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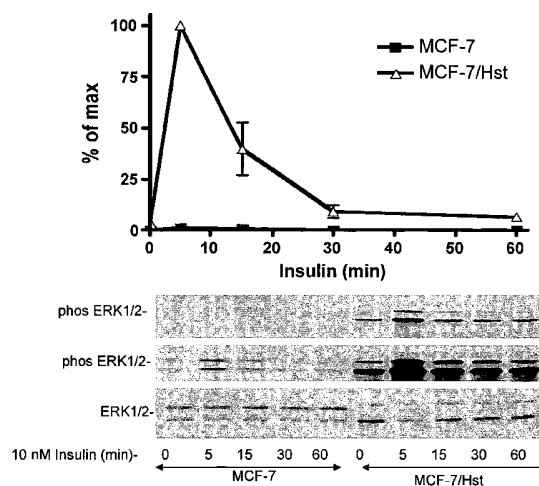
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(54) Title: COMPOSITIONS AND METHODS FOR TREATING DISEASE



(57) Abstract: The present invention discloses for the first time that the insulin receptor (IR) is a target of Herstatin, which modulates IR and IR-mediated intracellular signaling. In preferred aspects, Herstatin binds at nM concentrations to cell-surface IR, up-regulates basal IR expression by several-fold, induces the accumulation of pro-IR, and stimulates insulin activation of the ERK pathway. Moreover, these changes in insulin signaling are accompanied by alterations in IGF-IR expression, IRS-2 levels, and the serine phosphorylation state of both IRS-1 and IRS-2. Preferred aspects provide novel therapeutic methods and pharmaceutical compositions for treatment of conditions associated with altered IR expression or IR-mediated signaling, including but not limited to insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and combinations thereof, and cancer.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

COMPOSITIONS AND METHODS FOR TREATING DISEASE

FIELD OF THE INVENTION

Aspects of the invention relate generally to therapeutic molecules, compositions and methods for treatment of diseases through modulation of the insulin receptor (IR) and IR-mediated intracellular signaling by administration of Herstatin or variants thereof, and in more particular aspects relate to compositions and methods for cell targeting, and for the treatment of conditions or diseases associated with altered IR expression or altered IR-mediated signaling, including but not limited to insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and combinations thereof, and cancer.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to: United States Provisional Patent Application Serial No. 60/616,596, filed 05 October 2004 and entitled "COMPOSITIONS AND METHODS FOR TREATING DISEASE"; and to United States Provisional Patent Application Serial No. 60/688,355, filed 06 June 2005, of same title, both of which are incorporated by reference herein in their entireties.

BACKGROUND

The Insulin Receptor. The insulin receptor is the canonical member of the insulin receptor family of receptor tyrosine kinases, which also includes the IGF-IR and the insulin receptor-related receptor (IRR). These molecules share a heterotetrameric structure comprised of two extracellular ligand-binding α subunits, which are coupled to each other and to two transmembrane β subunits by disulfide linkages. The intracellular portion of the β subunit contains the intrinsic tyrosine kinase catalytic domain, which is activated by binding of extracellular ligand and a presumed conformational change in the β subunit. The activated receptor undergoes autophosphorylation of tyrosine residues in the kinase domain as well as residues in the flanking juxtamembrane and carboxyl-terminal domains. The phosphorylation of these residues, particularly in the juxtamembrane region, allows the recruitment of scaffolding adapter proteins such as IRS-1 and IRS-2 and Shc, which are then phosphorylated on tyrosine residues by the activated receptor to recruit a second level of signaling molecules to initiate the signaling cascades that are responsible for insulin action. These include the ERK arm of the

MAPK pathway, the P13K-Akt/PKB pathway, and the APS-Cbl-CrkII-TC10 pathway. In cells expressing both insulin and IGF-I receptors, hybrid receptors consisting of insulin and IGF-I receptor α - β hemireceptors can form. These are activated by IGF-I but not by insulin. The insulin receptor family of receptors differs from the erbB/Her receptors by virtue of their existence as pre-dimerized heterotetramers and their use of intermediates such as IRS and Shc proteins to couple to downstream signaling pathways.

