque	ence		
<400> 48					
Gin Val Gin Leu 1	Gin Giu Ser 5	Gly Pro Gly 10	Leu Val	Lys Pro	Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser Gy 25	His Ser	lle Ser 30	His Asp
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40		Gy Leu 45	Gu Trp
lle Gly Phe lle 50	Ser Tyr Ser 55	Gly IIe Thr	Asn Tyr 60	Asn Pro	Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys / 75	Asn Thr	Leu Tyr 80
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu Asp 90	Thr Ala	Val Tyr	Tyr Cys 95
Ala Arg Ser Leu 100		Thr Ala Met 105	Asp Tyr	Trp Gy 110	Gu Gy
Thr Leu Val Thr 115	Val Ser Ser	Ala Ser Thr 120		Pro Ser 125	Val Phe
Pro Leu Ala Pro 130	Ser Ser Lys 135	Ser Thr Ser	G y G y 140	Thr Ala	Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr 150	Phe Pro Giu	ProVal 155	Thr Val	Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser 165	Giy Val His 170	Thr Phe	Pro Ala	Val Leu 175
Gin Ser Ser Giy 180	Leu Tyr Ser	Leu Ser Ser 185	Val Val	Thr Val 190	Pro Ser
Ser Ser Leu Gry 195	Thr G n Thr	Tyr IIe Cys 200 Page	:	Asn His 205	Lys Pro

P084876D1	Sea	Listing

Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asn 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Яу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr IIe	Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu Pro	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn 385	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg	Tr p	GIn 420	GIn	Яу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu	His 435	Asn	His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
04.0														

<210> 49

P084876D1 Seq Listing <211> 447 <212> PRT										
<213> Artificial										
<220> <223> an artificially synthesized sequence										
<400> 49										
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15										
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30										
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45										
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60										
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80										
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95										
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Giy Giu Giy 100 105 110										
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125										
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140										
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160										
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 165 170 175										
Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190										
Ser Ser Leu Giy Thr Gin Thr Tyr Ile Cys Asn Val Asn His Lys Pro 195 200 205										
Ser Asn Thr Lys Val Asp Lys Lys Val G u Pro Lys Ser Cys Asp Lys 210 215 220 Page 78										

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Giu Leu Leu Giy Giy Asp 225 230 235 240	
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe Ser 245 250 255	
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His Giu Asp 260 265 270	
Giy Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285	
Ala Lys Thr Lys Pro Arg Gu Gu Gn Tyr Asn Ser Thr Tyr Arg Val 290 295 300	
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320	
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335	
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350	
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val Ser Leu Thr 355 360 365	
Cys Leu Val Lys Gly Phe Tyr Pro Ser Aspille Ala Val Glu Trp Glu 370 375 380	
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	
Ala Leu His Asn His Tyr Thr Cin Ciu Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 50 <211> 447 <212> PRT <213> Artificial	

<pre>P084876D1 Seq Listing</pre>											
<220> <223> an artificially synthesized sequence											
<400> 50											
Gin Val Gin 1	Leu Gin 5	Giu Ser	Giy Pr	o Giy Le 10	u Val	Lys	Pr o	Ser 15	Gu		
Thr Leu Ser	Leu Thr 20	Cys Ala	Val Se 25		s Ser	lle	Ser 30	His	Asp		
His Ala Trp 35	Ser Trp	Val Arg	Gin Pr 40	o Pro Gi	y Giu	G y 45	Leu	Gu	Tr p		
lle Gly Phe 50	lle Ser	Tyr Ser 55	G y II	e Thr As	n Tyr 60	Asn	Pr o	Ser	Leu		
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg As	p Asn Se 75	-	Asn	Thr	Leu	Tyr 80		
Leu Gin Met	Asn Ser 85	Leu Arg	Ala G	u Asp Th 90	r Ala	Val	Tyr	Tyr 95	Cys		
Ala Arg Ser	Leu Ala 100	Arg Thr	Thr Al 10		p Tyr	Tr p	G y 110	Gu	Gу		
Thr Leu Val 115	Thr Val	Ser Ser	Ala Se 120	r Thr Ly	s Giy	Pr o 125	Ser	Val	Phe		
Pro Leu Ala 130	Pro Ser	Ser Lys 135		r Ser G	y G y 140	Thr	Al a	Al a	Leu		
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe Pr	o Giu Pr 15	o Val 5	Thr	Val	Ser	Tr p 160		
Asn Ser Giy	Ala Leu 165	Thr Ser	Giy Va	l His Th 170	r Phe	Pr o	Al a	Val 175	Leu		
Gin Ser Ser	Gly Leu 180	Tyr Ser	Leu Se 18		l Val	Thr	Val 190	Pr o	Ser		
Ser Ser Leu 195	Giy Thr	G n Thr	Tyr II 200	e Cys As	n Val	Asn 205	His	Lys	Pr o		
Ser Asn Thr 210	Lys Val	Asp Lys 215		l Giu Pr	o Lys 220	Ser	Cys	Asp	Lys		
Thr His Thr 225	Cys Pro	Pro Cys 230	Pro Al	a Pro G 23 Page 8	5	Leu	Gу	Gу	Asp 240		

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe Ser 245 250 255									
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp 260 265 270									
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285									
Ala Lys Thr Lys Pro Arg Giu Giu Gin Asp Asn Ser Thr Tyr Arg Val 290 295 300									
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320									
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys 325 330 335									
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350									
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365									
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380									
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400									
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415									
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430									
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445									
<210> 51 <211> 447 <212> PRT <213> Artificial									
<220> <223> an artificially synthesized sequence									
<400> 51 Page 81									

	P084876D1 Seq Listing												
Gin Val G 1	In Leu	GIn 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu S	er Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	Hi s	Ser	lle	Ser 30	Hi s	Asp
His Ala T 3		Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle Gly P 50	he lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy A 65	rg Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin M	et Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg S	er Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu V 1	al Thr 15	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu A 130	la Pro	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gly Cys L 145	eu Val		A sp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser G	ly Ala	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser S	er Giy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser L	eu Giy 95	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn T 210	hr Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His T 225	hr Cys		Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val P	he Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250 Page		Thr	Leu	Met	e 255	Ser

FU64676DI Seq LISTINg	
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser 260 265	His Giu Asp 270
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu 275 280 285	Val His Asn
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr 290 295 300	Tyr Arg Val
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn 305 310 315	Gy Lys Gu 320
Tyr Lys Cys Lys IIe Ser Asn Lys Ala Leu Pro Ala Pro 325 330	lle Giu Lys 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin 340 345	Val Tyr Thr 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val 355 360 365	Ser Leu Thr
Cys Leu Val Lys Gly Phe Tyr Pro Ser Aspille Ala Val 370 375 380	Gu Trp Gu
Ser Asn Cly Cin Pro Clu Asn Asn Tyr Lys Thr Thr Pro 385 390 395	Pro Val Leu 400
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr 405 410	Val Asp Lys 415
	Met His Giu 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu 435 440 445	Ser Pro
<210> 52 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 52	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys 1 5 10	Pro Ser Giu 15

		P0	84876D1	Seq Listi	ng		
Thr Leu Ser L 2	⊥eu Thr Cys 20	s Ala Val	Ser Giy 25	His Ser	-	Ser His 30	Asp
His Ala Trp S 35	Ser Trp Val	Arg Gin 40	Pro Pro	G y G u	G y L 45	.eu Giu	Tr p
lle Giy Phe I 50	le Ser Tyr	Ser Giy 55	lle Thr	Asn Tyr 60	Asn P	Pro Ser	Leu
Gin Giy Arg V 65	/al Thr Ile 70	e Ser Arg	Asp Asn	Ser Lys 75	Asn T	「hr Leu	Tyr 80
Leu Gin Met A	Asn Ser Lei 85	ıArg Ala	Giu Asp 90	Thr Ala	Val T	Fyr Tyr 95	Cys
Ala Arg Ser L 1	_eu Ala Arç I00	g Thr Thr	Ala Met 105	Asp Tyr		aly Giu ∣10	Gу
Thr Leu Val T 115	Γhr Val Ser	Ser Ala 120		Lys Giy	ProS 125	Ser Val	Phe
Pro Leu Ala F 130	Pro Ser Ser	Lys Ser 135	Thr Ser	G y G y 140	Thr A	Na Ala	Leu
Gy Cys Leu V 145	/al Lys Asp 150		Pro Giu	Pro Val 155	Thr V	/al Ser	Tr p 160
Asn Ser Giy A	Ala Leu Thr 165	Ser Giy	Val His 170		Pro A	Na Val 175	Leu
Gin Ser Ser G 1	Giy Leu Tyr 180	Ser Leu	Ser Ser 185	Val Val		/al Pro 90	Ser
Ser Ser Leu G 195	Giy Thr Gir	n Thr Tyr 200		Asn Val	Asn H 205	⊩is Lys	Pr o
Ser Asn Thr L 210	_ys Val Asp	D Lys Lys 215	Val Gu	Pro Lys 220	Ser C	Cys Asp	Lys
Thr His Thr C 225	Cys Pro Pro 230		Ala Pro	G u Leu 235	Leu C	ay Gy	Asp 240
Ser Val Phe L	₋eu Phe Pro 245) Pro Lys	Pro Lys 250	Asp Thr	Leu N	Aet IIe 255	Ser
Arg Thr Pro G 2	Giu Val Thr 260	Cys Val	265	Asp Val e 84		His Giu 270	Asp

		P084876D1	Seq Listi	ng
Pro Clu Val Lys 275	Phe Asn Trp	Tyr Val Asp 280	Giy Val	Giu Val His Asn 285
Ala Lys Thr Lys 290	Pro Arg Giu 295		Asn Ser 300	Thr Tyr Arg Val
Val Ser Val Leu 305	Thr Val Leu 310	His Gin Asp	Trp Leu 315	Asn Ciy Lys Ciu 320
Tyr Lys Cys Lys	Leu Ser Asn 325	Lys Ala Leu 330		Pro Ile Giu Lys 335
Thr IIe Ser Lys 340		Gin Pro Arg 345	Giu Pro	Gin Val Tyr Thr 350
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360	Asn Gin	Val Ser Leu Thr 365
Cys Leu Val Lys 370	G y Phe Tyr 375		lle Ala 380	Val Giu Trp Giu
Ser Asn Ciy Cin 385	Pro Giu Asn 390	Asn Tyr Lys	Thr Thr 395	Pro Pro Val Leu 400
Asp Ser Asp Giy	Ser Phe Phe 405	Leu Tyr Ser 410		Thr Val Asp Lys 415
Ser Arg Trp Gin 420		Val Phe Ser 425	Cys Ser	Val Met His Giu 430
Ala Leu His Asn 435	His Tyr Thr	Gin Giu Ser 440	Leu Ser	Leu Ser Pro 445
<210> 53 <211> 447 <212> PRT <213> Artifici	al			
<220> <223> an artif	icially synt	hesized sequ	ence	
<400> 53				
Gin Val Gin Leu 1	GnGuSer 5	Giy Pro Giy 10	Leu Val	Lys Pro Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser Giy 25	His Ser	lle Ser His Asp 30

							P08	4876	5D1 S	Seq L	.isti	ng			
His	Ala	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	GIn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp Page	-	Val	G u 285	Val	His	Asn

										•		•			
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Βn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Met 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Яу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser	Ar g	Tr p	GI n 420	Βn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	Hi s	Gu
Al a	Leu	His 435	Asn	Hi s	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210 <211 <212 <213	> 4 2> F	54 147 PRT Artif	icia	al											
<220 <223		an ar	rtifi	ci al	lv s	synt f	nesi z	zed s	seque	ence					
<400		54			,	,									
Gn 1	Val	G n	Leu	Gn 5	Gu	Ser	Gу	Pr o	Gу 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p

			P0848	76D1 S	eq Li	sting			
lle Gy Phe 50	lle Ser	Tyr Ser 55	Giy II	e Thr	-	⊽yr Asn 30	Pr o	Ser	Leu
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg As	p Asn	Ser L 75	ys Asn.	Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu Arg	Ala Gi	u Asp 90	Thr A	Na Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg Thr	Thr Al 10		Asp T	⁻yr Trp	G y 110	Gu	Gу
Thr Leu Val 115	Thr Val	Ser Ser	Ala Se 120	er Thr	Lys C	Эју Pro 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 135		ır Ser		∃y Thr 40	Al a	Ala	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe Pr		ProV 155	/al Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Ser	Giy Va	ul His 170	Thr F	Phe Pro	Al a	Val 175	Leu
Gin Ser Ser	Giy Leu 180	Tyr Ser	Leu Se 18		Val V	/al Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	Gin Thr	Tyr II 200	e Cys	Asn V	/al Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		ıl Giu		ys Ser 20	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	Pro Al		G u L 235	.eu Leu	Gу	Gу	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro	Lys Pr	o Lys 250	Asp T	hr Leu	Met	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys	Val Va 26		Asp V	/al Ser	His 270	Gu	Asp
Pro Giu Val 275	Lys Phe	Asn Trp) Tyr Va 280	l Asp	Gy V	/al Giu 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro	Arg Giu 295		n Tyr Page	3	Ser Thr 300	Tyr	Ar g	Val

Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 55 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 55
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Pheille Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60

			P08487	'6D1 Se	əq Listi	ng			
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg As		Ser Lys 75	Asn [·]	Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu Arg	Ala G	u Asp ⁻ 90	Thr Ala	Val		Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg Thr	Thr Al a 10		Asp Tyr		G y 110	Gu	Яу
Thr Leu Val 115	Thr Val	Ser Ser	Ala Sei 120	^r Thr I	Lys Giy	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 135		^r Ser (Gy Gy 140	Thr .	Ala	Ala	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe Pr		Pro Val 155	Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Ser	Gy Va	His ⁻ 170	Thr Phe	Pro		Val 175	Leu
Gin Ser Ser	Giy Leu 180	Tyr Ser	Leu Se 18		Val Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	G n Thr	Tyr II 200	e Cys /	Asn Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		Gul	Pro Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	Pro Ala		G u Leu 235	Leu	Gу	Gу	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro	Lys Pr	b Lys / 250	Asp Thr	Leu		e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys	Val Val 26		Asp Val	Ser	His 270	Gu	Asp
Pro Gu Val 275	Lys Phe	Asn Trp	Tyr Val 280	Asp (Giy Val	G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro	Arg Giu 295		n Tyr <i>i</i>	Asn Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr	Val Leu 310	His G		315	Asn	Gу	Lys	G u 320

Tyr Lys Cys Lys Val Ser Asn Asp Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335	;
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350	
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365	
Cys Leu Val Lys Gly Phe Tyr Pro Ser Aspille Ala Val Glu Trp Glu 370 375 380	ı
Ser Asn Gly Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	;
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	ł
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 56 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 56	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15	ł
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30)
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45)
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60	ł
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80	

		P0	84876D1	Seq Listi	ng			
Leu Gin Met A	Asn Ser Leu 85	ıArg Ala	GuAsp 90	Thr Ala	Val	Tyr	Tyr 95	Cys
Ala Arg Ser L 1	⊥eu Ala Arg I00	I Thr Thr	Ala Met 105	Asp Tyr	Tr p	G y 110	Gu	Gу
Thr Leu Val T 115	Fhr Val Ser	Ser Ala 120		Lys Giy	Pr o 125	Ser	Val	Phe
Pro Leu Ala P 130	Pro Ser Ser	Lys Ser 135	Thr Ser	G y G y 140	Thr	Al a	Al a	Leu
G y Cys Leu V 145	/al Lys Asp 150		Pro Giu	Pro Val 155	Thr	Val	Ser	Tr p 160
Asn Ser Giy A	Ala Leu Thr 165	Ser Giy	Val His 170	Thr Phe	Pr o	Ala	Val 175	Leu
Gin Ser Ser G 1	∃y Leu Tyr ∣80	Ser Leu	Ser Ser 185	Val Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu G 195	Gly Thr Gir	Thr Tyr 200		Asn Val	Asn 205	His	Lys	Pr o
Ser Asn Thr L 210	_ys Val Asp	D Lys Lys 215	Val Giu	Pro Lys 220	Ser	Cys	Asp	Lys
Thr His Thr C 225	Cys Pro Pro 230		Ala Pro	G u Leu 235	Leu	Gу	Gу	Asp 240
Ser Val Phe L	∟eu Phe Pro 245	Pro Lys	Pro Lys 250		Leu	Met	e 255	Ser
Arg Thr Pro G 2	Glu Val Thr 260	Cys Val	Val Val 265	Asp Val	Ser	His 270	Gu	Asp
Pro Giu Val L 275	_ys Phe Asr	Trp Tyr 280		Giy Val	G u 285	Val	His	Asn
Ala Lys Thr L 290	_ys Pro Arg	GuGu 295	Gn Tyr	Asn Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val L 305	∟eu Thr Val 310		Gin Asp	Trp Leu 315	Asn	Gу	Lys	G u 320
Tyr Lys Cys L	₋ys Val Ser 325	Asn Giu	Ala Leu 330 Page		Pr o	l e	G u 335	Lys

340	Ala Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr	
Leu Pro Pro Sei 355	Arg Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr	
Cys Leu Val Lys 370	Giy Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu	
Ser Asn G y G i 385	ProGLU 390		Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400	
Asp Ser Asp G	Ser Phe 405	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys	
Ser Arg Trp Gi 420		Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu	
Ala Leu His Asi 435	ı His Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o		
<210> 57 <211> 447 <212> PRT <213> Artificial												
<213> Artificial <220> <223> an artificially synthesized sequence												
<220>		synt h	nesi z	ed s	seque	ence						
<220>		synt h	iesi z	ed s	seque	ence						
<220> <223> an artit	icially						Val	Lys	Pr o	Ser 15	Gu	
<220> <223> an artit <400> 57 Gin Val Gin Leu	icially IGnGu 5	Ser	Gу	Pr o	G y 10	Leu				15		
<220> <223> an artif <400> 57 G n Val G n Leu 1 Thr Leu Ser Leu	icially Gin Giu 5 IThr Cys	Ser Al a	G y Val	Pr o Ser 25	Giy 10 Giy	Leu His	Ser	lle	Ser 30	15 His	Asp	
<220> <223> an artif <400> 57 Gin Val Gin Lei 1 Thr Leu Ser Lei 20 His Ala Trp Sei	icially Gin Giu 5 Thr Cys Trp Val	Ala Arg	G y Val G n 40	Pr o Ser 25 Pr o	Giy 10 Giy Pro	Leu His Giy	Ser Gi u	IIe Gy 45	Ser 30 Leu	15 His Giu	Asp Tr p	
<220> <223> an artif <400> 57 G n Val G n Len 1 Thr Leu Ser Len 20 His Ala Trp Sen 35	icially Gin Giu 5 Thr Cys Trp Val	Ala Arg Ser 55	G y Val G n 40 G y	Pr o Ser 25 Pr o	G y G y Pr o Thr	Leu His Giy Asn	Ser G u Tyr 60	IIe Gy 45 Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu	

		P08	34876D1	Seq Li	sting		
Ala Arg Ser L 1	eu Ala Arg 00	Thr Thr	Ala Me 105	et Asp T	「yr Trp	Gy Gu 110	Gу
Thr Leu Val T 115	hr Val Ser	Ser Ala 120	Ser Th	ır Lys (Эју Pro 125	Ser Val	Phe
Pro Leu Ala P 130	ro Ser Ser	Lys Ser 135	Thr Se		∃iy Thr ∣40	Ala Ala	Leu
G y Cys Leu V 145	al Lys Asp 150	Tyr Phe	Pro Gi	u Pro V 155	/al Thr	Val Ser	Tr p 160
Asn Ser Gly A	la Leu Thr 165	Ser Giy	Val Hi 17		Phe Pro	Ala Val 175	Leu
Gin Ser Ser G 1	ly Leu Tyr 80	Ser Leu	Ser Se 185	er Val N	/al Thr	Val Pro 190	Ser
Ser Ser Leu G 195	ly Thr Gin	Thr Tyr 200	lle Cy	rs Asn ∖	/al Asn 205	His Lys	Pr o
Ser Asn Thr L 210	ys Val Asp	Lys Lys 215	Val G		_ys Ser 220	Cys Asp	Lys
Thr His Thr C 225	ys Pro Pro 230		Ala Pr	o G u L 235	_eu Leu	Gy Gy	Asp 240
Ser Val Phe L	eu Phe Pro 245	Pro Lys	ProLy 25		Thr Leu	Met IIe 255	Ser
Arg Thr Pro G 2	lu Val Thr 60	Cys Val	Val Va 265	ıl Asp ∖	/al Ser	His Giu 270	Asp
Pro Giu Val L 275	ys Phe Asn	Trp Tyr 280	Val As	рGу\	/al Gu 285	Val His	Asn
Ala Lys Thr L 290	ys Pro Arg	G u G u 295	Gn Ty		Ser Thr 300	Tyr Arg	Val
Val Ser Val L 305	eu Thr Val 310	Leu His	GinAs	p Trp L 315	_eu Asn	Gy Lys	G u 320
Tyr Lys Cys L	ys Val Ser 325	Asn Leu	Ala Le 33	-	Na Pro	lle Gu 335	Lys
Thr IIe Ser L 3	ys Ala Lys 40	Gy Gn	345	g Giu F de 94	Pro Gin	Val Tyr 350	Thr

355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 58 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 58
<400> 58 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu
<400> 58 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser IIe Ser His Asp
<400> 58 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser II e Ser His Asp 20 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp
<pre><400> 58 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser IIe Ser His Asp His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp IIe Giy Phe IIe Ser Tyr Ser Giy IIe Thr Asn Tyr Asn Pro Ser Leu</pre>
 <400> 58 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 15 Thr Leu Ser Leu Thr Oys Ala Val Ser Giy His Ser IIe Ser His Asp 25 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 45 IIe Giy Phe IIe Ser Tyr Ser Giy IIe Thr Asn Tyr Asn Pro Ser Leu 60 Gin Giy Arg Val Thr IIe Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

			P084	4876	D1 S	Seq L	isti	ng			
Thr Leu Val 115		Ser Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 135		Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165		Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	G y Leu 180	Tyr Ser		Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195		Gin Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	Pr o	Ala	Pr o	G u 235	Leu	Leu	Яу	Яу	Asp 240
Ser Val Phe	Leu Phe 245		Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	Glu Val 260	Thr Cys		Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu Val 275		Asn Trp	7yr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn
Ala Lys Thr 290	Lys Pro	Arg Ciu 295		Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr	Val Leu 310	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys	Lys Val 325		Met	Ala	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr IIe Ser	Lys Ala 340	Lys Gy		Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr
Leu Pro Pro 355		Asp G u	Leu 360		Lys Page		Gn	Val 365	Ser	Leu	Thr