Diabetes and Related Conditions. The epidemic of obesity occurring in the in the United States and around the world portends a significant increase in type 2 diabetes mellitus in the adult and, increasingly, in the pediatric populations. There is also growing concern regarding the prevalence of pre-diabetic conditions such as the metabolic syndrome, the incidence of which dwarfs that of clinically apparent diabetes *per se*. The hyperglycemia of type 2 diabetes results from defects in both insulin sensitivity and pancreatic β -cell function, leading to a relatively insulin-deficient state. There is also a growing appreciation that insulin resistance may play an important role in cardiac disease. A mainstay of current therapy is the use of insulin-sensitizing agents such as metformin and thiazolidinediones that act to enhance the ability of insulin to trigger appropriate cellular responses such as glucose transport in insulin-target tissues. These treatments suffer, however, from a lack of mechanistic specificity, high rates of unresponsiveness (up to 30% for thiazolidinediones), and frequent side effects. Although advances are being made in the generation of islets for transplant, the time frame for the successful application of these approaches in human patients with both type 1 and type 2 disease and their ability to affect insulin resistance remains unclear. Thus, there continues to be an urgent need to design new and novel therapies to treat insulin resistance (see, *e.g.*, Alsheikh-Ali & Karas, *Amer J Cardiology*, 93:1417-8, 2004; Ovalle & Fernando, *Southern Med J.*, 95:1188-94, 2002; and Zangeneh et al., *Mayo Clinic Proc.* 78:471-479, 2003).).

The ErbB Receptor Family. The ErbB receptor family consists of four receptor tyrosine kinases: EGFR (HER-1, erbB-1), HER-2 (neu, erbB-2), HER-3 (erbB-3) and HER-4 (erbB-4). Altered expression of ErbB receptors by mutational activation, receptor overexpression, and tumor production of ligands contributes to the development and maintenance of a variety of human cancers (Olayioye et al., *Embo J.*, 19:3159-67, 2000).

The ErbB receptors are activated by several ligands with an EGF core domain (EGF-related growth factors). The exception is the HER-2 receptor, which is recruited as a preferred dimer partner with other ligand binding erbB receptors (*Id.*). The eleven mammalian EGF-like ligands are all agonists, whereas *Drosophila* express the ligand Argos that inhibits activation of

the EGFR (Dougall et al., *Oncogene* 9:2109-23, 1994; Hynes & Stern, *Biochim. Biophys. Acta* 1198:165-84, 1994); Tzahar & Yarden, *Biochim. Biophys. Acta* 1377:25-37, 1998).

Insulin-like growth factor 1 receptor (IGF-IR). Anti-erbB receptor antibody agents, such as the HER-2-specific antibody rhuMab4D5 (HERCEPTIN™) have been approved for cancer therapy. Significantly, however, tumor cells may be inherently resistant, or gain resistance, to anti-erbB receptor therapies through activation of IGF-IR pathways (Chakravarti et al., *Cancer Res.* 62:200-7, 2002; Lu et al., *J. Biol. Chem.* 279:2856-65, 2004; Lu et al., *J. Natl. Cancer Inst.*, 93:1852-7, 2001). Activation of the IGF-IR by IGF-I promotes, *inter alia*, proliferation, survival, transformation, metastasis, and angiogenesis (Baserga, *Hum. Pathol.* 31, 275-6, 2000; Wang & Sun, *Curr. Cancer Drug Targets* 2:191-207, 2002), and signaling through both IGF-IR and EGF receptors is central to tumorigenesis. IGF-IR is in the same receptor family as the insulin receptor.

Herstatin. Although the HER-2 receptor does not directly bind EGF-like ligands, a secreted product of an HER-2 alternative transcript, Herstatin, binds with high affinity to the ectodomains of all members of the EGF receptor family, including EGFR/HER1/*erbB1*; HER2/*neu/erbB2*, HER3/*erbB3*, and HER4/*erbB4*, and to Δ EGFR and IGF-IR (Shamieh et al., *FEBS Letters*, 568:163-166, 2004). Herstatin was originally cloned from ovarian cancer cells, and consists of a segment (340 amino acids identical to the N-terminal subdomains I and II) of the HER-2 ectodomain, followed by 79 amino acids, encoded by intron 8 that function as a receptor binding domain (RBD) (Doherty et al., *Proc. Natl. Acad. Sci. USA* 96:10869-74, 1999). Herstatin blocks homomeric and heteromeric ErbB receptor interactions (*e.g.*, dimerization and activation), inhibits signaling by EGF ligands and by IGF-1 (*e.g.*, inhibits activation of the PI3K/Akt pathway initiated by EGF, TGF α , Heregulin and IGF-1) (Doherty et al., *Proc Natl Acad Sci.*, 96:10869-10874, 1999; Azios et al., *Oncogene*, 20:5199-5209, 2001; Justman & Clinton, *J Biol Chem.*, 277:20618-20624, 2002; Jhabvala-Romero et al., *Oncogene*, 22:8178-8186, 2003; and Shamieh et al., *supra*), causes growth arrest, and has utility as an anti-cancer agent (*Id.*, Azios et al., *Oncogene* 20:5199-209, 2001; Jhabvala-Romero et al., *Oncogene* 22:8178-86, 2003; Justman & Clinton, *J. Biol. Chem.* 277:20618-24, 2002).

There is, therefore, a need in the art to further investigate and characterize the interactions among the IR, the erbB family receptors, and the IGF-I receptor, and to identify modulators of the signaling mediated by these receptors.

There is a pronounced need in the art to identify and develop IR modulators as therapeutic agents.

There is a pronounced need in the art to design new and novel therapies to treat insulin resistance.

There is a need in the art to further assess and exploit the receptor-modulating utilities of Herstatin.

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SUMMARY OF THE INVENTION

The present invention relates to therapeutic molecules and compositions for modulation of the insulin receptor (IR) and IR-mediated intracellular signaling by administration of an isoform of a cell surface receptor, and in preferred aspects, to administration of Herstatin, which is an example of such a cell surface receptor isoform. Aspects of the invention are based upon the discovery that the insulin receptor (IR) is a target of Herstatin, which specifically binds to the IR with nM affinity. According to preferred aspects of the present invention, Herstatin alters the landscape of IR-mediated signaling, exerting a positive effect on IR expression, and substantially increasing IR-mediated ERK pathway activation. The MEK (MAPK kinase)-ERK pathway has been shown to be significantly involved in glucose transport (*e.g.*, Harmon et al., *Am. J. Physiol. Endocrinol. Metab.*, 287:E758-E766, 2004).

In particular aspects, Herstatin was shown herein to bind at nM concentrations to cell-surface IR, to up-regulate basal IR expression by several-fold, and to induce the accumulation of pro-IR.

In additional aspects, and with respect to signal transduction, Herstatin was shown herein to substantially (*e.g.*, >40-fold) stimulate insulin activation of the ERK pathway, but to have little effect on insulin-stimulated activation of the PI3K/Akt pathway.

In further aspects, these changes in insulin signaling were shown herein to be accompanied by about a 4-fold *decrease* in IGF-IR expression, a decrease in the apparent serine phosphorylation state of IRS-1, and a slight decrease in IRS-2 levels as well as a decrease in apparent serine phosphorylation of IRS-2.

Therefore, according to particular aspects of the present invention, Herstatin, a cell surface receptor isoform, has substantial utility for modulating insulin signaling in cells expressing IR.