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380	
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 59 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 59	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15	
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30	
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45	
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60	
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80	
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95	
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Giy Giu Giy 100 105 110	

	P084876D1 Seq Listing								
Pro Leu Ala 130	Pro Ser	Ser Lys 135		Thr Ser		ly Thr 40	Ala	Ala	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe F	Pro Giu	ProVa 155	al Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Ser	Gy∖	Val His 170	Thr Pl	he Pro		Val 175	Leu
Gin Ser Ser	G y Leu 180	Tyr Ser		Ser Ser 185	Val Va	al Thr	Val 190	Pr o	Ser
Ser Ser Leu 195		Gin Thr	Tyr I 200	le Cys	Asn Va	al Asn 205	Hisl	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		Val Giu		ys Ser 20	Cys /	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	;Pro <i>F</i>	Ala Pro	G u Lo 235	eu Leu	Giy	Gу	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro) Lys F	Pro Lys 250	Asp TI	hr Leu		e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys		Val Val 265	Asp Va	al Ser	His 270	Gu	Asp
Pro Giu Val 275	Lys Phe	Asn Trp) Tyr \ 280	Val Asp	Giy Va	al Gu 285	Val I	His	Asn
Ala Lys Thr 290	Lys Pro	Arg Giu 295		Gin Tyr		er Thr 00	Tyr /	Ar g	Val
Val Ser Val 305	Leu Thr	Val Leu 310	i His (Gin Asp	Trp Lo 315	eu Asn	Gyl	Lys	G u 320
Tyr Lys Cys	Lys Val 325	Ser Asr	n Asn A	Ala Leu 330	Pro Al	la Pro		G u 335	Lys
Thr IIe Ser	Lys Ala 340	Lys Giy		Pro Arg 345	Giu Pi	ro Gin	Val 350	Tyr	Thr
Leu Pro Pro 355		Asp Giu	ı Leu 1 360	Thr Lys	Asn G	In Val 365	Ser I	Leu	Thr
Cys Leu Val 370	Lys Gy	Phe Tyr 375		Ser Asp Page	38	la Val 80	Gu	Tr p	Gu

Ser Asn G y G n Pro G u Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Clu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 60 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 60
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140

	P084876D1 Seq Listing												
G y Cys Leu Va 145	I Lys Asp 150		Pro Giu	Pro Val 155	Thr Va	al Ser	Tr p 160						
Asn Ser G y Al	a Leu Thr 165	Ser Giy	Val His 170	Thr Phe	Pro Al	a Val 175	Leu						
Gin Ser Ser G 18		Ser Leu	Ser Ser 185	Val Val	Thr Va 19		Ser						
Ser Ser Leu G 195	y Thr Cin	Thr Tyr 200		Asn Val	Asn Hi 205	s Lys	Pr o						
Ser Asn Thr Ly 210	s Val Asp	Lys Lys 215	Val Giu	Pro Lys 220	Ser Cy	vs Asp	Lys						
Thr His Thr O <u>.</u> 225	s Pro Pro 230		Ala Pro	G u Leu 235	Leu G	y G y	Asp 240						
Ser Val Phe Lo	u Phe Pro 245	Pro Lys	ProLys 250	Asp Thr	Leu Me	et IIe 255	Ser						
Arg Thr Pro Gi 20		Cys Val	Val Val 265	Asp Val	Ser Hi 27		Asp						
Pro Giu Val Ly 275	s Phe Asn	Trp Tyr 280		Giy Val	G u Va 285	al His	Asn						
Ala Lys Thr Ly 290	s Pro Arg	GuGu 295	Gin Tyr	Asn Ser 300	Thr Ty	vr Arg	Val						
Val Ser Val Lo 305	u Thr Val 310		Gin Asp	Trp Leu 315	Asn G	y Lys	G u 320						
Tyr Lys Cys Ly	s Val Ser 325	Asn Gin	Ala Leu 330	Pro Ala	Pro II	e Gu 335	Lys						
Thr IIe Ser Ly 34		Gy Gn	Pro Arg 345	Giu Pro	Gin Va 35		Thr						
Leu Pro Pro So 355	r Arg Asp	G u Leu 360		Asn Gin	Val Se 365	er Leu	Thr						
Cys Leu Val Ly 370	s G y Phe	Tyr Pro 375	Ser Asp	lle Ala 380	Val G	u Trp	Gu						
Ser Asn G y G 385	n Pro Giu 390		Tyr Lys Page	395	Pro Pr	o Val	Leu 400						

Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415 Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430 Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445 <210> 61 <211> 447 <212> PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> 61 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45 lle Gry Phe Ile Ser Tyr Ser Gry Ile Thr Asn Tyr Asn Pro Ser Leu 50 60 Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Giy Giu Giy 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys G y Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu 130 135 140 130 Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser 145 150 155 Trp 155 160

P084876D1 Seq Listing

		P084876D	D1 Seq Listi	ng	
Asn Ser Giy Ala	Leu Thr Ser 165		His Thr Phe 170	Pro Ala	Val Leu 175
Gin Ser Ser Giy 180		Leu Ser S 185	Ser Val Val	Thr Val 190	Pro Ser
Ser Ser Leu Gly 195	Thr G n Thr	Tyr lle (200	Cys Asn Val	Asn His 205	Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys 215		GuProLys 220	Ser Cys	Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230	Pro Ala F	Pro G u Leu 235	Leu Gy	Gy Asp 240
Ser Val Phe Leu	Phe Pro Pro 245		Lys Asp Thr 250	Leu Met	IIe Ser 255
Arg Thr Pro Giu 260		Val Val \ 265	Val Asp Val	Ser His 270	Gu Asp
Pro Giu Val Lys 275	Phe Asn Trp	Tyr Val A 280	Asp G y Val	G u Val 285	His Asn
Ala Lys Thr Lys 290	Pro Arg Giu 295		Tyr Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val Leu 305	Thr Val Leu 310	His Gin A	Asp Trp Leu 315	Asn Giy	Lys Giu 320
Tyr Lys Cys Lys	Val Ser Asn 325		Leu Pro Ala 330	Pro IIe	GuLys 335
Thr IIe Ser Lys 340		Gin Pro <i>A</i> 345	Arg Clu Pro	G n Val 350	Tyr Thr
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr L 360	Lys Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val Lys 370	G y Phe Tyr 375		Asp IIe Ala 380	Val Giu	Trp Giu
Ser Asn G y G r 385	Pro Giu Asn 390	Asn Tyr L	Lys Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp G y	Ser Phe Phe 405		Ser Lys Leu 410 age 102	Thr Val	Asp Lys 415

2016262766 25 Nov 2016

Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430													
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445													
<210> 62 <211> 447 <212> PRT <213> Artificial													
<220> <223> an artificially synthesized sequence													
<pre><400> 62 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15</pre>													
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30													
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45													
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60													
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80													
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95													
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110													
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125													
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140													
Giy Cys Leu Val Lys Asp Tyr Phe Pro Giu Pro Val Thr Val Ser Trp 145 150 155 160													
Asn Ser Ciy Ala Leu Thr Ser Ciy Val His Thr Phe Pro Ala Val Leu 165 170 175													

P084876D1 Seq Listing

P084876D1 Seq Listing												
Gin Ser Ser G 18		Ser Lei	u Ser Ser 185	Val Val		/al Pro 90	Ser					
Ser Ser Leu G 195	y Thr Gin	Thr Tyr 20(Asn Val	Asn H 205	his Lys	Pr o					
Ser Asn Thr Ly 210	rs Val Asp	Lys Lys 215	s Val Giu	Pro Lys 220	Ser C	Dys Asp	Lys					
Thr His Thr Cy 225	rs Pro Pro 230		o Ala Pro	G u Leu 235	Leu G	Эу Gу	Asp 240					
Ser Val Phe Le	eu Phe Pro 245	Pro Lys	s Pro Lys 250		Leu N	Aet IIe 255	Ser					
Arg Thr Pro Gi 26		Cys Val	Val Val 265	Asp Val		his Giu ≀70	Asp					
Pro Giu Val Ly 275	rs Phe Asn	Trp Tyr 280		Giy Val	G u V 285	/al His	Asn					
Ala Lys Thr Ly 290	rs Pro Arg	G น G เ 295	ı Gin Tyr	Asn Ser 300		⊽yr Arg	Val					
Val Ser Val Le 305	u Thr Val 310		s Gin Asp	Trp Leu 315	Asn G	∃y Lys	G u 320					
Tyr Lys Cys Ly	s Val Ser 325	Asn Thr	Ala Leu 330		Pro I	le Giu 335	Lys					
Thr IIe Ser Ly 34		Giy Gir	Pro Arg 345	Giu Pro		/al Tyr 850	Thr					
Leu Pro Pro Se 355	er Arg Asp	G u Lei 360		Asn Gin	Val S 365	Ser Leu	Thr					
Cys Leu Val Ly 370	's Gy Phe	Tyr Pro 375) Ser Asp	lle Ala 380		∃u Trp	Gu					
Ser Asn G y G 385	n Pro Giu 390		n Tyr Lys	Thr Thr 395	Pro F	Pro Val	Leu 400					
Asp Ser Asp G	y Ser Phe 405	Phe Leu	u Tyr Ser 410		Thr V	/al Asp 415	Lys					
Ser Arg Trp G 42		Asn Val	425	Cys Ser		∧let His ⊪30	Gu					

P084876D1 Seq Listing

Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445 <210> 63 <211> 447 <212> PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> 63 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45 Ile Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 60 Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 80 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gy Gu Gy 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Giy Giy Thr Ala Ala Leu 130 135 140 130 Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160 155 160 Asn Ser Cly Ala Leu Thr Ser Cly Val His Thr Phe Pro Ala Val Leu 165 170 175 Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190

			P084	18761	D1 S	eq L	isti	ng			
Ser Ser Leu (195	Giy Thr G	n Thr	Tyr I 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr L 210	Lys Val A	sp Lys 215	Lys '	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr (225		ro Cys 30	Pro	Ala	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val Phe L	Leu Phe P 245	ro Pro	Lys I		Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro (2	Giu Val T 260	hr Cys		Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu Val L 275	Lys Phe A	sn Trp	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr L 290	Lys Pro A	rg Clu 295	Gu (GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val L 305	Leu Thr V 3	al Leu 10	His (GIn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys L	Lys Val S 325	er Asn	Lys /		Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr IIe Ser L	Lys Ala L 340	ys Giy		Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu Pro Pro S 355	Ser Arg A	sp G u	Leu ⁻ 360	Thr	Lys	Asn	Gin	Val 365	Ser	Leu	Thr
Cys Leu Val L 370	Lys Giy P	he Tyr 375	Pro 🕄	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G y (385	Gin Pro G 31	lu Asn 90	Asn ⁻	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp (Giy Ser P 405	he Phe	Leu ⁻	-	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp (Gin Gin G 420	ly Asn		Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His A 435	Asn His T	yr Thr	Gn (440		Ser Page		Ser	Leu 445	Ser	Pr o	

<210> <211> <212> <213>	64 447 PRT Arti	ficia	al											
<220> <223> an artificially synthesized sequence														
<400>	64													
Gin Va 1	GIn	Leu	GIn 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Le	u Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Яу	His	Ser	lle	Ser 30	His	Asp
His Ala	a Trp 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle G 50	/ Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n G 1 65	/Arg	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G	ר Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	g Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Le	u Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Le 13		Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y Cy: 145	s Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Se	. G à	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Se	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Se	- Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o

P084876D1 Seq Listing

					P08	4876	D1 S	Seq L	.isti	ng			
Ser Asn 210	Thr L	.ys Va	l Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr C	Cys Pr	o Pro 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe L	eu Ph. 24		Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr		∃iu Va 260	l Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val L 275	.ys Ph	e Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr L	.ys Pr	o Arg	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val L	.eu Th	r Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys L	ys Va. 32		Asn	Lys	Al a	Leu 330	Pr o	Met	Pr o	lle	G u 335	Lys
Thr Ile		_ys Al 840	a Lys	Gу	G n	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr
Leu Pro	Pro S 355	Ser Ar	g Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu 370	Val L	ys G	y Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn 385	Gyo	3in Pr	o G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser	Asp G	∃y Se 40		Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg		∃n G 120	n Giy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu	His A 435	Asn Hi	s Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
	5 47						Paga	100					

<212 <213															
<220 <223)>		rtifi		ly s	synt l	nesi z	zed s	seque	ence					
<400)> (65			-										
			Leu	Gin 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Ala	Ala	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Ala	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys

P084876D1 Seq Listing	
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Giu Leu Leu	GyGyAsp
225 230 235	240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu	Met IIe Ser
245 250	255
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser	His Clu Asp
260 265	270
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu 275 280 285	Val His Asn
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr 290 295 300	Tyr Arg Val
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn	Giy Lys Giu
305 310 315	320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Arg Pro	lle GuLys
325 330	335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln	Val Tyr Thr
340 345	350
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val 355 360 365	Ser Leu Thr
Cys Leu Val Lys Ciy Phe Tyr Pro Ser Asp lie Ala Val 370 375 380	Gu Trp Gu
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro	Pro Val Leu
385 390 395	400
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr	Val Asp Lys
405 410	415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val	Met His Giu
420 425	430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu 435 440 445	Ser Pro
<210> 66 <211> 447 <212> PRT <213> Artificial	
<220>	

<223			tifi	ci al	ly s	synt f				Seq L ence	isti	ng			
<400 G n 1		6 Gin	Leu	GIn 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	G
Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	As
His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Яу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Le
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Ty 80
Leu	Gn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Q
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	G
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	P
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	L
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	T) 10
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	L
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	S
Ser	Ser	Leu 195	Gу	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	P
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	L
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	A 2-

P084876D1 Seq Listing												
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe Ser 245 250 255												
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His Giu Asp 260 265 270												
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285												
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg Val 290 295 300												
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320												
Tyr Lys Cys Lys Met Ser Asn Lys Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335												
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350												
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365												
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380												
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400												
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415												
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430												
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445												
<210> 67 <211> 447 <212> PRT <213> Artificial												
<220> <223> an artificially synthesized sequence												
<400> 67												

Gin 1	Val	Gin	Leu	GIn 5	Gu	Ser				eq L Leu			Pr o	Ser 15	Gu
Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
l e	G y 50	Phe	lle	Ser	Tyr	Ser 55	Яу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	GIn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Яу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Яу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Ala	Val 175	Leu
Gn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Яу	Яу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser

		P	084876	6D1 8	Seq L	isti	ng			
Arg Thr Pro Gi 26		Cys Va	l Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu Val Ly: 275	s Phe Asn	Trp Ty 28		Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr Ly 290	s Pro Arg	G u G 295	uGin	Asp	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val Le 305	u Thr Val 310		s Gin	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys Ly	s Val Ser 325	Asn Ly	s Ala	Leu 330	Pr o	Al a	Pr o	lle	G u 335	Lys
Thr IIe Ser Ly 34		G y G	n Pro 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu Pro Pro Se 355	Arg Asp	GuLe 36		Lys	Asn	Gin	Val 365	Ser	Leu	Thr
Cys Leu Val Ly 370	s Gy Phe	Tyr Pr 375	o Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G y G 385	n Pro Giu 390		n Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp G	v Ser Phe 405	Phe Le	u Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp Gi 42		Asn Va	l Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His As 435	n His Tyr	Thr G 44		Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 68 <211> 447 <212> PRT <213> Artific	al									
	icially	synt hes	ized	sequ	ence					
<400> 68 Gin Val Gin Lo		Sor C	V Pro	Чv	Lou	Val	Lve	Dr o	Sor	G
Gin Val Gin Le 1	J GIN GIU 5		у ГТО	10 10	LUU	vai	∟уъ	110	15	чu

Thr	Leu	Ser	Leu 20	Thr	Cys	Al a				SeqL His			Ser 30	His	Asp
His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
l e	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	GIn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Ala	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	Gу 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	Hi s	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp

		P084876D1	Seq Listi	ng	
Pro Giu Val Lys Pl 275	ne Asn Trp	Tyr Val Asj 280	o Giy Val	G u Val 285	His Asn
Ala Lys Thr Lys Pr 290	o Arg Giu 295	Gu Gn Tyr	r Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val Leu Tl 305	nr Val Leu 310	His Gin As _l	o Trp Leu 315	Asn Giy	Lys Gu 320
Tyr Lys Cys Lys Va 33		Lys Ala Lei 331		Pro IIe	GuLys 335
Thr IIe Ser Lys Al 340	a Lys Giy	Gin Pro Arg 345	g Giu Pro	G n Val 350	Tyr Thr
Leu Pro Pro Ser An 355	g Asp Giu	Leu Thr Lys 360	s Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val Lys G 370	y Phe Tyr 375		olle Ala 380	Val Gu	Trp Giu
Ser Asn Ciy Cin Pi 385	o Giu Asn 390	Asn Tyr Lys	s Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp Giy S 40		Leu Tyr Sei 410		Thr Val	Asp Lys 415
Ser Arg Trp Gin G 420	n Giy Asn	Val Phe Sei 425	r Cys Ser	Val Met 430	His Giu
Ala Leu His Asn Hi 435	s Tyr Thr	Gin Giu Sei 440	r Leu Ser	Leu Ser 445	Pr o
<210> 69 <211> 447 <212> PRT <213> Artificial					
<220> <223> an artifici	ally synt	hesized seq	uence		
<400> 69					
Gin Val Gin Leu G 1 5	n Giu Ser	Giy Pro Giy 10	y Leu Val	Lys Pro	Ser Giu 15
Thr Leu Ser Leu TI 20	nr Cys Ala	Val Ser G 25	y His Ser	lle Ser 30	His Asp

His	Al a	Tr p 35	Ser	Tr p	Val	Ar g				Seq L Giy			Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Яу	Яу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn

P084876D1 Seq Listing
Ala Lys Thr Lys Pro Arg Giu Giu Gin Asp Asn Ser Thr Tyr Arg Val 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Lys Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 70 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 70
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45

lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Р08 G у	4876 11 e	D1 S Thr	Seq L Asn	isti Tyr 60	ng Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	Gin	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Яу	G y 140	Thr	Al a	Ala	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val

		P084876[D1 Seq Li	sting	
Val Ser Val Leu 305	Thr Val Leu 310	His Gin /	Asp Trp L 315	_eu Asn	Giy Lys Giu 320
Tyr Lys Cys Lys I	Met Ser Asn 325		Leu Pro L 330	_ys Pro	lle Glu Lys 335
Thr IIe Ser Lys / 340	Ala Lys Giy	Gin Pro 345	Arg Giu F		Val Tyr Thr 350
Leu Pro Pro Ser / 355	Arg Asp Giu	Leu Thr I 360	Lys Asn (Gin Val 365	Ser Leu Thr
Cys Leu Val Lys (370	G y Phe Tyr 375	Pro Ser J		Ala Val 380	Gu Trp Gu
Ser Asn Gly Gln 1 385	Pro Giu Asn 390	Asn Tyr I	Lys Thr 1 395	Thr Pro	Pro Val Leu 400
Asp Ser Asp G y	Ser Phe Phe 405		Ser Lys L 410	_eu Thr	Val Asp Lys 415
Ser Arg Trp Gin 420	Gin Giy Asn	Val Phe S 425	Ser Cys S		Met His Giu 430
Ala Leu His Asn I 435	His Tyr Thr	G n G u \$ 440	Ser Leu S	Ser Leu 445	Ser Pro
<210> 71 <211> 447 <212> PRT <213> Artificial	I				
<220> <223> an artific	cially synth	nesized se	eauence		
<400> 71	, <u>,</u> , ,				
Gin Val Gin Leu (1	Gin Giu Ser 5		Gy Leu \ 10	Val Lys	Pro Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser (25	Giy His S	Ser IIe	Ser His Asp 30
His Ala Trp Ser 35	Trp Val Arg	Gin Prol 40	Pro Giy (Giu Giy 45	Leu Giu Trp
lle Giy Phe lle 3 50	Ser Tyr Ser 55	Gylle ⁻	-	Tyr Asn 60	Pro Ser Leu

G n G y 65	Ar g	Val	Thr	e 70	Ser		4876 Asp					Thr	Leu	Tyr 80
Leu G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130		Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	Gу 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Яy	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290		Lys	Pr o	Ar g	G u 295	Gu	GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	GIn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
								_	404					

P084876D1 Seq Listing	
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Lys Pro Ile Giu 325 330 335	
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr 340 345 350	Thr
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu 355 360 365	ı Thr
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val Glu Trp 370 375 380	Gu
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val 385 390 395	Leu 400
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His 420 425 430	Gu
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445)
<210> 72 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 72	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser 1 5 10 15	Gu
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His 20 25 30	s Asp
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu 35 40 45	ı Trp
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser 50 55 60	Leu
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu 65 70 75	ı Tyr 80

P084876D1 Seq Listing Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Giy Giu Giy 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu 130 135 140 130 G y Cys Leu Val Lys Asp Tyr Phe Pro G u Pro Val Thr Val Ser Trp 145 150 155 160 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 170 165 175Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190 Ser Ser Leu Giy Thr Gin Thr Tyr Ile Cys Asn Val Asn His Lys Pro 195 200 205 195 Ser Asn Thr Lys Val Asp Lys Lys Val G u Pro Lys Ser Cys Asp Lys 210 215 220 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Gu Leu Leu Gy Gy Asp 225 235 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe Ser 245 250 250 255 Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His Giu Asp 260 265 270 Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285 275 285 Ala Lys Thr Lys Pro Arg Gu Gu Gn Tyr Asn Ser Thr Tyr Arg Val 290 295 300 Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320 320 310 Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Lys Pro Ile Giu Lys 325 330 335

Page 123

2016262766 25 Nov 2016

		P084	876D1 Seq L	isting	
Thr IIe Ser Ly 34			Pro Arg Giu 345	Pro Gin	Val Tyr Thr 350
Leu Pro Pro Se 355	Arg Asp	G u Leu T 360	Thr Lys Asn	Gin Val 365	Ser Leu Thr
Cys Leu Val Ly 370		Tyr Pro S 375	Ser Asp IIe	Ala Val 380	Gu Trp Gu
Ser Asn G y G 385	n Pro Giu 390	Asn Asn T	Fyr Lys Thr 395	Thr Pro	Pro Val Leu 400
Asp Ser Asp G	/ Ser Phe 405	Phe Leu T	⊺yr Ser Lys 410	Leu Thr	Val Asp Lys 415
Ser Arg Trp G 42			Phe Ser Cys 125	Ser Val	Met His Giu 430
Ala Leu His As 435	n His Tyr	Thr Gin G 440	9 u Ser Leu	Ser Leu 445	Ser Pro
<210> 73 <211> 447 <212> PRT <213> Artific	al				
<220> <223> an arti	icially s	ynt hesi ze	ed sequence		
<400> 73					
Gin Val Gin Le 1	u Gin Giu 5	Ser Giy F	Pro G y Leu 10	Val Lys	Pro Ser Giu 15
Thr Leu Ser Le 20	u Thr Cys	Ala Val S 2	Ser Ciy His 25	Ser IIe	Ser His Asp 30
His Ala Trp Se 35	Trp Val	Arg Gin P 40	Pro Pro Giy	GuGy 45	Leu Giu Trp
lle Giy Phe II 50		Ser Giy I 55	le Thr Asn	Tyr Asn 60	Pro Ser Leu
Gin Giy Arg Va 65	Thr IIe 70	Ser Arg A	Asp Asn Ser 75	Lys Asn	Thr Leu Tyr 80
Leu Gin Met As	n Ser Leu 85	Arg Ala G	Diu Asp Thr 90	Ala Val	Tyr Tyr Cys 95

Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr				Seq L Asp			G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Tyr	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	GIn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr

					P08	4876	5D1 S	Seq L	isti	ng			
Leu Pro Pro 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	G n	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn Gy 385	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	GIn 420	Βn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His 435	Asn	His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 74 <211> 447 <212> PRT <213> Artit	ficia	al											
<220>													
<223> an a	rtifi	ci al	lys	syntł	nesi z	zed s	seque	ence					
	rtifi	ci al	ly s	synt i	nesi z	zed s	seque	ence					
<223> an ai									Val	Lys	Pr o	Ser 15	Gu
<223> an ai <400> 74 Gin Val Gin	Leu	G n 5	Gu	Ser	Gу	Pr o	G y 10	Leu		-			
<223> an ai <400> 74 G n Val G n 1 Thr Leu Ser	Leu Leu	G n 5 Thr	Giu Cys	Ser Al a	G y Val	Pr o Ser 25	G y 10 G y	Leu His	Ser	lle	Ser 30	15 His	Asp
<223> an ai <400> 74 G n Val G n 1 Thr Leu Ser His Al a Trp	Leu 20 Ser	G n 5 Thr Tr p	G u Cys Val	Ser Al a Ar g	G y Val G n 40	Pr o Ser 25 Pr o	Giy 10 Giy Pro	Leu His Giy	Ser G u	IIe Gy 45	Ser 30 Leu	15 His Giu	Asp Tr p
<223> an ai <400> 74 G n Val G n 1 Thr Leu Ser His Ala Trp 35	Leu 20 Ser II e	G n 5 Thr Tr p Ser	G u Cys Val Tyr	Ser Al a Ar g Ser 55	G y Val G n 40 G y	Pr o Ser 25 Pr o I I e	G y 10 G y Pr o Thr	Leu His Giy Asn	Ser G u Tyr 60	IIe Gy 45 Asn	Ser 30 Leu Pr o	15 His Giu	Asp Trp Leu
<223> an ai <400> 74 G n Val G n 1 Thr Leu Ser His Al a Trp 35 Ile G y Phe 50 Phe	Leu 20 Ser IIe Val	Gin Thr Trp Ser Thr	Giu Cys Val Tyr IIe 70	Ser Al a Ar g Ser 55 Ser	Giy Val Gin Giy Arg	Pr o Ser 25 Pr o II e Asp	Giy Giy Pro Thr Asn	Leu His Giy Asn Ser 75	Ser G u Tyr 60 Lys	IIe Giy 45 Asn Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu Tyr

Thr	Leu	Val 115	Thr	Val	Ser	Ser	P08 Al a 120	4876 Ser	D1 S Thr	Geq L Lys	isti Giy	ng Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Ala	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	GIn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	GIn	Pr o 345	Ar g	Gu	Pr o	GIn	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gin	Val 365	Ser	Leu	Thr

P084876D1 Seq Listin	ıg												
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala N 370 375 380	Val Gu Trp Gu												
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr F	Pro Pro Val Leu												
385 390 395	400												
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu 7	Thr Val Asp Lys												
405 410	415												
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser V	Val Met His Giu												
420 425	430												
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser L	Leu Ser Pro												
435 440	445												
<210> 75 <211> 447 <212> PRT <213> Artificial													
<220> <223> an artificially synthesized sequence													
<400> 75													
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val L	Lys Pro Ser Giu												
1 5 10	15												
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser I	lle Ser His Asp												
20 25	30												
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu C	Gly Leu Glu Trp												
35 40 2	45												
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr A 50 55 60	Asn Pro Ser Leu												
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys A	Asn Thr Leu Tyr												
65 70 75	80												
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala N	Val Tyr Tyr Cys												
85 90	95												
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr 1	Trp Gy Gu Gy												
100 105	110												
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly F	Pro Ser Val Phe												
115 120 1	125												

	.eu Ala 30	Pro	Ser	Ser	Lys 135				Seq L Gy			Al a	Al a	Leu
GyC 145	ys Leı	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn S	Ser Giy	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Ala	Val 175	Leu
GnS	Ser Ser	G y 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser S	Ser Leu 195		Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
	sn Thr 10	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr H 225	lis Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Tyr	Leu	Gу	Gу	Asp 240
Ser V	al Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg T	ħr Pro	G u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro G	alu Val 275		Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
	ys Thr 90	Lys	Pr o	Ar g	G u 295	Gu	Gin	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val S 305	Ser Val	Leu	Thr	Val 310	Leu	Hi s	Gin	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr L	ys Cys	Lys	Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr I	le Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu P	Pro Pro 355		Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
	eu Val 70	Lys	Яу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu

			P084876	6D1 Seq I	_isting									
Ser Asn G y 385	Gin Pro	GuAsn 390	Asn Tyr	Lys Thr 395		o Pro Val	Leu 400							
Asp Ser Asp	Giy Ser 405	Phe Phe	Leu Tyr	Ser Lys 410	Leu Th	Val Asp 415	Lys							
Ser Arg Trp	Gin Gin 420	Giy Asn	Val Phe 425	Ser Cys	Ser Va	Met His 430	Gu							
Ala Leu His 435	Asn His	Tyr Thr	Gin Giu 440	Ser Leu	Ser Le 44									
<210> 76 <211> 447 <212> PRT <213> Artificial														
<220> <223> an ai	rtificia	lly synt	hesi zed	sequence										
<400> 76														
Gin Val Gin 1	Leu Gin 5	G u Ser	Giy Pro	G y Leu 10	Val Ly:	s Pro Ser 15	Gu							
Thr Leu Ser	Leu Thr 20	Cys Ala	Val Ser 25	Giy His	Ser II	e Ser His 30	Asp							
His Ala Trp 35	Ser Trp	Val Arg	Gin Pro 40	Pro Giy	GuG 45	/LeuGu	Tr p							
lle Gly Phe 50	lle Ser	Tyr Ser 55	Giy Ile	Thr Asn	Tyr As 60	n Pro Ser	Leu							
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg Asp	Asn Ser 75	Lys As	ו Thr Leu	Tyr 80							
Leu Gin Met	Asn Ser 85	Leu Arg	Ala Giu	Asp Thr 90	Ala Val	Tyr Tyr 95	Cys							
Ala Arg Ser	Leu Ala 100	Arg Thr	Thr Ala 105	Met Asp	Tyr Tr	o Gly Glu 110	Gу							
Thr Leu Val 115	Thr Val	Ser Ser	Ala Ser 120	Thr Lys	Giy Pro 12		Phe							
Pro Leu Ala 130	Pro Ser	Ser Lys 135	Ser Thr	Ser Giy	G y Thi 140	[.] Ala Ala	Leu							

GyCysLe 145	u Val Lys	Asp Tyr 150	P084 Phe I	4876D1 Pro G	Seq L u Pro 155	isti Val	ng Thr	Val	Ser	Tr p 160
Asn Ser G	y Ala Leu 165		Gу	Val Hi 17	s Thr 0	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Se	er Gly Leu 180	ı Tyr Ser		Ser Se 185	r Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Le 19		Gin Thr	Tyr I 200	lle Cy	s Asn	Val	Asn 205	Hi s	Lys	Pr o
Ser Asn Th 210	ır Lys Val	Asp Lys 215		Val G	u Pro	Lys 220	Ser	Cys	Asp	Lys
Thr His Th 225	ır Cys Pro	Pro Cys 230	Prov	Ala Pr	o Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val Ph	ie Leu Phe 245		Lys I	ProLy 25		Thr	Leu	Met	e 255	Ser
Arg Thr Pr	o Giu Val 260	Thr Cys		Val Va 265	l Asp	Val	Ser	His 270	Gu	Asp
Pro Giu Va 27		e Asn Trp	Tyr 280	Val As	р G у	Val	G u 285	Val	His	Asn
Ala Lys Tr 290	ır Lys Pro	Arg Clu 295		Gin As	p Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Va 305	I Leu Thr	Val Leu 310	His (Gin As	p Trp 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cy	s Lys Val 325		Lys /	Ala Le 33		Lys	Pr o	lle	G u 335	Lys
Thr Ile Se	er Lys Ala 340	ıLys Giy		Pro Ar 345	gGu	Pr o	Gη	Val 350	Tyr	Thr
Leu Pro Pr 35		IAsp Giu	Leu ⁻ 360	Thr Ly	s Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu Va 370	l Lys Giy	Phe Tyr 375		Ser As	p IIe	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G 385	y Gin Pro	9 Giu Asn 390	Asn ⁻	Tyr Ly	s Thr 395	Thr	Pr o	Pr o	Val	Leu 400
				Π.	- 101					

			P084876	6D1 Seq l	_istin	ıg								
Asp Ser Asp	Giy Ser 405	Phe Phe	Leu Tyr	Ser Lys 410	Leu -	Thr Val	Asp 415	Lys						
Ser Arg Trp	Gin Gin 420	Giy Asn	Val Phe 425		Ser \	Val Met 430	His	Gu						
Ala Leu His 435	Asn His	Tyr Thr	GnGu 440	Ser Leu		Leu Ser 445	Pr o							
<210> 77 <211> 447 <212> PRT <213> Artificial														
<220> <223> an artificially synthesized sequence														
<400> 77														
Gin Val Gin 1	Leu Gin 5	G u Ser	Giy Pro	G y Leu 10	Val I	Lys Pro	Ser 15	Gu						
Thr Leu Ser	Leu Thr 20	Cys Ala	Val Ser 25	Giy His	Ser I	lle Ser 30	His	Asp						
His Ala Trp 35	Ser Trp	Val Arg	Gin Pro 40	Pro Giy		G y Leu 45	Gu	Tr p						
lle Gly Phe 50	lle Ser	Tyr Ser 55	Giyille	Thr Asn	Tyr # 60	Asn Pro	Ser	Leu						
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg Asp	Asn Ser 75	Lys /	Asn Thr	Leu	Tyr 80						
Leu Gin Met	Asn Ser 85	Leu Arg	Ala Giu	Asp Thr 90	Ala	Val Tyr	Tyr 95	Cys						
Ala Arg Ser	Leu Ala 100	Arg Thr	Thr Ala 105	Met Asp	Tyr ⁻	Trp Gly 110	Gu	Gу						
Thr Leu Val 115	Thr Val	Ser Ser	Ala Ser 120	Thr Lys		Pro Ser 125	Val	Phe						
Pro Leu Ala 130	Pro Ser	Ser Lys 135	Ser Thr	Ser Giy	G y ⁻ 140	Thr Ala	Ala	Leu						
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe Pro	Giu Pro 155	Val ⁻	Thr Val	Ser	Tr p 160						

Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Р08 G у	4876 Val	6D1 S His 170				Al a	Val 175	Leu
GIn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gи	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Met 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	GIn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys

P084876D1 Seq Listing														
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His 420 425 430	Gu													
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445														
<210> 78 <211> 447 <212> PRT <213> Artificial														
<220> <223> an artificially synthesized sequence														
<400> 78														
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser 1 5 10 15	Gu													
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His 20 25 30	Asp													
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu 35 40 45	Tr p													
lle Giy Phe Ile Ser Tyr Ser Ciy Ile Thr Asn Tyr Asn Pro Ser 50 55 60	Leu													
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu 65 70 75	Tyr 80													
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr 85 90 95	Cys													
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu 100 105 110	Яу													
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val 115 120 125	Phe													
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala 130 135 140	Leu													
Giy Cys Leu Val Lys Asp Tyr Phe Pro Giu Pro Val Thr Val Ser 145 150 155	Tr p 160													
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val 165 170 175	Leu													

G n	Ser	Ser	GIy 180	Leu	Tyr	Ser				Seq L Val			Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Яу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gin	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	Hi s	Gin	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	Gin	Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gin	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Gгу	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser	Ar g	Tr p	GIn 420	Gn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu

Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro <210> <211> <212> PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp His Ala Trp Ser Trp Val Arg Gn Pro Pro Gy Gu Gy Leu Gu Trp lle Gly Phe Ile Ser Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser Leu Gin Giy Arg Val Thr IIe Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gy Gu Gy Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys G y Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu Gy Cys Leu Val Lys Asp Tyr Phe Pro G u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

P084876D1 Seq Listing

Ser Ser	Leu 195	Giy	Thr	Βn	Thr				Beq L Asn			His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr		G u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr Ile	Ser	Lys 340	Al a	Lys	Gу	Βn	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr
Leu Pro	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Βn	Val 365	Ser	Leu	Thr
Cys Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn 385	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg		GIn 420	Gη	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu	His 435	Asn	His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	

		P084	4876D1 S	Seq Listi	ng					
<210> 80 <211> 447 <212> PRT <213> Artific	i al									
<220> <223> an artificially synthesized sequence										
<400> 80										
Gin Val Gin Le 1	u Gin Giu 5	Ser Giy	Pro Giy 10	Leu Val	Lys Pro	Ser Giu 15				
Thr Leu Ser Le 20			Ser Giy 25	His Ser	IIe Ser 30	His Asp				
His Ala Trp Se 35	r Trp Val	Arg Gin 40	Pro Pro	Gy Gu	G y Leu 45	Gu Trp				
lle Gly Phe II 50	e Ser Tyr	Ser Giy 55	lle Thr	Asn Tyr 60	Asn Pro	Ser Leu				
Gin Giy Arg Va 65	I Thr IIe 70	Ser Arg	Asp Asn	Ser Lys 75	Asn Thr	Leu Tyr 80				
Leu Gin Met As	n Ser Leu 85	Arg Ala	Giu Asp 90	Thr Ala	Val Tyr	Tyr Cys 95				
Ala Arg Ser Le 10			Ala Met 105	Asp Tyr	Trp Giy 110	GuGy				
Thr Leu Val Ti 115	r Val Ser	Ser Ala 120	Ser Thr	Lys Gy	ProSer 125	Val Phe				
Pro Leu Ala Pr 130	o Ser Ser	Lys Ser 135	Thr Ser	Gy Gy 140	Thr Ala	Ala Leu				
Giy Cys Leu Va 145	I Lys Asp 150	Tyr Phe	Pro Giu	Pro Val 155	Thr Val	Ser Trp 160				
Asn Ser G y Al	a Leu Thr 165	Ser Giy	Val His 170	Thr Phe	Pro Ala	Val Leu 175				
Gin Ser Ser Gi 18	· ·		Ser Ser 185	Val Val	Thr Val 190	Pro Ser				
Ser Ser Leu G 195	y Thr Gin	Thr Tyr 200	lle Cys	Asn Val	Asn His 205	Lys Pro				

Ser As 21		Lys	Val	Asp	Lys 215				Seq L Pro			Cys	Asp	Lys
Thr Hi 225	s Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Gу	Gу	Asp 240
Ser Va	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Th	r Pro	G u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Gi	u Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Ly 29		Lys	Pr o	Ar g	G u 295	Gu	Gin	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Se 305	r Val	Leu	Thr	Val 310	Leu	His	Gin	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Ly	s Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr II	e Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu Pr	o Pro 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	G n	Val 365	Ser	Leu	Thr
Cys Le 37		Lys	Яу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser As 385	n Giy	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Se	r Asp	Gу	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Ar	g Trp	GIn 420	Gn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Le	u His 435	Asn	His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> <211> <212>	81 447 PRT							Paga	120					

	.1	P084876D1 S	Seq Listing	
<213> Artificia	1			
<220> <223> an artifi	cially synth	nesized seque	ence	
<400> 81				
Gin Val Gin Leu 1	Gin Giu Ser 5	GyProGy 10	Leu Val Lys	Pro Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser G y 25	His Ser IIe	Ser His Asp 30
His Ala Trp Ser 35		Gin Pro Pro 40	GyGuGy 45	Leu G u Trp
lle Giy Phe lle 50	Ser Tyr Ser 55	Giy IIe Thr	Asn Tyr Asn 60	Pro Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys Asn 75	Thr Leu Tyr 80
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu Asp 90	Thr Ala Val	Tyr Tyr Cys 95
Ala Arg Ser Leu 100	Ala Arg Thr	Thr Ala Met 105	Asp Tyr Trp	G y G u G y 110
Thr Leu Val Thr 115		Ala Ser Thr 120	Lys Giy Pro 125	Ser Val Phe
Pro Leu Ala Pro 130	Ser Ser Lys 135	Ser Thr Ser	GyGyThr 140	Ala Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr 150	Phe Pro Gu	Pro Val Thr 155	Val Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser 165	Giy Val His 170	Thr Phe Pro	Ala Val Leu 175
Gin Ser Ser Giy 180	Leu Tyr Ser	Leu Ser Ser 185	Val Val Thr	Val Pro Ser 190
Ser Ser Leu Giy 195		Tyr lle Cys 200	Asn Val Asn 205	His Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys 215	Lys Val Gu	Pro Lys Ser 220	Cys Asp Lys

P084876D1 Seq Listing Thr His Thr Cys Pro Pro Cys Pro Ala Pro Giu Tyr Leu Giy Giy Asp 225 230 235 240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe Ser 245 250 255
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His Giu Asp 260 265 270
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285
Ala Lys Thr Lys Pro Arg Gu Gu Gin Tyr Asn Ser Thr Tyr Arg Val 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380
Ser Asn G y G n Pro G u Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 82 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence Page 141

	P084876D1 Seq Listing										
<400> 82											
Gin Val Gin Leu 1	Gin Giu Ser 5	Giy Pro Gi 10	A .	ys Pro Ser Giu 15							
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser G 25	aly His Ser I	le Ser His Asp 30							
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pi 40		aly Leu Giu Trp 5							
lle Giy Phe Ile 50	Ser Tyr Ser 55	Gylle T	hr Asn Tyr A 60	sn Pro Ser Leu							
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp As	sn Ser Lys A 75	sn Thr Leu Tyr 80							
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu As 90		′al Tyr Tyr Cys 95							
Ala Arg Ser Leu 100	Ala Arg Thr	Thr Ala M 105	/et Asp Tyr T	rp Gly Glu Gly 110							
Thr Leu Val Thr 115	Val Ser Ser	Ala Ser Ti 120		ro Ser Val Phe 25							
Pro Leu Ala Pro 130	Ser Ser Lys 135		er Gy Gy T 140	ĥr Ala Ala Leu							
G y Cys Leu Val 145	Lys Asp Tyr 150	Phe Pro G	au Pro Val T 155	hr Val Ser Trp 160							
Asn Ser Giy Ala	Leu Thr Ser 165		lis Thr Phe P 70	ro Ala Val Leu 175							
Gin Ser Ser Giy 180	Leu Tyr Ser	Leu Ser Se 185	er Val Val T	hr Val Pro Ser 190							
Ser Ser Leu Giy 195	Thr Gin Thr	Tyr lle C 200		usn His Lys Pro 105							
Ser Asn Thr Lys 210	Val Asp Lys 215		lu Pro Lys S 220	er Cys Asp Lys							
Thr His Thr Cys 225	Pro Pro Cys 230	Pro Ala Pi	ro G u Leu L 235	eu Giy Asp Asp 240							

P084876D1 Seq Listing Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe 245 250 250	Ser
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His Giu 260 265 270	Asp
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His 275 280 285	Asn
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg 290 295 300	Val
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys 305 310 315	G u 320
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Ala Pro Ile Giu 325 330 335	Lys
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr 340 345 350	Thr
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu 355 360 365	Thr
Cys Leu Val Lys G y Phe Tyr Pro Ser Asp Ile Ala Val G u Trp 370 375 380	Gu
	Leu 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp 405 410 415	Lys
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His 420 425 430	Gu
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Pro 435 440 445	
<210> 83 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 83	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Page 143	Gu

1	5	P084876D1 \$ 10	Seq Listing	15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser Giy 25	His Ser Ile	Ser His Asp 30
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40	GyGuGy 45	Leu G u Trp
lle Giy Phe lle 50	Ser Tyr Ser 55	Giy Ile Thr	Asn Tyr Asn 60	Pro Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys Asn 75	Thr Leu Tyr 80
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu Asp 90	Thr Ala Val	Tyr Tyr Cys 95
Ala Arg Ser Leu 100	-	Thr Ala Met 105	Asp Tyr Trp	GyGuGy 110
Thr Leu Val Thr 115	Val Ser Ser	Ala Ser Thr 120	Lys Giy Pro 125	Ser Val Phe
Pro Leu Ala Pro 130	Ser Ser Lys 135		GyGyThr 140	Ala Ala Leu
Gy Cys Leu Val 145	Lys Asp Tyr 150	Phe Pro Gu	ProVal Thr 155	Val Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser 165	Giy Val His 170	Thr Phe Pro	Ala Val Leu 175
Gin Ser Ser Giy 180		Leu Ser Ser 185	Val Val Thr	Val Pro Ser 190
Ser Ser Leu Gly 195	Thr G n Thr	Tyr lle Cys 200	Asn Val Asn 205	His Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys 215		Pro Lys Ser 220	Cys Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230	Pro Ala Pro	G u Tyr Leu 235	Giy Asp Asp 240
Ser Val Phe Leu	Phe Pro Pro 245	Lys Pro Lys 250		Met IIe Ser 255

P084876D1 Seq Listing Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His Giu Asp 260 265 270
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg Val 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380
Ser Asn Gly Gin Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 84 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 84
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp Page 145