Preferred aspects of the present invention thus provide novel therapeutic methods and pharmaceutical compositions comprising a cell surface receptor isoform (*e.g.*, Herstatin, and/or variants thereof) for modulating IR, and IR-mediated signal transduction.

Alternative preferred aspects provide for a novel use of Herstatin in therapeutic methods and pharmaceutical compositions for treating various diseases associated with or characterized

by alterations in insulin sensitivity or resistance (*e.g.*, conditions or diseases characterized by altered IR expression and/or altered IR-related signaling).

In preferred embodiments, the invention provides novel methods and compositions for the treatment of conditions or diseases associated with altered IR expression or altered IR-mediated signaling, including but not limited to at least one of insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and cancer.

Additional aspects provide novel methods of targeted drug delivery.

Methods of treatment. Particularly preferred embodiments provide a method for treating or modulating a condition having an aspect related to, or associated with, or characterized by altered IR expression or altered IR-mediated signaling at a cellular level, comprising administering to a subject having such a condition, a therapeutically effective amount of a cell surface receptor isoform such as Herstatin, or a variant thereof (*e.g.*, a therapeutically effective amount of a Int8 RBD polypeptide, or a variant thereof), that binds to the extracellular domain of cellular target IR. Preferably, the condition is selected from the group consisting of insulin resistance, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, diabetes-associated lipid metabolism disorders, neurodegenerative disorders, and combinations thereof. In alternative related embodiments, the cell further expresses a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4); IGF-IR and combinations thereof.

Alternative related preferred embodiments further comprise administering a therapeutically effective amount of a molecule such as a small molecule, protein, peptide or receptor-specific antibody that binds to the extracellular domain of a target receptor selected from the group consisting of: IR, EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-IR.

Preferably, the methods further comprise administration of the cell surface receptor isoforms of this invention in combination with a therapeutically effective amount of an agent selected from the group consisting of: insulin, insulin-sensitizing agents, insulin secretagogues, and combinations thereof. Preferably, the insulin-sensitizing agent is selected from the group consisting of biguanides, metformin, thiazolidinediones (glitazones), and combinations thereof. Preferably, the insulin secretagogue is selected from the group consisting of sulfonylureas, meglitinides, and combinations thereof.

Pharmaceutical compositions. Additional preferred embodiments provide a pharmaceutical composition for treating a condition having an aspect related to, or associated with or characterized by altered IR expression or altered IR-mediated signaling at a cellular level, comprising, along with a pharmaceutically acceptable carrier or excipient, a cell surface receptor isoform such as Herstatin, or a variant thereof (*e.g.*, a Int8 RBD polypeptide, or a variant thereof), that binds to the extracellular domain of a cellular target IR. Preferably, the condition is selected from the group consisting of insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and combinations thereof. In alternative related preferred embodiments, the targeted cell further expresses a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4); IGF-IR, and combinations thereof. Preferably, the pharmaceutical composition further comprises an agent selected from the group consisting of: insulin, insulin-sensitizing agents, insulin secretagogues, and combinations thereof. Preferably, the insulin-sensitizing agent is selected from the group consisting of biguanides, metformin, thiazolidinediones (glitazones), and combinations thereof. Preferably, the insulin secretagogue is selected from the group consisting of sulfonylureas, meglitinides, and combinations thereof.

Cell targeting. Yet further preferred embodiments provide methods and compositions for targeting a therapeutic agent to a cell expressing IR, comprising attaching the therapeutic agent to the cell surface receptor isoform, such as Herstatin, or to a variant thereof (*e.g.*, a Int8 RBD polypeptide, or a variant thereof), that binds to the extracellular domain of a cellular target IR.

In related embodiments, the targeted cell further expresses a target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4); IGF-IR, and combinations thereof.

Preferably, in all of the above-described preferred embodiments, the Herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, wherein at least one N-linked glycosylation site is present, and wherein the polypeptide binds to the extracellular domain of insulin receptor with an affinity binding constant of at least 10^8 M^{-1} . In particular aspects, the Herstatin, or variant thereof, comprises a sequence selected from the group consisting of SEQ ID NOS:32-42.