	20		P08487 25	'6D1 Seq	Listi	ng	30		
His Ala Trp 35	Ser Trp '	Val Arg	Gin Pro 40	o Pro Gi	y Giu	G y 45	Leu	Gu	Tr p
lle Gy Phe 50	lle Ser	Tyr Ser 55	Giyilie	e Thr As	n Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy Arg 65		lle Ser 70	Arg Asp	o Asn Se 75		Asn	Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser I 85	Leu Arg	AlaGu	u Asp Th 90	r Ala	Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala / 100	Arg Thr	Thr Al a 10		p Tyr	Tr p	G y 110	Gu	Gу
Thr Leu Val 115	Thr Val S	Ser Ser	Ala Sei 120	^r Thr Ly	s Giy	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser S	Ser Lys 135	Ser Th	^r Ser G	y G y 140	Thr	Al a	Al a	Leu
G y Cys Leu 145		Asp Tyr 150	Phe Pro	o Giu Pr 15		Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Ser	Giy Val	His Th 170	r Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	Giy Leu 180	Tyr Ser	Leu Ser 18		I Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr (G n Thr	Tyr II e 200	e Cys As	n Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val <i>i</i>	Asp Lys 215	Lys Val	Giu Pr	o Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	Pro Ala	a Pro Gi 23		Leu	Gу	Asp	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro	Lys Pro	o Lys As 250	p Thr	Leu	Met	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys	Val Val 26		p Val	Ser	His 270	Gu	Asp

P084876D1 Seq Listing Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285
Ala Lys Thr Lys Pro Arg Ciu Ciu Cin Tyr Asn Ser Thr Tyr Arg Val 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Ala Pro Ile Glu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 85 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 85
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp Page 147

	35				P08 40	4876	5D1 S	Seq L	ng 45				
lle Giy 50	Phe II	e Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy 65	Arg Va	Thr	∣e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin	Met As	n Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	Ser Le 10		Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val Th 115	^r Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Ala Pr	o Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gly Cys 145	Leu Va	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	GIY AI	a Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser G 18		Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu G 195	y Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr Ly	s Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr Cy	s Pro	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Tyr	Leu	Gу	Asp	Asp 240
Ser Val	Phe Le	J Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pro Gi 26		Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val Ly 275	s Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn

P084876D1 Seq Listing Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg Val 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Lys Pro Ile Giu Lys 325 330 335
Thr IIe Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Aspille Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 86 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 86
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Gly Phe lle Ser Tyr Ser Gly lle Thr Asn Tyr Asn Pro Ser Leu Page 149

	50					55	P08	4876	D1 S	Seq L	isti 60	ng			
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Ala	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Ala	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Ala	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Gу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pr o	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val

Val Ser Val 305	Leu Th	nr Val 310	Leu				Seq L Trp 315			Яу	Lys	G u 320
Tyr Lys Cys	Lys Va 32		Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr IIe Ser	Lys Al 340	a Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu Pro Pro 355	Ser Ar	g Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys G	y Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn Giy 385	Gin Pr	o G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy Se 4(Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	G n G 420	n Giy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	Hi s	Gu
Ala Leu His 435	Asn Hi	s Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 87 <211> 447 <212> PRT <213> Artif	icial											
<220> <223> an ar	tifici	ally	syntł	nesi z	zed s	seque	ence					
<400> 87												
Gin Val Gin 1	Leu G 5	n Giu	Ser	Gу	Pr o	С у 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu Ser	Leu Th 20	nr Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala Trp 35	Ser Tr	p Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle Gly Phe 50	lle Se	er Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy Arg	Val Tr	nr Ile	Ser	Ar g		Asn Page		Lys	Asn	Thr	Leu	Tyr

65	P0)84876D1 Seq L 75	isting.	80
Leu Gin Met Asn Ser 85	Leu Arg Ala	a Giu Asp Thr 90		Tyr Cys 95
Ala Arg Ser Leu Ala 100	Arg Thr Thi	r Ala Met Asp 105	Tyr Trp Giy 110	Gu Gy
Thr Leu Val Thr Val 115	Ser Ser Al a 120		Giy Pro Ser 125	Val Phe
Pro Leu Ala Pro Ser 130	Ser Lys Ser 135	r Thr Ser Cly	Giy Thr Ala 140	Ala Leu
G y Cys Leu Val Lys 145	Asp Tyr Pho 150	e Pro Giu Pro 155	Val Thr Val	Ser Trp 160
Asn Ser Giy Ala Leu 165	Thr Ser Giy	y Val His Thr 170		Val Leu 175
Gin Ser Ser Giy Leu 180	Tyr Ser Lei	u Ser Ser Val 185	Val Thr Val 190	Pro Ser
Ser Ser Leu Gly Thr 195	Gin Thri Tyr 200		Val Asn His 205	Lys Pro
Ser Asn Thr Lys Val 210	Asp Lys Lys 215	s Val Giu Pro	Lys Ser Cys / 220	Asp Lys
Thr His Thr Cys Pro 225	Pro Cys Pro 230	o Ala Pro Asp 235	Tyr Leu Giy ,	Asp Asp 240
Ser Val Phe Leu Phe 245	Pro Pro Lys	s Pro Lys Asp 250		IIe Ser 255
Arg Thr Pro Giu Val 260	Thr Cys Val	Val Val Asp 265	Val Ser His 270	Gu Asp
Pro Giu Val Lys Phe 275	Asn Trp Tyr 28(•	Val G u Val 285	His Asn
Ala Lys Thr Lys Pro 290	Arg Giu Giu 295	u Cin Asp Asn	Ser Thr Tyr 7 300	Arg Val
Val Ser Val Leu Thr 305	Val Leu His 310	s Gin Asp Trp 315	Leu Asn G y I	Lys Gu 320

Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Lys Pro Ile Giu Lys 325 330 335	
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350	
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365	
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380	
Ser Asn Gly Gin Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 88 <211> 447 <212> PRT <213> Artificial	
<220>	
<223> an artificially synthesized sequence	
<223> an artificially synthesized sequence <400> 88	
<400> 88 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu	
<400> 88 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser IIe Ser His Asp	
<400> 88 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 Thr Leu Ser Leu Thr Cys Alia Val Ser Giy His Ser II e Ser His Asp 20 His Alia Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp	
<400> 88 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu Thr Leu Ser Leu Thr Cys Alia Val Ser Giy His Ser II e Ser His Asp 20 His Alia Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp II e Giy Phe II e Ser Tyr Ser Giy II e Thr Asn Tyr Asn Pro Ser Leu	

	85	P084876D1 Sec 90	q Listing	95
Ala Arg Ser Leu 100	Ala Arg Thr	Thr Ala Met A 105	Asp Tyr Trp Gly 110	GuGy
Thr Leu Val Thr 115	Val Ser Ser	Ala Ser Thr L 120	ys Gly Pro Ser. 125	Val Phe
Pro Leu Ala Pro 130	Ser Ser Lys 135		Hy Gly Thr Ala 140	Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr 150		Pro Val Thr Val 55	Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser 165	Giy Val His T 170	Thr Phe Pro Ala	Val Leu 175
Gin Ser Ser Giy 180	Leu Tyr Ser	Leu Ser Ser V 185	/al Val Thr Val 190	Pro Ser
Ser Ser Leu Giy 195	Thr G n Thr	Tyr lle Cys A 200	Asn Val Asn His 205	Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys 215		Pro Lys Ser Cys 220	Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230		∃u Tyr Leu Giy 235	Asp Asp 240
Ser Val Phe Leu	Phe Pro Pro 245	Lys Pro Lys A 250	Asp Thr Leu Met	lle Ser 255
Arg Thr Pro Giu 260	Val Thr Cys	Val Val Val A 265	Asp Val Ser His 270	Gu Asp
Pro Giu Val Lys 275	Phe Asn Trp	Tyr Val Asp G 280	Biy Val Giu Val 285	His Asn
Ala Lys Thr Lys 290	Pro Arg Giu 295		Asn Ser Thr Tyr 300	Arg Val
Val Ser Val Leu 305	Thr Val Leu 310		Trp Leu Asn Gly 315	Lys Giu 320
Tyr Lys Cys Lys	Val Ser Asn 325	Ala Ala Leu P 330	Pro Arg Pro Ile	G u Lys 335

Thr IIe Ser	Lys 340	Al a	Lys	Gу	P08 G n	4876 Pr o 345	D1 S Arg	ieq L Giu	isti Pro	ng G n	Val 350	Tyr	Thr
Leu Pro Pro 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G y 385	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Gу	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	GIn 420	G n	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	Hi s	Gu
Ala Leu His 435	Asn	Hi s	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 89 <211> 447 <212> PRT <213> Arti	ficia	al											
<220> <223> an ai	rtifi	ci al	ly s	synt l	nesi z	zed s	seque	ence					
	rtifi	ci al	ly s	synt i	nesi z	zed s	seque	ence					
<223> an a									Val	Lys	Pr o	Ser 15	Gu
<223> an a <400> 89 Gin Val Gin	Leu	G n 5	Gu	Ser	Gу	Pr o	G y 10	Leu		-		15	
<223> an a <400> 89 Gin Val Gin 1	Leu Leu 20	G n 5 Thr	Giu Cys	Ser Al a	G y Val	Pr o Ser 25	Gy 10 Gy	Leu His	Ser	lle	Ser 30	15 His	Asp
<223> an a <400> 89 G n Val G n 1 Thr Leu Ser His Ala Trp	Leu 20 Ser	G n 5 Thr Tr p	G u Cys Val	Ser Al a Ar g	G y Val G n 40	Pr o Ser 25 Pr o	Giy 10 Giy Pro	Leu His Giy	Ser G u	IIe Gy 45	Ser 30 Leu	15 His Giu	Asp Tr p
<223> an ai <400> 89 G n Val G n 1 Thr Leu Ser His Al a Trp 35	Leu 20 Ser	G n 5 Thr Tr p Ser	G u Cys Val Tyr	Ser Al a Ar g Ser 55	G y Val G n 40 G y	Pr o Ser 25 Pr o I I e	G y G y Pr o Thr	Leu His Gy Asn	Ser G u Tyr 60	IIe Gy 45 Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu
<223> an al <400> 89 G n Val G n 1 Thr Leu Ser His Al a Trp 35 Ile G y Phe 50 Phe	Leu 20 Ser IIe Val	Gin Thr Trp Ser Thr	Giu Cys Val Tyr IIe 70	Ser Al a Ar g Ser 55 Ser	Giy Val Gin Giy Arg	Pro Ser 25 Pro IIe Asp	Giy Giy Pro Thr Asn	Leu His Gy Asn Ser 75	Ser Giu Tyr 60 Lys	IIe Giy 45 Asn Asn	Ser 30 Leu Pr o Thr	15 His Giu Ser	Asp Trp Leu Tyr 80

	100	P08	34876D1 105	Seq Listi	ng	110		
Thr Leu Val 115	Thr Val Ser	Ser Ala 120		Lys Gy	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser Ser	Lys Ser 135	Thr Ser	GyGy 140	Thr	Ala	Al a	Leu
Gy Cys Leu 145	Val Lys Asp 150		Pro Giu	Pro Val 155	Thr	Val	Ser	Tr p 160
Asn Ser Gy	Ala Leu Thr 165	Ser Giy	Val His 170		Pr o		Val 175	Leu
Gin Ser Ser	G y Leu Tyr 180	Ser Leu	Ser Ser 185	Val Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Gly Thr Clr	i Thr Tyr 200	lle Cys	asn Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val Asp	Lys Lys 215	Val Giu	Pro Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro Pro 230		Ala Pro	Asp Tyr 235	Leu	Gу	Asp	Asp 240
Ser Val Phe	Leu Phe Pro 245	9 Pro Lys	Pro Lys 250		Leu		e 255	Ser
Arg Thr Pro	G u Val Thr 260	Cys Val	Val Val 265	Asp Val	Ser	His 270	Gu	Asp
Pro Giu Val 275	Lys Phe Asr	Trp Tyr 280		o Giy Val	G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro Arg	GuGu 295	Gin Tyr	Asn Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr Val 31(Gin Asp	Trp Leu 315	Asn	Gу	Lys	G u 320
Tyr Lys Cys	Lys Val Ser 325	Asn Ala	Ala Leu 330	Pro Arg	Pr o		G u 335	Lys
Thr IIe Ser	Lys Ala Lys 340	Gy Gin	Pro Arg 345	g Giu Pro	G n	Val 350	Tyr	Thr

Leu Pro	Pr o 355	Ser	Ar g	Asp	Gu					isti Gin		Ser	Leu	Thr
Cys Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn 385	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg	Tr p	GIn 420	Gn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu	His 435	Asn	His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<211> 4	90 147 PRT Artif	icia	al											
<220> <223> a	an ar	rtifi	ci al	lv s	svnt l	nesi z	zed s	seaue	ence					
				,	,									
<400> 9	90													
<400> 9 Gin Val 1		Leu	Gn 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
	G n		5			-		10			-			
Gin Val 1	G n Ser	Leu 20	5 Thr	Cys	Ala	Val	Ser 25	10 G y	Hi s	Ser	lle	Ser 30	15 His	Asp
G n Val 1 Thr Leu	G n Ser Tr p 35	Leu 20 Ser	5 Thr Tr p	Cys Val	Al a Ar g	Val G n 40	Ser 25 Pr o	10 G y Pr o	His Giy	Ser Giu	IIe Gy 45	Ser 30 Leu	15 His Giu	Asp Tr p
Gin Val 1 Thr Leu His Ala Ile Giy	G n Ser Trp 35 Phe	Leu 20 Ser IIe	5 Thr Tr p Ser	Cys Val	Al a Ar g Ser 55	Val G n 40 G y	Ser 25 Pr o	10 G y Pr o Thr	His Giy Asn	Ser G u Tyr 60	IIe Giy 45 Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu
Gin Val 1 Thr Leu His Ala IIe Giy 50 Gin Giy	GIn Ser Trp 35 Phe Arg	Leu 20 Ser IIe Val	5 Thr Tr p Ser Thr	Cys Val Tyr IIe 70	Al a Ar g Ser 55 Ser	Val G n 40 G y Ar g	Ser 25 Pr o I I e Asp	10 G y Pr o Thr Asn	His Giy Asn Ser 75	Ser G u Tyr 60 Lys	IIe Gy 45 Asn Asn	Ser 30 Leu Pr o Thr	15 His Giu Ser	Asp Trp Leu Tyr 80
Gin Val Thr Leu His Ala IIe Giy Gin Giy 65	GIn Ser Trp 35 Phe Arg Met	Leu 20 Ser IIe Val Asn	5 Thr Tr p Ser Thr Ser 85	Cys Val Tyr IIe 70	Al a Ar g Ser 55 Ser Ar g	Val G n 40 G y Ar g Al a	Ser 25 Pro I I e Asp Gi u	10 Giy Pro Thr Asn Asp 90	His Giy Asn Ser 75 Thr	Ser Giu Tyr 60 Lys Ala	II e Giy 45 Asn Asn Val	Ser 30 Leu Pr o Thr Tyr	15 His Giu Ser Leu Tyr 95	Asp Trp Leu Tyr 80 Cys

	115			P08 120	4876	6D1 S	Seq L	isti.	ng 125			
Pro Leu 130	Ala Pro	Ser Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Ala	Leu
Giy Cys 145	Leu Val	Lys Asp 150		Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Giy Ala	Leu Thr 165	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser Giy 180	Leu Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu Giy 195	Thr Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr Lys	Val Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr Cys	Pro Pro 230		Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Яу	Asp	Asp 240
Ser Val	Phe Leu	Phe Pro 245	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pro Giu 260	Val Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val Lys 275	Phe Asn	Tr p	Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr Lys	Pro Arg	G u 295	Gu	Gin	Asp	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val Leu	Thr Val 310		His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys Lys	Val Ser 325	Asn	Al a	Ala	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys
Thr IIe	Ser Lys 340	Ala Lys	Яy	Gin	Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu Pro	ProSer 355	Arg Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr

P084876D1 Seq Listing Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 91 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 91
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Page 159

130		P08 135	84876D1		sting 140		
G y Cys Leu 145	Val Lys Asp 150	Tyr Phe	Pro Gi	u Pro' 155	Val Thr	Val Ser	Tr p 160
Asn Ser Gy	Ala Leu Thr 165	Ser Giy	Val Hi 17		Phe Pro	Ala Val 175	
Gin Ser Ser	G y Leu Tyr 180	Ser Leu	Ser Se 185	r Val '	Val Thr	Val Pro 190	Ser
Ser Ser Leu 195	Gly Thr Cln	Thr Tyr 200		s Asn '	Val Asn 205	His Lys	Pr o
Ser Asn Thr 210	Lys Val Asp	Lys Lys 215	Val G		Lys Ser 220	Cys Asp	Lys
Thr His Thr 225	Cys Pro Pro 230	Cys Pro	Ala Pr	o Asp 235	Leu Leu	Gy Gy	Asp 240
Ser Val Phe	Leu Phe Pro 245	Pro Lys	ProLy 25		Thr Leu	Met IIe 255	
Arg Thr Pro	Giu Val Thr 260	Cys Val	Val Va 265	l Asp '	Val Ser	His Giu 270	Asp
Pro Giu Val 275	Lys Phe Asn	Trp Tyr 280		pGy	Val Giu 285	Val His	Asn
Ala Lys Thr 290	Lys Pro Arg	G u G u 295	Gin Ty		Ser Thr 300	Tyr Arg	Val
Val Ser Val 305	Leu Thr Val 310	Leu His	Gin As	p Trp 315	Leu Asn	Gy Lys	G u 320
Tyr Lys Cys	Lys Val Ser 325	Asn Asp	Ala Le 33		Lys Pro	lle Giu 335	
Thr IIe Ser	Lys Ala Lys 340	Giy Gin	Pro Ar 345	g Giu I	Pro Gin	Val Tyr 350	Thr
Leu Pro Pro 355	Ser Arg Asp	G u Leu 360		s Asn (Gin Val 365	Ser Leu	Thr
Cys Leu Val 370	Lys G y Phe	Tyr Pro 375	Ser As		Ala Val 380	Gu Trp	Gu

Ser Asn Gy 385	Gin Pro	G u Asn 390		6D1 Seq I Lys Thr 395	Thr Pro	Pro Val	Leu 400
Asp Ser Asp	Giy Ser 405	Phe Phe	Leu Tyr	Ser Lys 410	Leu Thr	Val Asp 415	
Ser Arg Trp	Gin Gin 420	Giy Asn	Val Phe 425	Ser Cys	Ser Val	Met His 430	s Giu
Ala Leu His 435	Asn His	Tyr Thr	Gin Giu 440	Ser Leu	Ser Leu 445)
<210> 92 <211> 447 <212> PRT <213> Arti	ficial						
<220> <223> an a	rtificia	lly synt	hesi zed	sequence			
<400> 92							
Gin Val Gin 1	Leu Gin 5	G u Ser	Giy Pro	Gy Leu 10	Val Lys	Pro Ser 15	Gu
Thr Leu Ser	Leu Thr 20	Cys Ala	Val Ser 25	Giy His	Ser IIe	Ser His 30	s Asp
His Ala Trp 35	Ser Trp	Val Arg	Gin Pro 40	Pro Giy	GuGy 45	Leu Gi	ı Trp
lle Gy Phe 50	lle Ser	Tyr Ser 55	Giy IIe	Thr Asn	Tyr Asn 60	Pro Ser	Leu
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg Asp	Asn Ser 75	Lys Asn	Thr Leu	J Tyr 80
Leu Gin Met	Asn Ser 85	Leu Arg	Ala Giu	Asp Thr 90	Ala Val	Tyr Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg Thr	Thr Ala 105		Tyr Trp	GyGu 110	Яу
Thr Leu Val 115	Thr Val	Ser Ser	Ala Ser 120	Thr Lys	Giy Pro 125		Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 135		Ser Giy	G y Thr 140	Ala Ala	a Leu
G y Cys Leu	Val Lys	Asp Tyr	Phe Pro	G u Pro Page 161	Val Thr	Val Ser	Trp

145	P(150	084876D1 Seq 155		160
Asn Ser Gly Ala Leu 165		y Val His Thr 170	Phe Pro Ala	Val Leu 175
Gin Ser Ser Giy Leu 180	Tyr Ser Le	u Ser Ser Val 185	Val Thr Val 190	Pro Ser
Ser Ser Leu Giy Thr 195	Gin Thr Ty 20		Val Asn His 205	Lys Pro
Ser Asn Thr Lys Val 210	Asp Lys Ly 215	s Val Giu Pro	Lys Ser Cys 220	Asp Lys
Thr His Thr Cys Pro 225	Pro Cys Pr 230	o Ala Pro Asp 235		Asp Asp 240
Ser Val Phe Leu Phe 245		s Pro Lys Asp 250	Thr Leu Met	IIe Ser 255
Arg Thr Pro Giu Val 260	Thr Cys Va	l Val Val Asp 265	Val Ser His 270	Gu Asp
Giy Giu Val Lys Phe 275	Asn Trp Ty 28		Val Giu Val 285	His Asn
Ala Lys Thr Lys Pro 290	Arg Giu Gi 295	u Gin Tyr Asn	Ser Thr Tyr 300	Arg Val
Val Ser Val Leu Thr 305	Val Leu Hi 310	s Gin Asp Trp 315	Leu Asn G y	Lys Giu 320
Tyr Lys Cys Lys Val 325	Ser Asn As	p Ala Leu Pro 330	Lys Pro Ile	G u Lys 335
Thr IIe Ser Lys Ala 340	Lys Gly G	n Pro Arg Giu 345	Pro Gin Val 350	Tyr Thr
Leu Pro Pro Ser Arg 355	Asp G u Le 36		G n Val Ser 365	Leu Thr
Cys Leu Val Lys Gy 370	Phe Tyr Pr 375	o Ser Asp Ile	Ala Val Giu 380	Trp Giu
Ser Asn Giy Gin Pro 385	Giu Asn As 390	n Tyr Lys Thr 395		Val Leu 400

P084876D1 Seq Listing Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 93 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 93
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140
Giy Cys Leu Val Lys Asp Tyr Phe Pro Giu Pro Val Thr Val Ser Trp 145 150 155 160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Page 163

	165	P084876D1 S 170	eq Listing	175
Gin Ser Ser Giy 180		Leu Ser Ser 185	Val Val Thr Va 19	
Ser Ser Leu Giy 195	Thr Gin Thr	Tyr lle Cys 200	Asn Val Asn Hi 205	s Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys 215		Pro Lys Ser Cy 220	s Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230		Asp Leu Leu G 235	y Asp Asp 240
Ser Val Phe Leu	ı Phe Pro Pro 245	Lys Pro Lys 250	Asp Thr Leu Me	t IIe Ser 255
Arg Thr Pro Giu 260		Val Val Val 265	Asp Val Ser Hi 27	
GyGuValLys 275	Phe Asn Trp	Tyr Val Asp 280	Giy Val Giu Va 285	His Asn
Ala Lys Thr Lys 290	Pro Arg Giu 295		Asn Ser Thr Ty 300	r Arg Val
Val Ser Val Leu 305	ı Thr Val Leu 310	His Gin Asp	Trp Leu Asn G 315	y Lys Giu 320
Tyr Lys Cys Lys	: Val Ser Asn 325	Lys Ala Leu 330	Pro Lys Pro II	e Giu Lys 335
Thr IIe Ser Lys 340		Gin Pro Arg 345	Giu Pro Gin Va 35	
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360	Asn Gin Val Se 365	r Leu Thr
Cys Leu Val Lys 370	GyPheTyr 375		lle Ala Val G 380	u Trp Giu
Ser Asn G y G r 385	n Pro Giu Asn 390		Thr Thr Pro Pr 395	o Val Leu 400
Asp Ser Asp G	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu Thr Va	Asp Lys 415

P084876D1 Seq Listing Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 94 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 94
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Giy Pheille Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60
Gin Giy Arg Val Thr IIe Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140
G y Cys Leu Val Lys Asp Tyr Phe Pro G u Pro Val Thr Val Ser Trp 145 150 155 160
Asn Ser Giy Ala Leu Thr Ser Giy Val His Thr Phe Pro Ala Val Leu 165 170 175
Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Page 165

	180	P084876 185	iD1 Seq Listin	190 190
Ser Ser Leu 195	Gly Thr Cln	Thr Tyr IIe 200		Asn His Lys Pro 205
Ser Asn Thr 210	Lys Val Asp	Lys Lys Val 215	Giu Pro Lys S 220	Ser Cys Asp Lys
Thr His Thr 225	Cys Pro Pro 230	Cys Pro Ala	Pro Giu Leu L 235	∟eu Giy Asp Asp 240
Ser Val Phe	Leu Phe Pro 245	Pro Lys Pro	Lys Asp Thr L 250	∟eu Met IIe Ser 255
Arg Thr Pro	Glu Val Thr 260	Cys Val Val 265	Val Asp Val S	Ser His Clu Asp 270
GyGuVal 275	Lys Phe Asn	Trp Tyr Val 280		Giu Val His Asn 285
Ala Lys Thr 290	Lys Pro Arg	GuGuGn 295	Tyr Asn Ser 1 300	Thr Tyr Arg Val
Val Ser Val 305	Leu Thr Val 310	Leu His Gin	Asp Trp Leu A 315	Asn Ciy Lys Ciu 320
Tyr Lys Cys	Lys Val Ser 325	Asn Ala Ala	Leu Pro Lys F 330	Prolle Glu Lys 335
Thr IIe Ser	Lys Ala Lys 340	Gly Gin Pro 345	Arg Clu Pro (Gin Val Tyr Thr 350
Leu Pro Pro 355	Ser Arg Asp	G u Leu Thr 360		Val Ser Leu Thr 365
Cys Leu Val 370	Lys G y Phe	Tyr Pro Ser 375	Asp Ile Ala \ 380	Val Gu Trp Gu
Ser Asn G y 385	Gin Pro Giu 390	Asn Asn Tyr	Lys Thr Thr F 395	Pro Pro Val Leu 400
Asp Ser Asp	G y Ser Phe 405	Phe Leu Tyr	Ser Lys Leu 1 410	Thr Val Asp Lys 415
Ser Arg Trp	Gin Gin Giy 420	Asn Val Phe 425	Ser Cys Ser \	Val Met His Giu 430

P084876D1 Seq Listing Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445 <210> 95 <211> <212> 447 PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> 95 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45 Ile Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 60 Gin Giy Arg Val Thr IIe Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 65 80 70 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 90 95 85 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp G y G u G y 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu 130 135 140 G y Cys Leu Val Lys Asp Tyr Phe Pro G u Pro Val Thr Val Ser Trp 145 150 155 160 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 165 170 175 Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190 Ser Ser Leu Giy Thr Gin Thr Tyr Ile Cys Asn Val Asn His Lys Pro Page 167

195		P084876D1 200	1 Seq Listi	ng 205	
Ser Asn Thr Lys 210	Val Asp Lys 215	Lys Val G	alu Pro Lys 220	Ser Cys	Asp Lys
Thr His Thr Cys 225	Pro Pro Cys 230	Pro Ala P	ro Giu Leu 235	Leu Gy	Asp Asp 240
Ser Val Phe Leu	Phe Pro Pro 245		ys Asp Thr 50	Leu Met	IIe Ser 255
Arg Thr Pro Giu 260	Val Thr Cys	Val Val Va 265	al Asp Val	Ser His 270	Gu Asp
Giy Giu Val Lys 275	Phe Asn Trp	Tyr Val A 280	sp G y Val	G u Val 285	His Asn
Ala Lys Thr Lys 290	ProArgGu 295	Gu Gn T	yr Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val Leu 305	Thr Val Leu 310	His Gin Ad	sp Trp Leu 315	Asn Giy	Lys Gu 320
Tyr Lys Cys Lys	Val Ser Asn 325		eu Pro Lys 30	Pro IIe	Giu Lys 335
Thr Ile Ser Lys 340	Ala Lys Giy	Gin Pro A 345	rg Giu Pro	Gin Val 350	Tyr Thr
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Ly 360	ys Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val Lys 370	G y Phe Tyr 375	Pro Ser A	splle Ala 380	Val Giu	Trp Giu
Ser Asn Giy Gin 385	Pro Giu Asn 390	Asn Tyr Ly	ys Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp Giy	Ser Phe Phe 405		er Lys Leu 10	Thr Val	Asp Lys 415
Ser Arg Trp Gin 420	Gin Giy Asn	Val Phe S 425	er Cys Ser	Val Met 430	His Giu
Ala Leu His Asn 435	His Tyr Thr	Gin Giu So 440	er Leu Ser	Leu Ser 445	Pr o

					P08	4876	D1 S	Seq L	isti	ng			
<211> 4 <212> F	96 ∣47 PRT Artifi	ci al						·		0			
<220> <223> a	an art	ificial	ly s	ynt h	nesi z	ed s	eque	ence					
<400> 9	96												
Gin Val 1	GnL	.eu Gin 5	Gu	Ser	Gу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu		eu Thr 0	Cys	Ala	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala	Trp S 35	Ser Trp	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle Gy 50	Phe I	le Ser		Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy 65	Arg V	al Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G n	Met A	sn Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg		.eu Ala 00	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val T 115	hr Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Яy	Pr o 125	Ser	Val	Phe
Pro Leu 130	Ala P	Pro Ser		Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys 145	Leu V	′al Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	GуА	la Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser		aly Leu 80	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu G 195	bly Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn	Thr L	ys Val	Asp	Lys	Lys	Val	Gu	Pr o	Lys	Ser	Cys	Asp	Lys

210	P084876D1 Se 215	eq Listing 220
Thr His Thr Cys Pro Pro 225 230	,	Asp Leu Leu G y G y Asp 235 240
Ser Val Phe Leu Phe Pro	Pro Lys Pro Lys	Asp Thr Leu Met IIe Ser
245	250	255
Arg Thr Pro Giu Val Thr	Cys Val Val Val .	Asp Val Ser His Giu Asp
260	265	270
Giy Giu Val Lys Phe Asn	Trp Tyr Val Asp	Giy Val Giu Val His Asn
275	280	285
Ala Lys Thr Lys Pro Arg	GuGuGnTyr	Asn Ser Thr Tyr Arg Val
290	295	300
Val Ser Val Leu Thr Val 305 310		Trp Leu Asn Giy Lys Giu 315 320
Tyr Lys Cys Lys Val Ser	Asn Ala Ala Leu	Pro Lys Pro Ile Giu Lys
325	330	335
Thr Ile Ser Lys Ala Lys	Giy Cin Pro Arg	Giu Pro Gin Val Tyr Thr
340	345	350
Leu Pro Pro Ser Arg Asp	G u Leu Thr Lys .	Asn G n Val Ser Leu Thr
355	360	365
Cys Leu Val Lys G y Phe	Tyr Pro Ser Asp	lle Ala Val Giu Trp Giu
370	375	380
Ser Asn Giy Gin Pro Giu 385 390		Thr Thr Pro Pro Val Leu 395 400
Asp Ser Asp G y Ser Phe	Phe Leu Tyr Ser	Lys Leu Thr Val Asp Lys
405	410	415
Ser Arg Trp Gin Gin Giy	Asn Val Phe Ser	Cys Ser Val Met His Glu
420	425	430
Ala Leu His Asn His Tyr	Thr Gin Giu Ser	Leu Ser Leu Ser Pro
435	440	445
<210> 97 <211> 447 <212> PRT <213> Artificial	Paga	170

			P084	4876D1 S	Seq Li	sting			
<220> <223> an a	artificia	ally synt	hesi zo	ed seque	ence				
<400> 97									
Gin Val Gin 1	n Leu Gir 5	n Giu Ser	Gу	ProGiy 10	Leu \	Val Ly:	s Pro	Ser 15	Gu
Thr Leu Ser	Leu Thr 20	Cys Ala		Ser Giy 25	His	Ser II e	e Ser 30	His	Asp
His Ala Trp 35	o Ser Trp	o Val Arç	G n 40	Pro Pro	Gy(GuGy 45	/ Leu	Gu	Tr p
lle Gly Phe 50	elle Ser	Tyr Ser 55	Gу	lle Thr		Tyr Ası 60	ı Pro	Ser	Leu
Gin Giy Arg 65	y Val Thr	lle Ser 70	Arg <i>i</i>	Asp Asn	Ser L 75	Lys Ası	ו Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu Arg	Ala	Giu Asp 90	Thr A	Ala Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	a Arg Thr		Ala Met 105	Asp ⊺	Tyr Trj	9 G y 110	Gu	Gу
Thr Leu Val 11		Ser Ser	Al a 3 120	Ser Thr	Lys (Giy Pro 12		Val	Phe
Pro Leu Ala 130	a Pro Ser	Ser Lys 135	Ser	Thr Ser		Gly Thi 140	Al a	Al a	Leu
G y Cys Leu 145	ı Val Lys	Asp Tyr 150	Phe	Pro Giu	Pro \ 155	Val Thi	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165		Gу	Val His 170	Thr F	Phe Pro	Ala	Val 175	Leu
Gin Ser Ser	Gly Leu 180	ı Tyr Ser		Ser Ser 185	Val N	Val Thi	Val 190	Pr o	Ser
Ser Ser Leu 195		G n Thr	Tyr 200	lle Cys	Asn \	Val Ası 20	h His 5	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		Val Giu		Lys Sei 220	Cys	Asp	Lys
Thr His Thr	Cys Pro) Pro Cys	Pro	Ala Pro Page	-	Leu Lei	ЧĠу	Яу	Asp

P084876D1 Seq Listing

225	230	P084876D1 Seq L 235	_isting	240
Ser Val Phe Leu Phe 245		ys Pro Lys Asp. 250	Thr Leu Met IIe 255	Ser
Arg Thr Pro Giu Val 260	Thr Cys V	/al Val Val Asp 265	Val Ser His Giu 270	Asp
Gy Gu Val Lys Phe 275		Fyr Val Asp Gly 280	Val Giu Val His 285	Asn
Ala Lys Thr Lys Pro 290	Arg Clu C 295	Giu Gin Asp Asn	Ser Thr Tyr Arg 300	Val
Val Ser Val Leu Thr 305	Val Leu H 310	His Gin Asp Trp 315	Leu Asn G y Lys	G u 320
Tyr Lys Cys Lys Val 325		ys Ala Leu Pro. 330	Lys Prolle Giu 335	Lys
Thr IIe Ser Lys Ala 340	Lys Gly C	Gin Pro Arg Giu 345	Pro Gin Val Tyr 350	Thr
Leu Pro Pro Ser Arg 355	Asp Giu L 3	_eu Thr Lys Asn 360	Gin Val Ser Leu 365	Thr
Cys Leu Val Lys Gy 370	Phe Tyr P 375	Pro Ser Asp Ile	Ala Val Giu Trp 380	Gu
Ser Asn Gly Gin Pro 385	Giu Asn A 390	Asn Tyr Lys Thr 395	Thr Pro Pro Val	Leu 400
Asp Ser Asp G y Ser 405		eu Tyr Ser Lys_ 410	Leu Thr Val Asp 415	Lys
Ser Arg Trp Gin Gin 420	Giy Asn V	/al Phe Ser Cys 425	Ser Val Met His 430	Gu
Ala Leu His Asn His 435		3 n G u Ser Leu 140	Ser Leu Ser Pro 445	
<210> 98 <211> 447 <212> PRT <213> Artificial				
<220> <223> an artificia	lly synthe	esized sequence		

<400> 98		P084876D1	Seq Listing	
Gin Val Gin Le 1	u Gin Giu Ser 5	GyProGy 10	Leu Val Lys	Pro Ser Giu 15
Thr Leu Ser Le 20	u Thr Cys Ala	a Val Ser Giy 25	His Ser IIe	Ser His Asp 30
His Ala Trp Se 35	r Trp Val Arg	g Gin Pro Pro 40	GyGuGy 45	Leu G u Trp
lle Giy Phe II 50	e Ser Tyr Ser 55	Gylle Thr	Asn Tyr Asn 60	Pro Ser Leu
Gin Giy Arg Va 65	Thr IIe Ser 70	· Arg Asp Asn	Ser Lys Asn 75	Thr Leu Tyr 80
Leu Gin Met As	n Ser Leu Arg 85	g Ala Giu Asp 90	Thr Ala Val	Tyr Tyr Cys 95
Ala Arg Ser Le 10		Thr Ala Met 105	Asp Tyr Trp	G y G u G y 110
Thr Leu Val Th 115	r Val Ser Ser	Ala Ser Thr 120	Lys Giy Pro 125	
Pro Leu Ala Pr 130	o Ser Ser Lys 135		GyGyThr 140	Ala Ala Leu
Gly Cys Leu Va 145	Lys Asp Tyr 150	Phe Pro Giu	ProVal Thr 155	Val Ser Trp 160
Asn Ser Giy Al	a Leu Thr Ser 165	GyValHis 170		Ala Val Leu 175
Gin Ser Ser G 18		Leu Ser Ser 185	Val Val Thr	Val Pro Ser 190
Ser Ser Leu G 195	y Thr Gin Thr	Tyr lle Cys 200	Asn Val Asn 205	
Ser Asn Thr Ly 210	s Val Asp Lys 215		Pro Lys Ser 220	Cys Asp Lys
Thr His Thr Cy 225	s Pro Pro Cys 230	s Pro Ala Pro	Asp Tyr Leu 235	GyGyAsp 240
Ser Val Phe Le	u Phe Pro Pro	• •	Asp Thr Leu 173	Met lle Ser

	245	P084876D1 S 250	Seq Listing	255
Arg Thr Pro Giu 260	Val Thr Cys	Val Val Val 265	Asp Val Se	r His Giu Asp 270
Giy Giu Val Lys 275	Phe Asn Trp	Tyr Val Asp 280	Giy Val G 28	u Val His Asn 5
Ala Lys Thr Lys 290	Pro Arg Giu 295	Gu Gn Tyr	Asn Ser Th 300	r Tyr Arg Val
Val Ser Val Leu 305	Thr Val Leu 310	His Gin Asp	Trp Leu As 315	n Giy Lys Giu 320
Tyr Lys Cys Lys	Val Ser Asn 325	Ala Ala Leu 330	Pro Lys Pr	olle Giu Lys 335
Thr Ile Ser Lys 340	Ala Lys Giy	Gin Pro Arg 345	Giu Pro Gi	n Val Tyr Thr 350
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360	Asn Gin Va 36	
Cys Leu Val Lys 370	G y Phe Tyr 375	Pro Ser Asp	lle Ala Va 380	Gu Trp Gu
Ser Asn Giy Gin 385	Pro Giu Asn 390	Asn Tyr Lys	Thr Thr Pr 395	o Pro Val Leu 400
Asp Ser Asp Gry	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu Th	r Val Asp Lys 415
Ser Arg Trp Gin 420	Gin Giy Asn	Val Phe Ser 425	Cys Ser Va	Met His Giu 430
Ala Leu His Asn 435	His Tyr Thr	GnGuSer 440	Leu Ser Le 44	
<210> 99 <211> 447 <212> PRT <213> Artifici	al			
	icially syntl	hesized sequ	ence	
<400> 99 Gin Val Gin Leu	Gin Giu Ser	Gy Pro Gv	Leu Val Lv	s Pro Ser Giu
1	5	10 Page	-	15

Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	Hi s	Asp
His	Ala	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	GIn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	Hi s	Lys	Pr o
	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	Glu	Val	Thr	Cys	Val		Val Page		Val	Ser	His	Gu	Asp

	260		P08487 265	6D1 Seq	Listing	270	
GyGuVal 275	Lys Phe	Asn Trp	Tyr Val 280	Asp Giy	Val G 28	u Val His 5	Asn
Ala Lys Thr 290	Lys Pro	Arg Giu 295		n Tyr Asr	Ser Th 300	r Tyr Arg	Val
Val Ser Val 305	Leu Thr	Val Leu 310	His Gir	n Asp Trp 315		n Giy Lys	G u 320
Tyr Lys Cys	Lys Val 325		Lys Ala	a Leu Pro 330	9 Lys Pr	olle Giu 335	Lys
Thr IIe Ser	Lys Ala 340	Lys Giy	Gin Pro 345		Pro Gi	n Val Tyr 350	Thr
Leu Pro Pro 355	Ser Arg	Asp Giu	Leu Thr 360	Lys Asr	ı Gin Va 36		Thr
Cys Leu Val 370	Lys Giy	Phe Tyr 375		Asp IIe	e Ala Va 380	l Giu Trp	Gu
Ser Asn Giy 385	Gin Pro	Giu Asn 390	Asn Tyr	Lys Thr 395		o Pro Val	Leu 400
Asp Ser Asp	Giy Ser 405		Leu Tyr	Ser Lys 410	Leu Th	r Val Asp 415	Lys
Ser Arg Trp	Gin Gin 420	Giy Asn	Val Phe 425	e Ser Cys 5	Ser Va	l Met His 430	Gu
Ala Leu His 435	Asn His	Tyr Thr	G n G เ 440	ı Ser Leu	ı Ser Le 44	u Ser Pro 5	
<210> 100 <211> 447 <212> PRT <213> Artif	ficial						
<220> <223> an ar	rtificia	lly synt	hesi zed	sequence)		
<400> 100							
Gin Val Gin 1	Leu Gin 5	G u Ser	Giy Pro	o G y Leu 10	ı Val Ly	s Pro Ser 15	Gu
Thr Leu Ser	Leu Thr 20	Cys Ala	Val Ser 25	Giy His Page 176		e Ser His 30	Asp

His	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
l I e	G y 50	Phe	lle	Ser	Tyr	Ser 55	Яу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Gу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Gу	Gu	Val	Lys	Phe	Asn	Tr p	Tyr		Asp Page	-	Val	Gu	Val	His	Asn

275		P084876 280	D1 Seq Listi	ng 285	
Ala Lys Thr 290	Lys Pro Arg	GuGuGn 295	Tyr Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val 305	Leu Thr Val 310	Leu His Gin	Asp Trp Leu 315	Asn Giy	Lys Giu 320
Tyr Lys Cys	Lys Val Ser , 325	Asn Ala Ala	Leu Pro Lys 330		G u Lys 335
Thr IIe Ser	Lys Ala Lys 340	GyGnPro 345	Arg Clu Pro	Gin Val 350	Tyr Thr
Leu Pro Pro 355	Ser Arg Asp	G u Leu Thr 360	Lys Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val 370	Lys G y Phe	Tyr Pro Ser 375	Asp Ile Ala 380	Val Gu	Trp Gu
Ser Asn G y 385	Gin Pro Giu 390	Asn Asn Tyr	Lys Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp	Giy Ser Phe 405	Phe Leu Tyr	Ser Lys Leu 410		Asp Lys 415
Ser Arg Trp	Gin Gin Giy 420	Asn Val Phe 425	Ser Cys Ser	Val Met 430	His Giu
Ala Leu His 435	Asn His Tyr	Thr Gin Giu 440	Ser Leu Ser	Leu Ser 445	Pr o
<210> 101 <211> 447 <212> PRT <213> Artit	ficial				
<220> <223> an ai	rtificially s	ynthesized s	equence		
<400> 101					
Gin Val Gin 1	Leu G n G u 5 5	Ser Gly Pro	G y Leu Val 10	Lys Pro	Ser Giu 15
Thr Leu Ser	Leu Thr Cys , 20	Ala Val Ser 25	Giy His Ser	lle Ser 30	His Asp
His Ala Trp 35	Ser Trp Val .	40	Pro Gy Gu Page 178	G y Leu 45	Gu Trp

lle Giy 50	Phe II	e Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy 65	Arg Va	al Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G n	Met As	sn Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg		eu Ala DO	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G у 110	Gu	Gу
Thr Leu	Val Th 115	nr Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Яу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Ala Pr	o Ser	Ser	Lys 135	Ser	Thr	Ser	Яу	G y 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu Va	al Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gy Al	a Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser		y Leu 30	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu G 195	y Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr Ly	ys Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr Cy	∕s Pro	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Яу	Asp	Asp 240
Ser Val	Phe Le	eu Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr		u Val 50	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Gy Gu	Val Ly 275	ys Phe	Asn	Tr p	Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Ala Lys	Thr Ly	∕s Pro	Ar g	Gu	Gu		Asp Page		Ser	Thr	Tyr	Ar g	Val

P084876D1 Seq Listing 290 295 300
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Lys Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 102 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 102
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45
lle Gly Phe Ile Ser Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60 Page 180

P084876D1	Seq	Listing

Gin Giy 65	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu G n	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Яу	G y 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Tyr	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Gy Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser	Val	Leu	Thr	Val	Leu	Hi s		Asp Page	-	Leu	Asn	Gу	Lys	Gu

305	P08 310	34876D1 Seq Listing 315	320
Tyr Lys Cys Lys Val 325		Ala Leu Pro Lys Pro Ile Giu 330 335	Lys
Thr IIe Ser Lys Ala 340	ı Lys Gy Gn	Pro Arg Giu Pro Gin Val Tyr 345 350	Thr
Leu Pro Pro Ser Arg 355	Asp G u Leu 360	Thr Lys Asn Gin Val Ser Leu 365	Thr
Cys Leu Val Lys Giy 370	Phe Tyr Pro 375	Ser Asp IIe Ala Val Giu Trp 380	Gu
Ser Asn Giy Gin Pro 385	9 Giu Asn Asn 390	Tyr Lys Thr Thr Pro Pro Val 395	Leu 400
Asp Ser Asp Giy Ser 405		Tyr Ser Lys Leu Thr Val Asp 410 415	Lys
Ser Arg Trp Gin Gin 420	n Giy Asn Val	Phe Ser Cys Ser Val Met His 425 430	Gu
Ala Leu His Asn His 435	Tyr Thr Gin 440	G u Ser Leu Ser Leu Ser Pro 445	
<210> 103 <211> 447 <212> PRT <213> Artificial			
<220> <223> an artificia	ally synthesi	zed sequence	
<400> 103			
Gin Val Gin Leu Gir 1 5	n Giu Ser Giy	Pro G y Leu Val Lys Pro Ser 10 15	Gu
Thr Leu Ser Leu Thr 20	Cys Ala Val	Ser Ciy His Ser Ile Ser His 25 30	Asp
His Ala Trp Ser Trp 35	val Arg Gin 40	Pro Pro Gly Glu Gly Leu Glu 45	Tr p
lle Giy Phe Ile Ser 50	Tyr Ser Giy 55	lle Thr Asn Tyr Asn Pro Ser 60	Leu
Gin Giy Arg Val Thr 65	lle Ser Arg 70	Asp Asn Ser Lys Asn Thr Leu 75 Page 182	Tyr 80