Preferably, the Herstatin or variant thereof comprises SEQ ID NO:32. Preferably, the Herstatin or variant thereof consists of SEQ ID NO:32.

Preferably, the Int8 RBD polypeptide, or a variant thereof comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the extracellular domain of insulin receptor with an affinity binding constant of at least 10^8 M^{-1} . In particular aspects, the Int8 RBD polypeptide, or a variant thereof, comprises a sequence selected from the group consisting of SEQ ID NOS:21-31. Preferably, the Int8 RBD polypeptide or variant thereof comprises SEQ ID NO:21. Preferably, the Int8 RBD polypeptide or variant thereof consists of SEQ ID NO:21.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows, according to particular aspects of the present invention as described in more detail in EXAMPLE II below, that Herstatin bound at nM concentrations to 3T3 cells over-expressing insulin receptor (IR), but not to 3T3 parental cells.

Figures 2A and 2B show, according to particular aspects as described in more detail in EXAMPLE III below, that Herstatin expression up-regulated IR expression and activation in MCF-7 cells.

Figures 3A and 3B show, according to particular aspects as described in more detail in EXAMPLE IV below, that in MCF-7 cells Herstatin expression substantially amplified insulin-stimulated ERK activation.

Figures 4A, 4B, 4C and 4D show, according to particular aspects as described in more detail in EXAMPLE V below, that Herstatin altered the expression of an array of proteins that are directly involved in insulin action.

Figure 5 shows, according to particular aspects, that the EGFR inhibitor AS1478 does not affect insulin signaling.

Figure 6 shows, according to particular aspects, that inhibition of the EGF receptor with an EGF receptor-specific inhibitor does not lead to an increase in insulin receptor.

DETAILED DESCRIPTION OF THE INVENTION

Herstatin is an example of a cell surface receptor isoform, that may also be referred to as an alternative receptor product or an intron fusion protein, which functions as a receptor ligand, and functions as a secreted ligand that inhibits members of the EGF receptor family. Herstatin binds with high affinity to all members of the EGF receptor family, including

EGFR/HER1/*erbB1*, HER2/*neu/erbB2*, HER3/*erbB3*, HER4/*erbB4*, and to Δ EGFR, and further binds to the IGF-IR.

The present invention discloses for the first time that the insulin receptor (IR) is a target of the cell surface receptor isoform, Herstatin, which specifically binds to the IR with nM affinity. According to preferred aspects of the present invention, Herstatin binds at nM concentrations to cell-surface IR, and further modulates insulin signaling in cells (*e.g.*, MCF-7 human breast cancer cells, etc) expressing IR.

Herstatin is disclosed herein to alter expression of the IR and in particular to up-regulate basal IR expression by several-fold, and induce the accumulation of pro-IR.

Herstatin is further disclosed herein to modulate insulin activation. Herstatin stimulates insulin activation of the ERK pathway in a range of about 5- to about 80-fold, while having a more modest to little effect on insulin-stimulated (IR-mediated) activation of the PI3K/Akt pathway.

Significantly, these changes in insulin signaling were shown herein to be accompanied by a *decrease* in IGF-IR expression in the range of about a 2- to about a 10-fold decrease, a decrease in the apparent serine phosphorylation state of IRS-1, and a slight decrease in IRS-2 levels as well as a decrease in apparent serine phosphorylation of IRS-2.

Therefore, preferred aspects of the present invention provide for uses of Herstatin in novel methods and compositions for treating a condition having an aspect related to, or associated with or characterized by altered IR expression or IR-mediated signal transduction.

The instant description and Examples, in various aspects, disclose the ability of Herstatin to modulate insulin action in cell models (*e.g.*, a breast cancer cell model that consists of the well-characterized MCF-7 human breast cancer cell line, and two derivative clones that express human Herstatin from a stably transfected expression vector).