Leu G	n Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Ar	g Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Le	u Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Le 13		Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y Cy 145	s Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Se	r Giy	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Se	r Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Se	r Leu 195	Gу	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	Hi s	Lys	Pr o
Ser As 21		Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr Hi 225	s Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Asp	Asp 240
Ser Va	l Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Th	r Pro	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
GyG	u Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Ly 29		Lys	Pr o	Ar g	G u 295	Gu	Gη	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Se 305	r Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Ly	s Cys	Lys	Val	Ser	Asn	Lys		Leu Page		Lys	Pr o	lle	Gu	Lys

	325	P084876D1 S 330	Seq Listing	335
Thr IIe Ser Lys 340		Gin Pro Arg 345	GuProGnVa 35	
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360	Asn Gin Val Se 365	er Leu Thr
Cys Leu Val Lys 370	Gy Phe Tyr 375	Pro Ser Asp	lle Ala Val G 380	u Trp Giu
Ser Asn Gly Gir 385	ı Pro Giu Asn 390	Asn Tyr Lys	Thr Thr Pro Pr 395	o Val Leu 400
Asp Ser Asp G y	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu Thr Va	al Asp Lys 415
Ser Arg Trp Gir 420		Val Phe Ser 425	Cys Ser Val Me 43	-
Ala Leu His Asr 435	ı His Tyr Thr	GnGuSer 440	Leu Ser Leu Se 445	r Pro
<210> 104 <211> 447 <212> PRT <213> Artifici	al			
<220> <223> an artif	icially synt	hesized seque	ence	
<400> 104				
Gin Val Gin Leu 1	IGNGUSer 5	Giy Pro Giy 10	Leu Val Lys Pr	o Ser Giu 15
Thr Leu Ser Leu 20	IThr Cys Ala	Val Ser Gy 25	His Ser IIe Se 30	
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40	GyGuGyLe 45	eu Giu Trp
lle Gly Phe lle 50	e Ser Tyr Ser 55	Gylle Thr	Asn Tyr Asn Pr 60	o Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys Asn Th 75	nr Leu Tyr 80
Leu Gin Met Asr	i Ser Leu Arg 85	Ala Glu Asp 90 Page		r Tyr Cys 95

Ala Arg	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	Hi s	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
Gy Gu	Val 275	Lys	Phe	Asn	Trp	Tyr	Val				<u> </u>	Val	His	Asn
					•	280	vai	Asp	Gу	Val	285	vai		
Ala Lys 290		Lys	Pr o			280					285			
290	Thr	Lys Leu		Ar g	G u 295	280 G u	G n	Tyr	Asn	Ser 300	285 Thr	Tyr	Ar g	Val
290 Val Ser	Thr Val	Leu	Thr	Ar g Val 310	G u 295 Leu	280 Giu His	Gn Gn	Tyr Asp	Asn Trp 315	Ser 300 Leu	285 Thr Asn	Tyr Gy	Arg Lys	Val Gi u 320

	340			P08	4876 345	D1 S	eq L	isti	ng	350		
Leu Pro Pro 355	Ser Arç	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys Gy	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn Giy 385	Gin Pro	9 G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy Ser 405		Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	Gin Gir 420	Gy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His 435	Asn His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 105 <211> 447 <212> PRT <213> Artif	i ci al											
<220> <223> an ar	tificia	ılly s	synt h	nesi z	zed s	seque	ence					
<400> 105												
Gin Val Gin 1	Leu Gr 5	Gu	Ser	Яу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu Ser	Leu Thr 20	Cys	Ala	Val	0							
	20				Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala Trp 35		o Val	Ar g		25	-				30		·
	Ser Trp	_	-	G n 40	25 Pr o	Pr o	Gу	Gu	G y 45	30 Leu		Tr p
35 Ile Gly Phe	Ser Trp Ile Ser	Tyr	Ser 55	Gn 40 Gy	25 Pro	Pr o Thr	G y Asn	G u Tyr 60	G y 45 Asn	30 Leu Pr o	G u Ser	Tr p Leu
35 IIe Giy Phe 50 Gin Giy Arg	Ser Trp Ile Ser Val Thr	Tyr IIe 70	Ser 55 Ser	G n 40 G y Ar g	25 Pro IIe Asp	Pr o Thr Asn	Giy Asn Ser 75	G u Tyr 60 Lys	Giy 45 Asn Asn	30 Leu Pr o	G u Ser	Trp Leu Tyr 80

Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
G n	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gгу	Thr	Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	Hi s	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
Gу	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gin	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Ala	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu	Pr o	Pr o	Ser	Ar g	Asp	Gu	Leu		Lys Page		GIn	Val	Ser	Leu	Thr

355		P084876D1 S 360		ე 65
Cys Leu Val Lys 370	G y Phe Tyr 375	Pro Ser Asp	lle Ala V 380	al Giu Trp Giu
Ser Asn Giy Gin 385	Pro Giu Asn 390	Asn Tyr Lys	Thr Thr P 395	ro Pro Val Leu 400
Asp Ser Asp Giy	Ser Phe Phe 405	Leu Tyr Ser 410	Lys Leu T	hr Val Asp Lys 415
Ser Arg Trp Gin 420	Gin Giy Asn	Val Phe Ser 425	Cys Ser V	al Met His Giu 430
Ala Leu His Asn 435	His Tyr Thr	GnGuSer 440		eu Ser Pro 45
<210> 106 <211> 447 <212> PRT <213> Artifici	al			
<220> <223> an artif	icially synt	hesized sequ	ence	
<400> 106				
Gn Val Gn Leu 1	GnGuSer 5	Giy Pro Giy 10	Leu Val L	ys Pro Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser Gy 25	His Ser I	le Ser His Asp 30
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40	Giy Giu G 4	
lle Gly Phe lle 50	Ser Tyr Ser 55	Gylle Thr	Asn Tyr A 60	sn Pro Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys A 75	sn Thr Leu Tyr 80
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu Asp 90	Thr Ala V	al Tyr Tyr Cys 95
Ala Arg Ser Leu 100	Ala Arg Thr	Thr Ala Met 105	Asp Tyr T	rp Gy Gu Gy 110
Thr Leu Val Thr 115	Val Ser Ser	Al a Ser Thr 120 Page	1	ro Ser Val Phe 25

Pro Leu 130	Ala F	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu \	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gy A		Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser		GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu (195	Зу	Thr	G n	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr L	_ys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr (Cys	Pr o	Pr o 230	Cys	Pr o	Ala	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe L		Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr		Glu 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
G y G u	Val L 275	_ys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr L	_ys	Pr o	Ar g	G u 295	Gи	Βn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val L	_eu	Thr	Val 310	Leu	His	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys L		Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr IIe		_ys 340	Ala	Lys	Gу	GIn	Pr o 345	Ar g	Gu	Pr o	GIn	Val 350	Tyr	Thr
Leu Pro	Pro \$ 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	GIn	Val 365	Ser	Leu	Thr
Cys Leu	Val L	_ys	Gу	Phe	Tyr	Pr o		Asp Page		Al a	Val	Gu	Tr p	Gu

370		P08487 375	76D1 Seq Listi 380	ng
Ser Asn G y 385	Gin Pro Giu 390		r Lys Thr Thr 395	Pro Pro Val Leu 400
Asp Ser Asp	Giy Ser Phe 405	Phe Leu Ty	r Ser Lys Leu 410	Thr Val Asp Lys 415
Ser Arg Trp	Gin Gin Giy 420	Asn Val Pho 42	e Ser Cys Ser 5	Val Met His Giu 430
Ala Leu His 435	Asn His Tyr	Thr Gn G 440	u Ser Leu Ser	Leu Ser Pro 445
<210> 107 <211> 447 <212> PRT <213> Arti	ficial			
<220> <223> an a	rtificially	synt hesi zed	sequence	
<400> 107				
Gin Val Gin 1	Leu G n G u 5	Ser Giy Pro	o G y Leu Val 10	Lys Pro Ser Giu 15
Thr Leu Ser	Leu Thr Cys 20	Ala Val Sei 25	r Ciy His Ser	lle Ser His Asp 30
His Ala Trp 35	Ser Trp Val	Arg Gin Pro 40	o Pro Giy Giu	GyLeuGuTrp 45
lle Gly Phe 50	lle Ser Tyr	Ser Giy II 55	e Thr Asn Tyr 60	Asn Pro Ser Leu
Gin Giy Arg 65	Val Thr IIe 70	Ser Arg As	o Asn Ser Lys 75	Asn Thr Leu Tyr 80
Leu Gin Met	Asn Ser Leu 85	Arg Ala G	u Asp Thr Ala 90	Val Tyr Tyr Cys 95
Ala Arg Ser	Leu Ala Arg 100	Thr Thr Al a 10		Trp Gy Gu Gy 110
Thr Leu Val 115	Thr Val Ser	Ser Ala Sei 120	r Thr Lys Giy	Pro Ser Val Phe 125
Pro Leu Ala 130	Pro Ser Ser	Lys Ser Thi 135	r Ser G y G y 140 Page 190	Thr Ala Ala Leu

Seq Listing

Giy Cys Lei 145	u Val Lys	s Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Gy	/ Ala Lei 16		Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Sei	Giy Lei 180	ı Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Lei 19		Gn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thi 210	Lys Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thu 225	Cys Pro	Pro 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val Pho	e Leu Pho 24		Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	o Giu Val 260	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
GyGuVal 279		e Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn
Ala Lys Thi 290	Lys Pro	o Arg	G u 295	Gu	Βn	Asp	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thi	Val 310	Leu	Hi s	Βn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys	s Lys Val 32	Ser 5	Asn	Lys	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr IIe Sei	Lys Ala 340	a Lys	Gу	Βn	Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr
Leu Pro Pro 35		g Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys G	/ Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G	/Gin Pro	Gu	Asn	Asn	-	Lys Page		Thr	Pr o	Pr o	Val	Leu

385	39	P0	84876D1 \$	Seq Listi 395	ng	400
Asp Ser Asp G	ay Ser Pr 405	ne Phe Lei	u Tyr Ser 410	Lys Leu	Thr Val	Asp Lys 415
Ser Arg Trp G 4	ln Gin G 20	y Asn Val	Phe Ser 425	Cys Ser	Val Met 430	His Giu
Ala Leu His A 435	sn His Ty	vr Thr Gir 44(Leu Ser	Leu Ser 445	Pr o
<210> 108 <211> 447 <212> PRT <213> Artifi	ci al					
<220> <223> an art	ificially	v synthesi	zed sequ	ence		
<400> 108						
Gin Val Gin L 1	eu Gin G 5	u Ser Giy	/ProGiy 10	Leu Val	Lys Pro	Ser Giu 15
Thr Leu Ser L 2	eu Thr Cy 0	vs Ala Val	Ser Giy 25	His Ser	lle Ser 30	His Asp
His Ala Trp S 35	er Trp Va	al Arg Gin 40	n Pro Pro	G y G u	G y Leu 45	Gu Trp
lle Gly Phe I 50	le Ser Ty	vr Ser Giy 55	/IIe Thr	Asn Tyr 60	Asn Pro	Ser Leu
Gin Giy Arg V 65	al Thr II 7(e Ser Arç)	g Asp Asn	Ser Lys 75	Asn Thr	Leu Tyr 80
Leu Gin Met A	sn Ser Le 85	eu Arg Ala	a Ciu Asp 90	Thr Ala	Val Tyr	Tyr Cys 95
Ala Arg Ser L 1	eu Ala Ar 00	g Thr Thr	Ala Met 105	Asp Tyr	Trp Gy 110	GuGy
Thr Leu Val T 115	hr Val Se	er Ser Ala 120		Lys Gy	ProSer 125	Val Phe
Pro Leu Ala F 130	ro Ser Se	er Lys Ser 135	Thr Ser	G y G y 140	Thr Ala	Ala Leu
G y Cys Leu V 145	al Lys As 15		e Pro Gu Page	155	Thr Val	Ser Trp 160

Asn Ser G	aly Ala	Leu ⁻ 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Ala	Val 175	Leu
Gin Ser S	Ser Giy 180	Leu ⁻	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser L 1	.eu Giy 95	Thr (Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn T 210	hr Lys	Val /	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His T 225	hr Cys		Pr o 230	Cys	Pr o	Ala	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val P	he Leu	Phe F 245	Pro	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr P	Pro Giu 260	Val ⁻	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
GyGuV 2	/al Lys 275	Phe A	Asn [·]	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys T 290	hr Lys	Pro A		G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser V 305	al Leu	Thr N	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys C	∛s Lys	Val 8 325	Ser ,	Asn	Lys	Ala	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr Ile S	Ser Lys 340	Alal	Lys	Gу	Gin	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr
Leu Pro P 3	Pro Ser 55	Arg A	Asp	Gu	Leu 360	Thr	Lys	Asn	G n	Val 365	Ser	Leu	Thr
Cys Leu V 370	al Lys/	GIYI		Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G 385	aly Gin		G u / 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser A	sp Giy	Ser I	Phe	Phe	Leu		Ser Page		Leu	Thr	Val	Asp	Lys

	405	P084876D1 Seq List 410	i ng 415
Ser Arg Trp Gir		Val Phe Ser Cys Ser	Val Met His Giu
420		425	430
Ala Leu His Asr	His Tyr Thr	Gin Giu Ser Leu Ser	Leu Ser Pro
435		440	445
<210> 109 <211> 447 <212> PRT <213> Artifici	al		
<220> <223> an artif	icially synt	hesized sequence	
<400> 109			
Gin Val Gin Leu	ı Gin Giu Ser	Giy Pro Giy Leu Val	Lys Pro Ser Giu
1	5	10	15
Thr Leu Ser Leu	IThr Cys Ala	Val Ser Giy His Ser	IIe Ser His Asp
20		25	30
His Ala Trp Ser	Trp Val Arg	Gin Pro Pro Giy Giu	J G y Leu G u Trp
35		40	45
lle Cly Phe Ile	e Ser Tyr Ser	Giy Ile Thr Asn Tyr	Asn Pro Ser Leu
50	55	60	
Gin Giy Arg Val	Thr IIe Ser	Arg Asp Asn Ser Lys	s Asn Thr Leu Tyr
65	70	75	80
Leu Gin Met Asr	i Ser Leu Arg	Ala Giu Asp Thr Ala	a Val Tyr Tyr Cys
	85	90	95
Ala Arg Ser Leu		Thr Ala Met Asp Tyr	Trp Gy Gu Gy
100		105	110
Thr Leu Val Thr	Val Ser Ser	Ala Ser Thr Lys Giy	/ Pro Ser Val Phe
115		120	125
Pro Leu Ala Pro	Ser Ser Lys	Ser Thr Ser G y G y	
130	135	14(
G y Cys Leu Val	Lys Asp Tyr	Phe Pro Giu Pro Val	Thr Val Ser Trp
145	150	155	160
Asn Ser Ciy Ala	Leu Thr Ser 165	G y Val His Thr Phe 170 Page 194	e Pro Ala Val Leu 175

Gin Se	r Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Se	r Leu 195	Gу	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser As 21	n Thr D	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr Hi 225	s Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Gу	Asp	Asp 240
Ser Va	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Th	r Pro	G u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
G y G	u Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	Hi s	Asn
Ala Ly 29		Lys	Pr o	Ar g	G u 295	Gu	GIn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Se 305	r Val	Leu	Thr	Val 310	Leu	Hi s	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Ly	s Cys	Lys	Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr II	e Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr
Leu Pr	o Pro 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gin	Val 365	Ser	Leu	Thr
Cys Le 37		Lys	Яу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser As 385	n Giy	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Se	r Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Ar	g Trp	GIn	Gin	Gу	Asn	Val		Ser Page	-	Ser	Val	Met	His	Gu

	420	P084876[425	D1 Seq Listing	g 430
Ala Leu His 435	Asn His Tyr	Thr Gin Giu S 440		eu Ser Pro 145
<210> 110 <211> 447 <212> PRT <213> Artifi	i ci al			
<220> <223> an ar	tificially s	synthesized so	equence	
<400> 110				
Gin Val Gin 1	Leu G n G u 5		G y Leu Val L 10	ys Pro Ser Giu. 15
Thr Leu Ser	Leu Thr Cys 20	Ala Val Ser 25	Giy His Ser I	le Ser His Asp 30
His Ala Trp 35	Ser Trp Val	Arg Cin Prol 40		Ay Leu Giu Trp !5
lle Gly Phe 50	lle Ser Tyr	Ser Giy Ile ⁻ 55	Thr Asn Tyr A 60	Asn Pro Ser Leu
Gin Giy Arg 65	Val Thr Ile 70	Ser Arg Asp /	Asn Ser Lys A 75	Asn Thr Leu Tyr 80
Leu Gin Met ,	Asn Ser Leu 85	Arg Ala Giu A	Asp Thr Ala V 90	/al Tyr Tyr Cys 95
	Leu Ala Arg 100	Thr Thr Alal 105	Met Asp Tyr T	rp Gly Glu Gly 110
Thr Leu Val 115	Thr Val Ser	Ser Ala Ser 120		Pro Ser Val Phe 25
Pro Leu Ala 130	Pro Ser Ser	Lys Ser Thr 3 135	Ser Giy Giy T 140	⁻ hr Ala Ala Leu
G y Cys Leu 145	Val Lys Asp 150	Tyr Phe Pro	Giu Pro Val T 155	⁻hr Val Ser Trp 160
Asn Ser Giy ,	Ala Leu Thr 165	•	His Thr Phe F 170	Pro Ala Val Leu 175
	Giy Leu Tyr 180	Ser Leu Ser S 185 P	Ser Val Val T age 196	⁻ hr Val Pro Ser 190

Ser	Ser	Leu 195	Gу	Thr	Βn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Яу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
Gу	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Asp	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	Gη	Pr o 345	Ar g	Gu	Pr o	Gη	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gη	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Gу	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser	Ar g	Tr p	GIn 420	Gn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Al a	Leu	His	Asn	His	Tyr	Thr	Gn		Ser		Ser	Leu	Ser	Pr o	

P084876D1 Seq Listing <210> <211> <212> PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp His Ala Trp Ser Trp Val Arg Gn Pro Pro Gy Gu Gy Leu Gu Trp lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gy Gu Gy Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys G y Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu G y Cys Leu Val Lys Asp Tyr Phe Pro G u Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Giy Thr Gin Thr Tyr IIe Cys Asn Val Asn His Lys Pro

	\sim	 	
	50 a	 C t 1	na
P084876D1	- CEU	 511	TIU.
	004	 ••••	

Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	Hi s	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Tyr	Leu	Gу	Gу	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
Gу	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	Gn	Asp	Tr p 315	Leu	Asn	Яу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Al a	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys
Thr	lle	Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	GIn	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Яу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser	Ar g	Tr p	GIn 420	GIn	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Al a	Leu	His 435	Asn	His	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
-01	0.	110													

<210> 112

<211> 447 <212> PRT <213> Artif	i ci al	P08487	6D1 Seq Listi	ng
<220> <223> an ar	tificially s	synt hesi zed	sequence	
<400> 112				
Gin Val Gin 1	Leu Gin Giu 5	Ser Ciy Pro	GyLeuVal 10	Lys Pro Ser Giu 15
	Leu Thr Cys 20	Ala Val Ser 25	Giy His Ser	lle Ser His Asp 30
His Ala Trp 35	Ser Trp Val	Arg Cin Pro 40	Pro Gly Glu	Giy Leu Giu Trp 45
lle Gy Phe 50	lle Ser Tyr	Ser Ciylle 55	e Thr Asn Tyr 60	Asn Pro Ser Leu
Gin Ciy Arg 65	Val Thr IIe 70	Ser Arg Asp	o Asn Ser Lys 75	Asn Thr Leu Tyr 80
Leu Gin Met	Asn Ser Leu 85	Arg Ala Giu	Asp Thr Ala 90	Val Tyr Tyr Cys 95
	Leu Ala Arg 100	Thr Thr Ala 105		Trp Gly Glu Gly 110
Thr Leu Val 115	Thr Val Ser	Ser Ala Ser 120	Thr Lys Giy	Pro Ser Val Phe 125
Pro Leu Ala 130	Pro Ser Ser	Lys Ser Thr 135	Ser Giy Giy 140	Thr Ala Ala Leu
Gy Cys Leu 145	Val Lys Asp 150	Tyr Phe Pro	o Giu Pro Val 155	Thr Val Ser Trp 160
Asn Ser Giy	Ala Leu Thr 165	Ser G y Val	His Thr Phe 170	Pro Ala Val Leu 175
Gin Ser Ser	Gly Leu Tyr 180	Ser Leu Ser 185		Thr Val Pro Ser 190
Ser Ser Leu 195	Gly Thr Gin	Thr Tyr II e 200	e Cys Asn Val	Asn His Lys Pro 205
Ser Asn Thr 210	Lys Val Asp	Lys Lys Val 215	G u Pro Lys 220 Page 200	Ser Cys Asp Lys

P084876D1	Sea	Listing

Thr His Thr Cy 225	rs Pro Pro 230		Ala Pro	Asp Tyr 235	Leu Gy	Asp Asp 240
Ser Val Phe Le	eu Phe Pro 245	Pro Lys	Pro Lys 250		Leu Met	lle Ser 255
Arg Thr Pro Gi 26		Cys Val	Val Val 265	Asp Val	Ser Asp 270	Gu Asp
GyGuValLy 275	s Phe Asn	Trp Tyr 280	Val Asp	o Giy Val	G u Val 285	His Asn
Ala Lys Thr Ly 290	rs Pro Arg	G u G u 295	Gin Asp	Asn Ser 300	Thr Tyr	Arg Val
Val Ser Val Le 305	u Thr Val 310		Gin Asp	Trp Leu 315	Asn Giy	Lys Giu 320
Tyr Lys Cys Ly	s Val Ser 325	Asn Asp	Ala Leu 330		Pro IIe	GuLys 335
Thr IIe Ser Ly 34		Giy Gin	Pro Arg 345	g Giu Pro	G n Val 350	Tyr Thr
Leu Pro Pro Se 355	er Arg Asp	G u Leu 360	Thr Lys	Asn Gin	Val Ser 365	Leu Thr
Cys Leu Val Ly 370	s Giy Phe	Tyr Pro 375	Ser Asp	olle Ala 380	Val Giu	Trp Giu
Ser Asn G y G 385	n Pro Giu 390	Asn Asn	Tyr Lys	Thr Thr 395	Pro Pro	Val Leu 400
Asp Ser Asp G	y Ser Phe 405	Phe Leu	Tyr Ser 410		Thr Val	Asp Lys 415
Ser Arg Trp G 42		Asn Val	Phe Ser 425	Cys Ser	Val Met 430	His Giu
Ala Leu His As 435	n His Tyr	Thr G n 440	Giu Ser	Leu Ser	Leu Ser 445	Pr o
<210> 113 <211> 447 <212> PRT <213> Artific	i al					

202	F	P084876D1 Seq l	₋isting	
<220> <223> an artifi	cially synthes	sized sequence		
<400> 113				
Gin Val Gin Leu 1	Gin Giu Ser Gi 5	ly Pro Gly Leu 10	Val Lys Pro	Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala Va	al Ser Giy His 25	Ser IIe Ser 30	His Asp
His Ala Trp Ser 35	Trp Val Arg G 40		GuGyLeu 45	Gu Trp
lle Giy Phe lle 50	Ser Tyr Ser G 55	lylle Thr Asn	Tyr Asn Pro 60	Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser An 70	rg Asp Asn Ser 75	Lys Asn Thr	Leu Tyr 80
Leu Gin Met Asn	Ser Leu Arg Al 85	la Giu Asp Thr 90	Ala Val Tyr	Tyr Cys 95
Ala Arg Ser Leu 100	Ala Arg Thr Th	hr Ala Met Asp 105	Tyr Trp Gy 110	Gu Gy
Thr Leu Val Thr 115		la Ser Thr Lys 20	Gry Pro Ser 125	Val Phe
Pro Leu Ala Pro 130	Ser Ser Lys Se 135	er Thr Ser Giy	Giy Thr Ala 140	Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr Pl 150	he Pro Giu Pro 155	Val Thr Val	Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser G 165	ly Val His Thr 170	Phe Pro Ala	Val Leu 175
Gin Ser Ser Giy 180	Leu Tyr Ser Le	eu Ser Ser Val 185	Val Thr Val 190	Pro Ser
Ser Ser Leu Giy 195		yr lle Cys Asn 00	Val Asn His 205	Lys Pro
Ser Asn Thr Lys 210	Val Asp Lys Ly 215	ys Val Giu Pro	Lys Ser Cys 220	Asp Lys
Thr His Thr Cys 225	Pro Pro Cys Pr 230	ro Ala Pro Asp 235 Page 202	Tyr Leu Giy	GyAsp 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met IIe Ser 245 250 255	
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser Asp Giu Asp 260 265 270	
Giy Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His Asn 275 280 285	
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg Val 290 295 300	
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys Giu 305 310 315 320	
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Lys Pro Ile Giu Lys 325 330 335	
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350	
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365	
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu 370 375 380	
Ser Asn Ciy Cin Pro Ciu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400	
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415	
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430	
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 114 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 114 Page 203	

				P08	4876	D1 S	Seq L	.isti	ng			
Gin Val G 1	ain Leu (t	Gin Giu 5	Ser	Gу	Pr o	С у 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu S	Ser Leu 20	Thr Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala T 3	⁻rp Ser ⁻ 5	Trp Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle Gly P 50	helle S	Ser Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy A 65	wrg Val ⁻	Thr IIe 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin M		Ser Leu 85	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg S	Ser Leu / 100	Ala Arg	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu V 1	/al Thr N 15	Val Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu A 130	Na Pro S	Ser Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Giy Cys L 145	.eu Val I	Lys Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser G		Leu Thr 165	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser S	Ser Giyl 180	Leu Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser L 1	.eu Giy ⁻ 95	Thr Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn T 210	hr Lys N	Val Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His T 225	⊡hr Cys F	Pro Pro 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val P		Phe Pro 245	Pr o	Lys		Lys 250 Page		Thr	Leu	Met	e 255	Ser

TOOTODI Geq LISTINg						
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser His 0 260 265 270	Gu Asp					
Pro Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val I 275 280 285	His Asn					
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr / 290 295 300	Arg Val					
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy I 305 310 315	Lys Gu 320					
Tyr Lys Cys Lys Val Ser Asn Asp Ala Leu Pro Arg Pro Ile 0 325 330	G u Lys 335					
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val 340 345 350	Tyr Thr					
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val Ser I 355 360 365	Leu Thr					
Cys Leu Val Lys Cly Phe Tyr Pro Ser Asp Ile Ala Val Clu 370 375 380	Trp Giu					
Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro 1 385 390 395	Val Leu 400					
	Asp Lys 415					
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met I 420 425 430	His Giu					
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser I 435 440 445	Pr o					
<210> 115 <211> 447 <212> PRT <213> Artificial						
<220> <223> an artificially synthesized sequence						
<400> 115						
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro S 1 5 10	Ser Giu 15					

	P084876D1 Seq Listing										
Thr Leu Ser	Leu Thr 20	Cys Ala	a Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala Trp 35	Ser Trp	Val Arg	g Gin 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle Gy Phe 50	lle Ser	Tyr Sei 55	Gy	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy Arg 65	Val Thr	lle Sen 70	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu Ar (g Ala	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg Thu	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu Val 115	Thr Val	Ser Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 13		Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Ciy	Ala Leu 165	Thr Ser	Gy	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	Giy Leu 180	Tyr Sei	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	G n Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 21		Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	s Pro	Al a	Pr o	Asp 235	Tyr	Leu	Gу	Asp	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro	b Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys	s Val	Val 265	Val Page	Asp 206	Val	Ser	His 270	Gu	Asp
					02						

	P084876D1 Seq Listing							
Gy Gu Val Lys 275	Phe Asn Trp	o Tyr Val Asp 280	Giy Val	Giu Val His Asn 285				
Ala Lys Thr Lys 290	Pro Arg Giu 295		Asn Ser 300	Thr Tyr Arg Val				
Val Ser Val Leu 305	Thr Val Leu 310	ıHis Gin Asp	Trp Leu 315	Asn Ciy Lys Ciu 320				
Tyr Lys Cys Lys	Val Ser Asn 325	n Asp Ala Leu 330		Prolle Giu Lys 335				
Thr IIe Ser Lys 340		r Gin Pro Arg 345	Giu Pro	Gin Val Tyr Thr 350				
Leu Pro Pro Ser 355	Arg Asp Giu	Leu Thr Lys 360	Asn Gin	Val Ser Leu Thr 365				
Cys Leu Val Lys 370	G y Phe Tyr 375		lle Ala 380	Val Gu Trp Gu				
Ser Asn Ciy Cir 385	Pro Giu Asn 390	n Asn Tyr Lys	Thr Thr 395	Pro Pro Val Leu 400				
Asp Ser Asp Giy	Ser Phe Phe 405	e Leu Tyr Ser 410		Thr Val Asp Lys 415				
Ser Arg Trp Gir 420		val Phe Ser 425	Cys Ser	Val Met His Giu 430				
Ala Leu His Asr 435	His Tyr Thr	Gin Giu Ser 440	Leu Ser	Leu Ser Pro 445				
<210> 116 <211> 447 <212> PRT <213> Artifici	al							
<220> <223> an artif	icially synt	hesized sequ	ence					
<400> 116								
Gin Val Gin Leu 1	Gin Giu Ser 5	Giy Pro Giy 10	Leu Val	Lys Pro Ser Giu 15				
Thr Leu Ser Leu 20	Thr Cys Ala	a Val Ser Giy 25	His Ser	lle Ser His Asp 30				

							P08	4876	5D1 S	Seq L	.isti	ng			
His	Ala	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
lle	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Gу	Ar g	Val	Thr	e 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	GIn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Gу	Gu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280		Asp Page	-	Val	G u 285	Val	His	Asn

									•		-			
Ala Lys 290		Lys	Pr o	Ar g	G u 295	Gu	G n	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys
Thr Ile	e Ser	Lys 340	Al a	Lys	Яу	GIn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu Pro	9 Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	GIn	Val 365	Ser	Leu	Thr
Cys Leu 370		Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asr 385	Зу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser	Asp	Gгу	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg	ı Trp	GIn 420	G n	Gу	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu	I His 435	Asn	Hi s	Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> <211> <212> <213>	117 447 PRT Arti	ficia	al											
<220> <223>	an a	rtifi	ci al	ly s	synt l	nesi z	zed s	seque	ence					
<400>	117													
Gin Val 1	Gn	Leu	GIn 5	Gu	Ser	Яу	Pr o	G y 10	Leu	Val	Lys	Pr o	Ser 15	Gu
Thr Leu	ı Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
His Ala	ι Trp 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p

			P08	84876	D1 S	Seq L	.isti	ng			
lle Gy Phe 50	lle Ser	Tyr S 5		lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
Gin Giy Arg 65	Val Thr	lle S 70	er Arg	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu A	rg Ala	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg T	'nr Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu Val 115	Thr Val	Ser S	er Ala 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser		ys Ser 35	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys Leu 145	Val Lys	Asp T 150	yr Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Gy	Ala Leu 165	Thr S	er Gly	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	Giy Leu 180	Tyr S	er Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	GnT	hr Tyr 200	lle	Cys	Asn	Val	Asn 205	Hi s	Lys	Pr o
Ser Asn Thr 210	Lys Val		ys Lys 15	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro C 230	lys Pro	Al a	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser Val Phe	Leu Phe 245	Pro P	ro Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr C	ys Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
GyGuVal 275	Lys Phe	Asn T	rp Tyr 280	Val	Asp	Яу	Val	G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro		alu Giu 95		Tyr Page		Ser 300	Thr	Tyr	Ar g	Val

Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys G 305 310 315 33	u 20
Tyr Lys Cys Lys Val Ser Asn Ala Ala Leu Pro Arg Pro Ile Giu Ly 325 330 335	/s
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr T 340 345 350	٦r
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Th 355 360 365	٦r
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val Glu Trp G 370 375 380	u
	эu 00
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Ly 405 410 415	/S
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His G 420 425 430	u
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445	
<210> 118 <211> 447 <212> PRT <213> Artificial	
<220> <223> an artificially synthesized sequence	
<400> 118	
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser G 1 5 10 15	u
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His A 20 25 30	зр
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Tr 35 40 45	р
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Lo 50 55 60	эu

			P084	4876	D1 S	eq L	isti	ng			
Gin Giy Arg 65	Val Thr	lle Ser 70	Arg.	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu Gin Met	Asn Ser 85	Leu Arg	Ala	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg Thr		Al a 105	Met	Asp	Tyr	Tr p	Gу 110	Gи	Gу
Thr Leu Val 115	Thr Val	Ser Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 135		Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	Gly Leu 180	Tyr Ser		Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	Gin Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	Pro	Ala	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cys		Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
GyGuVal 275	Lys Phe	Asn Trp	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro	Arg Giu 295		G n	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr	Val Leu 310	His		Asp Page	315	Leu	Asn	Gу	Lys	G u 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Arg Pro Ile Giu Lys 325 330 335
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr Thr 340 345 350
Leu Pro Pro Ser Arg Asp G u Leu Thr Lys Asn G n Val Ser Leu Thr 355 360 365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp lle Ala Val Glu Trp Glu 370 375 380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445
<210> 119 <211> 447 <212> PRT <213> Artificial
<220> <223> an artificially synthesized sequence
<400> 119
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15
Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30
His Ala Trp Ser Trp Val Arg G n Pro Pro G y G u G y Leu G u Trp 35 40 45
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80

			P0848	376D1 S	eq Li	sti	ng			
Leu Gin Met	Asn Ser 85	Leu Arg	Ala G	lu Asp 90	Thr .	Al a	Val	Tyr	Tyr 95	Cys
Ala Arg Ser	Leu Ala 100	Arg Thr		la Met 05	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr Leu Val 115	Thr Val	Ser Ser	Ala Se 120	er Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Lys 135		hr Ser		G y 140	Thr	Al a	Al a	Leu
G y Cys Leu 145	Val Lys	Asp Tyr 150	Phe Pi	ro Giu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Ser	Giy Va	al His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	Gly Leu 180	Tyr Ser		er Ser 85	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	Gin Thr	Tyr II 200	le Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Lys 215		al Gu		Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	Pro Cys 230	Pro Al	la Pro	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pro	Lys Pr	ro Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	G u Val 260	Thr Cys		al Val 65	Asp	Val	Ser	His 270	Gu	Asp
Giy Giu Val 275	Lys Phe	Asn Trp	Tyr Va 280	al Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro	Arg Giu 295		In Tyr		Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr	Val Leu 310	His Gi	In Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys	Lys Val 325	Ser Asn	Ala Al	la Leu 330 Page		Ar g	Pr o	lle	G u 335	Lys

	Lys Al 340	a Lys	Gу	Gin	Pr o 345	Ar g	Gu	Pr o	G n	Val 350	Tyr	Thr
Leu Pro Pro 355	Ser Ar	g Asp	Gu	Leu 360	Thr	Lys	Asn	GIn	Val 365	Ser	Leu	Thr
Cys Leu Val 370	Lys G	y Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser Asn G y 385	Gin Pr	o Gu 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp Ser Asp	Giy Se 40		Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser Arg Trp	Gin Gi 420	n Giy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu
Ala Leu His 435	Asn Hi	s Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o	
<210> 120 <211> 447 <212> PRT <213> Artif	i ci al											
<220> <223> an ar	tifici	ally	syntł	nesi z	zed s	seque	ence					
	tifici	ally	synt I	nesi z	zed s	seque	ence					
<223> an ar		-	-			-		Val	Lys	Pr o	Ser 15	Gu
<223> an ar <400> 120 Gin Val Gin 1 Thr Leu Ser	Leu G 5	n Giu	Ser	Gу	Pr o	G y 10	Leu				15	
<223> an ar <400> 120 Gin Val Gin 1 Thr Leu Ser	Leu G 5 Leu Th 20	n Giu r Cys	Ser Al a	G y Val	Pr o Ser 25	G y 10 G y	Leu His	Ser	lle	Ser 30	15 His	Asp
<223> an ar <400> 120 Gin Val Gin 1 Thr Leu Ser His Ala Trp	Leu G 5 Leu Th 20 Ser Tr	n Giu r Cys o Val	Ser Al a Ar g	G y Val G n 40	Pr o Ser 25 Pr o	Giy 10 Giy Pro	Leu His Giy	Ser Giu	IIe Gy 45	Ser 30 Leu	15 His Giu	Asp Tr p
<223> an ar <400> 120 Gin Val Gin 1 Thr Leu Ser His Ala Trp 35	Leu G 5 Leu Th 20 Ser Tr 11 e Se	n Giu r Cys o Val r Tyr	Ser Al a Ar g Ser 55	G y Val G n 40 G y	Pr o Ser 25 Pr o I I e	G y 10 G y Pr o Thr	Leu His Giy Asn	Ser G u Tyr 60	IIe Gy 45 Asn	Ser 30 Leu Pr o	15 His Giu Ser	Asp Trp Leu

			P08	4876	D1 S	ieq L	isti	ng			
Ala Arg Ser I	Leu Ala 100	Arg Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Яу
Thr Leu Val ⁻ 115	Thr Val	Ser Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala I 130	Pro Ser	Ser Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys Leu 145	Val Lys	Asp Tyr 150	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Giy /	Ala Leu 165	Thr Ser	Яу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser (Gly Leu 180	Tyr Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu (195	Gly Thr	Gin Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr I 210	Lys Val	Asp Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr (225	Cys Pro	Pro Cys 230	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Яy	Яу	Asp 240
Ser Val Phe I	Leu Phe 245	Pro Pro	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro (Glu Val 260	Thr Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
GyGuVall 275	Lys Phe	Asn Trp	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr I 290	Lys Pro	Arg Giu 295	Gu	Gn	Asp	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val I 305	Leu Thr	Val Leu 310	His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys I	Lys Val 325	Ser Asn	Lys	Ala	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys
Thr IIe Ser I	Lys Ala 340	Lys Giy	G n	345	Arg Page		Pr o	Gn	Val 350	Tyr	Thr
					uyo	210					

	al Ser Leu Thr 65
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala V 370 375 380	al Giu Trp Giu
Ser Asn Cly Cln Pro Clu Asn Asn Tyr Lys Thr Thr P 385 390 395	ro Pro Val Leu 400
Asp Ser Asp Giy Ser Phe Phe Leu Tyr Ser Lys Leu T 405 410	hr Val Asp Lys 415
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser V 420 425	al Met His Giu 430
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser L 435 440 4	eu Ser Pro 45
<210> 121 <211> 447 <212> PRT <213> Artificial	
<220>	
<223> an artificially synthesized sequence	
<223> an artificially synthesized sequence <400> 121	
	ys Pro Ser Clu 15
<400> 121 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val L	15
<400> 121 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Li 1 5 10 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser I	15 Ie Ser His Asp 30
<400> 121 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Li 1 Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser I 20 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Gia	15 Ie Ser His Asp 30 Iy Leu Giu Trp 5
<400> 121 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Li Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser I 20 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Gi 40 Ile Giy Phe IIe Ser Tyr Ser Giy IIe Thr Asn Tyr Arg	15 Ie Ser His Asp 30 Iy Leu Giu Trp 5 sn Pro Ser Leu
<400> 121 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Ling Thr Leu Ser Leu Thr Cys Alia Val Ser Giy His Ser I His Alia Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Gia His Giy Phe II e Ser Tyr Ser Giy II e Thr Asn Tyr A Gin Giy Arg Val Thr II e Ser Arg Asp Asn Ser Lys A	15 Ie Ser His Asp 30 Iy Leu Giu Trp 5 Sn Pro Ser Leu sn Thr Leu Tyr 80

			P08	84876	6D1 S	Seq L	.isti	ng			
Thr Leu Val 115	Thr Val	Ser Se	⁷ Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pro Leu Ala 130	Pro Ser	Ser Ly 13		Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Gy Cys Leu 145	Val Lys	Asp Ty 150	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser Giy	Ala Leu 165	Thr Se	Gy	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser Ser	Giy Leu 180	Tyr Se	^r Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser Leu 195	Giy Thr	Gn Th	- Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn Thr 210	Lys Val	Asp Ly 21		Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His Thr 225	Cys Pro	ProCy 230	s Pro	Al a	Pr o	Asp 235	Leu	Leu	Яу	Gу	Asp 240
Ser Val Phe	Leu Phe 245	Pro Pr	o Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr Pro	Giu Val 260	Thr Cy	s Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
GyGuVal 275	Lys Phe	Asn Tr	o Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys Thr 290	Lys Pro	Arg G 29		G n	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser Val 305	Leu Thr	Val Le 310	JHis	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys Cys	Lys Val 325	Ser As	ו Lys	Al a	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys
Thr IIe Ser	Lys Ala 340	Lys G	y Gin	Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu Pro Pro 355	Ser Arg	Asp G	u Leu 360		Lys Page		Gn	Val 365	Ser	Leu	Thr

Cys Leu Val Lys G y 370	Phe Tyr Pro 375	Ser Asp IIe	Ala Val C 380	Э́и Trp Ǵu
Ser Asn Gly Gin Pro 385	Giu Asn Asn 390	Tyr Lys Thr 395	Thr Pro F	Pro Val Leu 400
Asp Ser Asp G y Ser 405	Phe Phe Leu	Tyr Ser Lys 410	Leu Thr V	/al Asp Lys 415
Ser Arg Trp Gin Gin 420	Giy Asn Val	Phe Ser Cys 425		∧let His Giu ∔30
Ala Leu His Asn His 435	Tyr Thr G n 440	Giu Ser Leu	Ser Leu S 445	Ser Pro
<210> 122 <211> 447 <212> PRT <213> Artificial				
<220> <223> an artificial	ly synthesi:	zed sequence		
<400> 122	, ,	·		
Gin Val Gin Leu Gin 1 5	Giu Ser Giy	Pro Gy Leu 10	Val Lys F	Pro Ser Giu 15
Thr Leu Ser Leu Thr 20	Cys Ala Val	Ser Giy His 25	Ser Ile S	Ser His Asp
		20		30
His Ala Trp Ser Trp 35	Val Arg Gin 40		Э	30
	40	Pro Pro Giy	3 GuGyL 45	30 _eu Giu Trp
35 Ile Ciy Phe Ile Ser 50	40 Tyr Ser Giy 55	Pro Pro Giy	G u G y L 45 Tyr Asn F 60	30 ∟eu Giu Trp Pro Ser Leu
35 Ile Giy Phe Ile Ser 50 Gin Giy Arg Val Thr	40 Tyr Ser Gry 55 Ile Ser Arg 70	Pro Pro Gry Ile Thr Asn Asp Asn Ser 75	G u G y L 45 Tyr Asn F 60 Lys Asn T	30 Leu Giu Trp Pro Ser Leu Thr Leu Tyr 80
35 Ile G y Phe Ile Ser G n G y Arg Val Thr 65 Leu G n Met Asn Ser	40 Tyr Ser Giy 55 Ile Ser Arg 70 Leu Arg Ala	Pro Pro G y II e Thr Asn Asp Asn Ser 75 G u Asp Thr 90	G u G y L Tyr Asn F 60 Lys Asn T Al a Val T Tyr Trp C	30 Leu Giu Trp Pro Ser Leu Thr Leu Tyr 80 Tyr Tyr Cys 95

						P08	4876	6D1 S	Seq L	.isti	ng			
Pro Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
Giy Cys 145	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
Gin Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser Ser	Leu 195	Giy	Thr	Gin	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr His 225	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Leu	Leu	Gу	Gу	Asp 240
Ser Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Arg Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp
Pro Giu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Ala Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val Ser 305	Val	Leu	Thr	Val 310	Leu	His	GIn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys
Thr IIe	Ser	Lys 340	Al a	Lys	Gу	Gin	Pr o 345	Ar g	Gu	Pr o	Gin	Val 350	Tyr	Thr
Leu Pro	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gin	Val 365	Ser	Leu	Thr
Cys Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o		Asp Page		Al a 380	Val	Gu	Tr p	Gu

Ser Asn Giy Gin Pro Giu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 385 390 395 400												
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415												
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430												
Ala Leu His Asn His Tyr Thr Gin Clu Ser Leu Ser Leu Ser Pro 435 440 445												
<210> 123 <211> 447 <212> PRT <213> Artificial												
<220> <223> an artificially synthesized sequence												
<400> 123												
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15												
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30												
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45												
lle Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60												
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80												
Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95												
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Glu Gly 100 105 110												
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125												
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140												