In particular aspects, Herstatin binding to cell-surface IR was investigated using IR-expressing 3T3 cells (IRA-3T3). Moreover, the effects of Herstatin on the expression and activation of the IR itself, and upon the expression and activation of the major signaling pathways that emanate from the activated insulin receptor (*e.g.*, the ERK pathway and the PI3K/Akt pathway) were investigated in MCF-7 and in Herstatin-expressing MCF-7 cells. All of the individual assays were repeated a minimum of three times with similar, if not identical, results, and many of the findings have been replicated and confirmed in experiments with an independent Herstatin-expressing MCF-7 clone.

According to preferred aspects of the present invention, Herstatin upregulates IR expression and IR-mediated signal transduction (*e.g.*, substantially (>40-fold) stimulating insulin

activation of the ERK pathway). Therefore, Herstatin and/or RBD Int8 polypeptides, and Herstatin- and/or RBD Int8 polypeptide-based agents (e.g., conjugates with drugs, toxins, radionuclides, etc.) have utility as therapeutic agents for treatment of diseases or conditions having an aspect related to, or associated with or characterized by altered IR expression or altered IR-mediated signaling at a cellular level (e.g., insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and combinations thereof).

Preferred aspects provide novel methods and compositions for treating cellular insulin resistance (for discussion of insulin resistance see, e.g., Alsheikh-Ali & Karas, *Amer J Cardiology*, 93:1417-8, 2004; Ovalle & Fernando, *Southern Med J.*, 95:1188-94, 2002; and Zangeneh et al., *Mayo Clinic Proc.* 78:471-479, 2003).

According to additional preferred aspects, Herstatin and/or Herstatin-based agents can be used to target IR-expressing cells and/or modulate IR-mediated signaling.

DEFINITIONS

"Herstatin," an example of a cell surface receptor isoform (also referred to as an intron fusion protein) refers to the polypeptides of SEQ ID NO:2 (including SEQ ID NOS:32-42), and additionally includes functional (e.g., target receptor-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof.

As used herein, an isoform of a cell surface receptor (also referred to herein as a CSR isoform), such as an isoform of a receptor tyrosine kinase, refers to a receptor that lacks a domain or portion thereof sufficient to alter or modulate a biological activity of the receptor or modulate a biological activity compared to a wildtype and/or predominant form of the receptor. A CSR isoform refers to a receptor that lacks a domain or portion of a domain sufficient to alter or modulate a biological activity of the receptor, for example the insulin receptor. Generally, a biological activity is altered in an isoform at least 0.1, 0.5, 1, 2, 3, 4, 5, or 10-fold compared to a wildtype and/or predominant form of the receptor. Typically, a biological activity is altered 10-, 20-, 50-, 100- or 1000-fold or more. With reference to an isoform, alteration of activity refers to difference in activity between the particular isoform, which is shortened, compared to the unshortened form of the receptor. Alteration of biological activity includes an enhancement or a reduction of activity. In particular embodiments, alteration of a biological activity is a reduction in the activity. In particular embodiments, an alteration of a biological activity is a reduction in

biological activity, and the reduction can be at least 0.1 0.5 1, 2, 3, 4, 5, or 10-fold compared to a wildtype and/or predominant form of the receptor. Typically, a biological activity is reduced 5, 10, 20, 50, 100 or 1000-fold or more. Reference herein to a CSR isoform with altered activity refers to the alteration in an activity by virtue of the different structure or sequence of the CSR isoform compared to a cognate receptor.

Reference herein to modulating the activity of a target cell surface receptor means that a CSR isoform interacts in some manner with the target receptor and activity, such as ligand binding or dimerization or other signal-transduction-related activity is altered.