	P084876D1 Seq Listing												
Gy Cys Leu 145	Val Lys	Asp Ty 150	r Phe/	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160		
Asn Ser Gy	Ala Leu 165	Thr Se	er Giy	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu		
Gin Ser Ser	Gly Leu 180	Tyr Se	er Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser		
Ser Ser Leu 195	Giy Thr	Gn Th	nr Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o		
Ser Asn Thr 210	Lys Val		vs Lys 15	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys		
Thr His Thr 225	Cys Pro	Pro O 230	vs Pro	Al a	Pr o	Asp 235	Leu	Leu	Gу	Asp	Asp 240		
Ser Val Phe	Leu Phe 245	Pro Pi	o Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser		
Arg Thr Pro	Giu Val 260	Thr Q	/s Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp		
GyGuVal 275	Lys Phe	Asn Tr	p Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn		
Ala Lys Thr 290	Lys Pro		uGu 95	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val		
Val Ser Val 305	Leu Thr	Val Le 310	eu His	Gn	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320		
Tyr Lys Cys	Lys Val 325	Ser As	sn Lys	Al a	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys		
Thr IIe Ser	Lys Ala 340	Lys G	y Gin	Pr o 345	Ar g	Gu	Pr o	GIn	Val 350	Tyr	Thr		
Leu Pro Pro 355	Ser Arg	Asp G	u Leu 360	Thr	Lys	Asn	GIn	Val 365	Ser	Leu	Thr		
Cys Leu Val 370	Lys Giy		vr Pro 75	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu		
Ser Asn Gy 385	Gin Pro	G u As 390	sn Asn	-	Lys Page	395	Thr	Pr o	Pr o	Val	Leu 400		

Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys 405 410 415 415 Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His Giu 420 425 430 Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445 <210> 124 <211> 447 <212> PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> 124 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45 lle Gry Phe Ile Ser Tyr Ser Gry Ile Thr Asn Tyr Asn Pro Ser Leu 50 60 Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 65 70 75 80 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 95 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Giy Giu Giy 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys G y Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gy Gy Thr Ala Ala Leu 130 135 140

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

130

Page 223

P084876D1 Seq Listing

	P084876D1 Seq Listing												
Asn Ser G y A	la Leu Thr 165	Ser Giy	Val Hi 17		Phe Pro	Ala Val 175	Leu						
	ay Leu Tyr 80	Ser Leu	Ser Se 185	r Val \	Val Thr	Val Pro 190	Ser						
Ser Ser Leu G 195	ly Thr Gin	Thr Tyr 200		s Asn \	Val Asn 205	His Lys	Pr o						
Ser Asn Thr L 210	ys Val Asp	Lys Lys 215	Val G		_ys Ser 220	Cys Asp	Lys						
Thr His Thr C 225	ys Pro Pro 230		Ala Pr	o Giu L 235	_eu Leu	Gy Asp	Asp 240						
Ser Val Phe L	eu Phe Pro 245	Pro Lys	ProLy 25		Thr Leu	Met IIe 255	Ser						
Arg Thr Pro G 2	lu Val Thr 60	Cys Val	Val Va 265	Asp \	Val Ser	Asp Giu 270	Asp						
GyGuValL 275	ys Phe Asn	Trp Tyr 280		pGy\	Val Gu 285	Val His	Asn						
Ala Lys Thr L 290	ys Pro Arg	G u G เ 295	Gin Ty		Ser Thr 300	Tyr Arg	Val						
Val Ser Val L 305	eu Thr Val 310		Gin As	p Trp L 315	_eu Asn	Gy Lys	G u 320						
Tyr Lys Cys L	ys Val Ser 325	Asn Ala	Ala Le 33		Arg Pro	lle Giu 335	Lys						
Thr IIe Ser L 3	ys Ala Lys 40	Gy Gr	Pro Ar 345	g Giu F	Pro Gin	Val Tyr 350	Thr						
Leu Pro Pro S 355	er Arg Asp	G u Leu 360		s Asn (Gin Val 365	Ser Leu	Thr						
Cys Leu Val L 370	ys Giy Phe	Tyr Pro 375	Ser As		Ala Val 380	Gu Trp	Gu						
Ser Asn G y G 385	aln Pro Giu 390		Tyr Ly	s Thr 1 395	Thr Pro	Pro Val	Leu 400						
Asp Ser Asp G	ay Ser Phe 405	Phe Leu	41		_eu Thr	Val Asp 415	Lys						

2016262766 25 Nov 2016

Ser Arg Trp Gin Gin Giy Asn Va	al Phe Ser Cys Ser Val Met His Giu											
420	425 430											
	an Giu Ser Leu Ser Leu Ser Pro 40 445											
<210> 125 <211> 447 <212> PRT <213> Artificial												
<220> <223> an artificially synthesized sequence												
<400> 125												
Gin Val Gin Leu Gin Giu Ser G	ly Pro Gly Leu Val Lys Pro Ser Glu											
1 5	10 15											
Thr Leu Ser Leu Thr Cys Ala Va	al Ser Gly His Ser IIe Ser His Asp											
20	25 30											
His Ala Trp Ser Trp Val Arg Gi	in Pro Pro Gly Glu Gly Leu Glu Trp											
35 40	0 45											
lle Giy Phe Ile Ser Tyr Ser G	ly lle Thr Asn Tyr Asn Pro Ser Leu											
50 55	60											
Gin Giy Arg Val Thr Ile Ser Ar	rg Asp Asn Ser Lys Asn Thr Leu Tyr											
65 70	75 80											
Leu Gin Met Asn Ser Leu Arg Al	la Giu Asp Thr Ala Val Tyr Tyr Cys											
85	90 95											
Ala Arg Ser Leu Ala Arg Thr Th	hr Ala Met Asp Tyr Trp Gly Glu Gly											
100	105 110											
	la Ser Thr Lys Gly Pro Ser Val Phe 20 125											
Pro Leu Ala Pro Ser Ser Lys Se	er Thr Ser Cly Cly Thr Ala Ala Leu											
130 135	140											
Giy Cys Leu Val Lys Asp Tyr Pl	he Pro Giu Pro Val Thr Val Ser Trp											
145 150	155 160											
Asn Ser Gly Ala Leu Thr Ser G	ly Val His Thr Phe Pro Ala Val Leu											
165	170 175											

P084876D1 Seq Listing

							P08	4876	5D1 S	Seq L	isti.	ng			
Gn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Giy	Thr	GIn	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	G u 235	Leu	Leu	Gу	Asp	Asp 240
Ser	Val	Phe	Leu	Phe 245	Pr o	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser
Ar g	Thr	Pr o	GI u 260	Val	Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	Asp 270	Gu	Asp
Яу	Яu	Val 275	Lys	Phe	Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn
Al a	Lys 290	Thr	Lys	Pr o	Ar g	G u 295	Gu	Gn	Tyr	Asn	Ser 300	Thr	Tyr	Ar g	Val
Val 305	Ser	Val	Leu	Thr	Val 310	Leu	His	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320
Tyr	Lys	Cys	Lys	Val 325	Ser	Asn	Lys	Al a	Leu 330	Pr o	Ar g	Pr o	lle	G u 335	Lys
Thr	l e	Ser	Lys 340	Al a	Lys	Gу	Gn	Pr o 345	Ar g	Gu	Pr o	Gn	Val 350	Tyr	Thr
Leu	Pr o	Pr o 355	Ser	Ar g	Asp	Gu	Leu 360	Thr	Lys	Asn	Gn	Val 365	Ser	Leu	Thr
Cys	Leu 370	Val	Lys	Gу	Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu
Ser 385	Asn	Gу	Gin	Pr o	G u 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400
Asp	Ser	Asp	Giy	Ser 405	Phe	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys
Ser	Ar g	Tr p	GIn 420	Gin	Gу	Asn	Val	425	Ser Page	Cys 226	Ser	Val	Met 430	His	Gu

Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445 <210> 126 <211> 447 <212> PRT <213> Artificial <220> <223> an artificially synthesized sequence <400> 126 Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly His Ser Ile Ser His Asp 20 25 30 His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45 Ile Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 60 Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 70 75 80 Leu Gin Met Asn Ser Leu Arg Ala Giu Asp Thr Ala Val Tyr Tyr Cys 85 90 Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gy Gu Gy 100 105 110 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Giy Giy Thr Ala Ala Leu 130 135 140 130 Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160 155 160 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu 165 170 175 Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190

		P084876D1 S	Seq Listing	
Ser Ser Leu G 195	y Thr Cin Th	nr Tyr Ile Cys 200	Asn Val As 20	
Ser Asn Thr Ly 210	s Val Asp Ly 21	vs Lys Val Giu 15	Pro Lys Se 220	r Cys Asp Lys
Thr His Thr Cy 225	s Pro Pro Cy 230	vs Pro Ala Pro	Asp Leu Le 235	u Ciy Ciy Asp 240
Ser Val Phe Le	u Phe Pro Pr 245	o Lys Pro Lys 250	Asp Thr Le	u Met IIe Ser 255
Arg Thr Pro Gi 26		vs Val Val Val 265	Asp Val Se	r Asp Giu Asp 270
Giy Giu Val Ly 275	s Phe Asn Tr	p Tyr Val Asp 280	Giy Val G 28	
Ala Lys Thr Ly 290	s Pro Arg G 29		Asn Ser Th 300	r Tyr Arg Val
Val Ser Val Le 305	u Thr Val Le 310	eu His Gin Asp	Trp Leu As 315	n Giy Lys Giu 320
Tyr Lys Cys Ly	s Val Ser As 325	sn Ala Ala Leu 330	Pro Arg Pr	olle Glu Lys 335
Thr IIe Ser Ly 34		y Gin Pro Arg 345	Giu Pro Gi	n Val Tyr Thr 350
Leu Pro Pro Se 355	r Arg Asp Gi	u Leu Thr Lys 360	Asn Gin Va 36	
Cys Leu Val Ly 370	s G y Phe Ty 37		lle Ala Va 380	l Gu Trp Gu
Ser Asn Giy Gi 385	n Pro Giu As 390	sn Asn Tyr Lys	Thr Thr Pr 395	o Pro Val Leu 400
Asp Ser Asp G	y Ser Phe Ph 405	ne Leu Tyr Ser 410	Lys Leu Th	r Val Asp Lys 415
Ser Arg Trp Gi 42		sn Val Phe Ser 425	Cys Ser Va	l Met His Giu 430
Ala Leu His As 435	n His Tyr Th	nr Gin Giu Ser 440 Page	44	_

<210> 127 <211> 447 <212> PRT <213> Artificial	I			
<220> <223> an artific	cially synth	nesized seque	ence	
<400> 127				
Gin Val Gin Leu 1	Gin Giu Ser 5	Giy Pro Giy 10	Leu Val Lys	Pro Ser Giu 15
Thr Leu Ser Leu 20	Thr Cys Ala	Val Ser Gy 25	His Ser IIe	Ser His Asp 30
His Ala Trp Ser 35	Trp Val Arg	Gin Pro Pro 40	GyGuGy 45	Leu G u Trp
lle Giy Phe lle 5 50	Ser Tyr Ser 55	Giy Ile Thr	Asn Tyr Asn 60	Pro Ser Leu
Gin Giy Arg Val 65	Thr IIe Ser 70	Arg Asp Asn	Ser Lys Asn 75	Thr Leu Tyr 80
Leu Gin Met Asn	Ser Leu Arg 85	Ala Giu Asp 90	Thr Ala Val	Tyr Tyr Cys 95
Ala Arg Ser Leu 100	Ala Arg Thr	Thr Ala Met 105	Asp Tyr Trp	GуGuGy 110
Thr Leu Val Thr 1 115	Val Ser Ser	Ala Ser Thr 120	Lys Giy Pro 125	Ser Val Phe
Pro Leu Ala Pro 5 130	Ser Ser Lys 135	Ser Thr Ser	GyGyThr 140	Ala Ala Leu
G y Cys Leu Val 145	Lys Asp Tyr 150	Phe Pro Gu	Pro Val Thr 155	Val Ser Trp 160
Asn Ser Giy Ala	Leu Thr Ser 165	Giy Val His 170	Thr Phe Pro	Ala Val Leu 175
Gin Ser Ser Giy 180	Leu Tyr Ser	Leu Ser Ser 185	Val Val Thr	Val Pro Ser 190
Ser Ser Leu G y 195	Thr G n Thr	Tyr lle Cys 200	Asn Val Asn 205	His Lys Pro

P084876D1 Seq Listing

	P084876D1 Seq Listing												
Ser Asn Thr Ly 210	s Val Asp Lys/ 215	Lys Val Giu P	ro Lys Ser (220	Cys Asp Lys									
Thr His Thr O 225	/s Pro Pro Cys 230	Pro Ala Pro A 2	sp Leu Leu (35	Эу Gy Asp 240									
Ser Val Phe Lo	eu Phe Pro Pro 245	b Lys Pro Lys A 250	sp Thr Leu N	Vet IIe Ser 255									
Arg Thr Pro Gi 20	u Val Thr Cys 50	Val Val Val A 265		Asp Giu Asp 270									
GyGuValL <u>y</u> 275	/s Phe Asn Trp) Tyr Val Asp G 280	ay Val Giu N 285	/al His Asn									
Ala Lys Thr Ly 290	/s Pro Arg Giu 295	ı Gu Gn Asp A	sn Ser Thr 1 300	Fyr Arg Val									
Val Ser Val Lo 305	eu Thr Val Leu 310	ıHis Cin Asp T 3	rp Leu Asn (15	Giy Lys Giu 320									
Tyr Lys Cys Ly	/s Val Ser Asr 325	ı Lys Ala Leu P 330	ro Arg Pro I	le Glu Lys 335									
	/s Ala Lys Giy 40	Gin Pro Arg G 345		/al Tyr Thr 350									
Leu Pro Pro So 355	er Arg Asp Giu	I Leu Thr Lys A 360	sn Gin Val S 365	Ser Leu Thr									
Cys Leu Val Ly 370	/s G y Phe Tyr 375	Pro Ser Asp I	le Ala Val C 380	Giu Trp Giu									
Ser Asn G y G 385	n Pro Giu Asr 390	n Asn Tyr Lys T 31	hr Thr Pro F 95	Pro Val Leu 400									
Asp Ser Asp G	y Ser Phe Phe 405	e Leu Tyr Ser L 410	ys Leu Thr \	/al Asp Lys 415									
Ser Arg Trp G 42	n Gin Giy Asr 20	Val Phe Ser C 425	,	√let His Giu ∔30									
Ala Leu His A 435	sn His Tyr Thr	GnGuSerL 440	eu Ser Leu S 445	Ser Pro									
<210> 128 <211> 447		Page 2	20										

P084876D1 Seq Listing													
<212> PRT <213> Artificial													
<220> <223> an artificially synthesized sequence													
<400> 128													
Gin Val Gin Leu Gin Giu Ser Giy Pro Giy Leu Val Lys Pro Ser Giu 1 5 10 15													
Thr Leu Ser Leu Thr Cys Ala Val Ser Giy His Ser Ile Ser His Asp 20 25 30													
His Ala Trp Ser Trp Val Arg Gin Pro Pro Giy Giu Giy Leu Giu Trp 35 40 45													
le Giy Phe Ile Ser Tyr Ser Giy Ile Thr Asn Tyr Asn Pro Ser Leu 50 55 60													
Gin Giy Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr 55 70 75 80													
∟eu Gin Met Asn Ser Leu Arg Ala Ciu Asp Thr Ala Val Tyr Tyr Cys 85 90 95													
Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Giy Giu Giy 100 105 110													
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe 115 120 125													
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu 130 135 140													
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 145 150 155 160													
Asn Ser Giy Ala Leu Thr Ser Giy Val His Thr Phe Pro Ala Val Leu 165 170 175													
Gin Ser Ser Giy Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser 180 185 190													
Ser Ser Leu Giy Thr Gin Thr Tyr Ile Cys Asn Val Asn His Lys Pro 195 200 205													
Ser Asn Thr Lys Val Asp Lys Lys Val G u Pro Lys Ser Cys Asp Lys 210 215 220													

P084876D1 Seq Listing												
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Asp Leu Leu Giy Giy 225 230 235	y Asp 240											
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met II 245 250 251	e Ser 5											
Arg Thr Pro Giu Val Thr Cys Val Val Val Asp Val Ser Asp Gi 260 265 270	u Asp											
Giy Giu Val Lys Phe Asn Trp Tyr Val Asp Giy Val Giu Val His 275 280 285	s Asn											
Ala Lys Thr Lys Pro Arg Giu Giu Gin Tyr Asn Ser Thr Tyr Arg 290 295 300	g Val											
Val Ser Val Leu Thr Val Leu His Gin Asp Trp Leu Asn Giy Lys 305 310 315	s Giu 320											
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Arg Pro Ile Gi 325 330 330 331												
Thr Ile Ser Lys Ala Lys Gly Gin Pro Arg Giu Pro Gin Val Tyr 340 345 350	r Thr											
Leu Pro Pro Ser Arg Asp Giu Leu Thr Lys Asn Gin Val Ser Le 355 360 365	u Thr											
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trj 370 375 380	pGu											
Ser Asn Gly Gin Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val 385 390 395	Leu 400											
Asp Ser Asp G y Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val As 405 410 411												
Ser Arg Trp Gin Gin Giy Asn Val Phe Ser Cys Ser Val Met His 420 425 430	s Giu											
Ala Leu His Asn His Tyr Thr Gin Giu Ser Leu Ser Leu Ser Pro 435 440 445	0											
<210> 129 <211> 447 <212> PRT <213> Artificial												
<220>												

<223	P084876D1 Seq Listing <223> an artificially synthesized sequence														
<400		129	1	a	a	0	a	D	a	1	1/-1	1	D	0	a
Gin 1	Val	Gn	Leu	G n 5	Gu	Ser	Gy	Pr o	G y 10	Leu	Val	Lys	Pro	Ser 15	Gu
Thr	Leu	Ser	Leu 20	Thr	Cys	Al a	Val	Ser 25	Gу	His	Ser	lle	Ser 30	His	Asp
Hi s	Al a	Tr p 35	Ser	Tr p	Val	Ar g	G n 40	Pr o	Pr o	Gу	Gu	G y 45	Leu	Gu	Tr p
l e	G y 50	Phe	lle	Ser	Tyr	Ser 55	Gу	lle	Thr	Asn	Tyr 60	Asn	Pr o	Ser	Leu
G n 65	Яу	Ar g	Val	Thr	lle 70	Ser	Ar g	Asp	Asn	Ser 75	Lys	Asn	Thr	Leu	Tyr 80
Leu	GIn	Met	Asn	Ser 85	Leu	Ar g	Al a	Gu	Asp 90	Thr	Al a	Val	Tyr	Tyr 95	Cys
Al a	Ar g	Ser	Leu 100	Al a	Ar g	Thr	Thr	Al a 105	Met	Asp	Tyr	Tr p	G y 110	Gu	Gу
Thr	Leu	Val 115	Thr	Val	Ser	Ser	Al a 120	Ser	Thr	Lys	Gу	Pr o 125	Ser	Val	Phe
Pr o	Leu 130	Al a	Pr o	Ser	Ser	Lys 135	Ser	Thr	Ser	Gу	G y 140	Thr	Al a	Al a	Leu
G y 145	Cys	Leu	Val	Lys	Asp 150	Tyr	Phe	Pr o	Gu	Pr o 155	Val	Thr	Val	Ser	Tr p 160
Asn	Ser	Gу	Al a	Leu 165	Thr	Ser	Gу	Val	His 170	Thr	Phe	Pr o	Al a	Val 175	Leu
GIn	Ser	Ser	GIy 180	Leu	Tyr	Ser	Leu	Ser 185	Ser	Val	Val	Thr	Val 190	Pr o	Ser
Ser	Ser	Leu 195	Gіу	Thr	Gη	Thr	Tyr 200	lle	Cys	Asn	Val	Asn 205	His	Lys	Pr o
Ser	Asn 210	Thr	Lys	Val	Asp	Lys 215	Lys	Val	Gu	Pr o	Lys 220	Ser	Cys	Asp	Lys
Thr 225	His	Thr	Cys	Pr o	Pr o 230	Cys	Pr o	Al a	Pr o	Asp 235	Tyr	Leu	Gу	Asp	Asp 240

		P084876D1 Seq Listing											
Ser Val F	Phe Leu	Phe Pro 245	Pr o	Lys	Pr o	Lys 250	Asp	Thr	Leu	Met	e 255	Ser	
Arg Thr F	Pro Giu 260	Val Thr	Cys	Val	Val 265	Val	Asp	Val	Ser	His 270	Gu	Asp	
Pro Giu V 2	Val Lys 275	Phe Asn	Tr p	Tyr 280	Val	Asp	Gу	Val	G u 285	Val	His	Asn	
Ala Lys T 290	Thr Lys	Pro Arg	G u 295	Gи	G n	Asp	Asn	Ser 300	Thr	Tyr	Ar g	Val	
Val Ser V 305	Val Leu	Thr Val 310	Leu	Hi s	G n	Asp	Tr p 315	Leu	Asn	Gу	Lys	G u 320	
Tyr Lys C	Cys Lys	Val Ser 325	Asn	Asp	Al a	Leu 330	Pr o	Lys	Pr o	lle	G u 335	Lys	
Thr Ile S	Ser Lys 340	Ala Lys	Яу	Βn	Pr o 345	Ar g	Gu	Pr o	Βn	Val 350	Tyr	Thr	
Leu Pro F 3	Pro Ser 355	Arg Asp	Gu	Leu 360	Thr	Lys	Asn	G n	Val 365	Ser	Leu	Thr	
Cys Leu V 370	Val Lys	Gy Phe	Tyr 375	Pr o	Ser	Asp	lle	Al a 380	Val	Gu	Tr p	Gu	
Ser Asn C 385	Giy Gin	Pro Giu 390	Asn	Asn	Tyr	Lys	Thr 395	Thr	Pr o	Pr o	Val	Leu 400	
Asp Ser A	Asp Giy	Ser Phe 405	Phe	Leu	Tyr	Ser 410	Lys	Leu	Thr	Val	Asp 415	Lys	
Ser Arg T	Frp Gin 420	Gn Gy	Asn	Val	Phe 425	Ser	Cys	Ser	Val	Met 430	His	Gu	
Ala Leu H 4	His Asn 135	His Tyr	Thr	G n 440	Gu	Ser	Leu	Ser	Leu 445	Ser	Pr o		

2