Intron fusion proteins (IFPs) are exemplary CSR isoforms. IFPs, for purposes herein include natural and combinatorial IFPs. A natural IFP refers to a polypeptide that is encoded by an alternatively spliced RNA that contains one or more amino acids encoded by an intron operatively linked to one or more portions of the polypeptide encoded by one or more exons of a gene. Alternatively spliced mRNA is one that is isolated or is one that can be prepared synthetically by joining splice donor and acceptor sites in a gene. A natural IFP contains one or more amino acids and/or one or more stop codons encoded by an intron sequence. A combinatorial IFP refers to a polypeptide that is shortened compared to a wildtype or predominant form of a polypeptide. Typically, the shortening removes one or more domains or a portion thereof from a polypeptide such that a biological activity is altered. Combinatorial IFPs often mimic a natural IFP in that one or more domains or a portion thereof that is/are deleted in a natural IFP derived from the same gene sequence or derived from a gene sequence in a related gene family.

As used herein, natural with reference to IFP, refers to any protein, polypeptide or peptide or fragment thereof (by virtue of the presence of the appropriate splice acceptor/donor sites) that is encoded within the genome of an animal and/or is produced or generated in an animal or that could be produced from a gene. Natural IFPs include allelic variant. IFPs can be modified post-translationally.

“RBD Int8 polypeptide” refers to the polypeptides of SEQ ID NO:1 (including SEQ ID NOS:21-31), and additionally includes functional (*e.g.*, target receptor-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins, derivatives and fusion proteins thereof.

“Mutant RBD Int8 polypeptide” or “mutant Int8 RBD polypeptide” refers to the intron 8-encoded receptor binding domain variants (with an Arg to Ile mutation at residue 31 thereof) of SEQ ID NO:3), and additionally includes functional (*e.g.*, target receptor non-binding) variants (including conservative amino acid sequence variants as described herein), fragments, muteins,

derivatives and fusion proteins thereof. Representative, corresponding Herstatin variants (Arg to Ile mutation at residue 371) are given as SEQ ID NO:4.

“EGFR,” “HER-1” or “erbB-1” refer to the art-recognized human epidermal growth factor receptor, erbB-1 (cDNA: NM_005228, SEQ ID NO:5; protein: NP_005219, SEQ ID NO:6), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

“ΔEGFR” refers to the art-recognized receptor, ΔEGFR (cDNA: SEQ ID NO:7; protein: SEQ ID NO:8) (*see* Ekstrand et al., *PNAS* 89:4309-4313, 1992; and Nishikawa et al., *PNAS* 91:7727-7731, 1994) (comprising a deletion in the ECD; cDNA positions 275 through 1075, corresponding to exons 2-7 of the EGFR gene), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

“HER-2” or “erbB-2” refers to the art-recognized human receptor, erbB-2 (cDNA: NM_004448, SEQ ID NO:9; protein: NP_004439, SEQ ID NO:10), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

“HER-3” or “erbB-3” refers to the art-recognized human receptor, erbB-3 (cDNA: NM_001982, SEQ ID NO:11; protein: NP_001973, SEQ ID NO:12), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

The phrase “mutant form of HER-3” refers to a HER-3 protein having a substitution of Glu for Gly in the ectodomain of HER-3 corresponding to a single point mutation at nucleotide position 1877 (“a” instead of “g” at this position), resulting in substitution of Glu instead of Gly at residue position 560) (cDNA: SEQ ID NO:13; protein: SEQ ID NO:14).

“HER-4” or “erbB-4” refers to the art-recognized human receptor, erbB-4 (cDNA: NM_005235, SEQ ID NO:15; protein: NP_005226, SEQ ID NO:16), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

“IGF-IR” refers to the art recognized insulin-like growth factor I receptor (cDNA: NM_000875, SEQ ID NO:17; protein: NP_000866, SEQ ID NO:18), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

“Insulin receptor” or IR refers to the art-recognized insulin receptor (cDNA: NM_000208, SEQ ID NO:19; protein: NP_000199, SEQ ID NO:20), and including Herstatin-, and/or Int8 RBD polypeptide-binding variants thereof.

TABLE 1. Summary of key SEQ ID NOS and accession numbers:

MOLECULE	cDNA	PROTEIN
RBD Int8 polypeptide(s))		SEQ ID NO:1
Herstatin(s)		SEQ ID NO:2 SEQ ID NOS:32-42
Mutant Int8 RBD polypeptide(s)		SEQ ID NO:3 SEQ ID NOS:21-31
Mutant Herstatin(s)		SEQ ID NO:4
EGFR (HER-1 or erbB-1)	SEQ ID NO:5 (NM_005228)	SEQ ID NO:6 (NP_005219)
Δ EGFR	SEQ ID NO:7	SEQ ID NO:8
HER-2 (erbB-2)	SEQ ID NO:9 (NM_004448)	SEQ ID NO:10 (NP_004439)
HER-3 (erbB-3)	SEQ ID NO:11 (NM_001982)	SEQ ID NO:12 (NP_001973)
Mutant form of HER-3	SEQ ID NO:13	SEQ ID NO:14
HER-4 (erbB-4)	SEQ ID NO:15 (NM_005235)	SEQ ID NO:16 (NP_005226)
IGF-IR	SEQ ID NO:17 (NM_000875)	SEQ ID NO:18 (NP_000866)
Insulin receptor (IR)	SEQ ID NO:19 (NM_000208)	SEQ ID NO:20 (NP_000199.1)

Cell Surface Receptor (CSR) Isoforms

Provided herein are cell surface receptor (CSR) isoforms (including intron fusion proteins; IFPs) having the novel biological activity of altering IR expression or altered IR mediated signaling. The CSR isoforms differ from the cognate receptors in that there are insertions and/or deletions, and the resulting CSR isoforms exhibit a difference in one or more activities or functions compared to the cognate receptor. Such differences include, for example elimination of all or part of a transmembrane domain, and/or a change in a biological activity of the CSR (e.g., as disclosed herein, the ability to modulate insulin receptor (IR) expression or IR-mediated signaling). The CSR isoforms provided herein can be used for modulating the activity of a cell surface receptor (e.g., the IR). They also can be used as targeting agents (e.g., targeting

IR) for delivery of molecules, such as drugs or toxins or nucleic acids, to targeted cells or tissues.

A CSR isoform refers to a receptor that lacks a domain or portion of a domain sufficient to alter a biological activity (e.g., an activity with respect to the IR). Thus, an isoform may differ from a wildtype and/or predominant form of the receptor, in that it lacks one or more biological activities of the receptor. Additionally, CSR isoforms can contain a new domain and/or biological function as compared to a wildtype and/or predominant form of the receptor. For example, intron-encoded amino acids can introduce a new domain or portion thereof into a CSR isoform. Biological activities that can be altered (or gained) include, but are not limited to, protein-protein interactions such as dimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and relocalization, membrane anchoring, enzymatic activity such as kinase activity, response to regulatory molecules including regulatory proteins, cofactors, and other signaling molecules, such as in a signal transduction pathway. Generally, a biological activity is altered in an isoform at least 0.1, 0.5, 1, 2, 3, 4, 5, or 10-fold as compared to a wildtype and/or predominant form of the receptor. Typically, a biological activity is altered 10, 20, 50, 100 or 1000-fold or more. For example, an isoform can be reduced with respect to a particular biological activity.

CSR isoforms can also modulate an activity of a wildtype and/or predominant form of the cognate receptor. For example, a CSR isoform can interact directly or indirectly with a CSR isoform and modulate a biological activity of the cognate receptor. Biological activities that can be altered include, but are not limited to, protein-protein interactions such as dimerization, multimerization and complex formation, specificity and/or affinity for ligand, cellular localization and relocalization, membrane anchoring, enzymatic activity such as kinase activity, response to regulatory molecules including regulatory proteins, cofactors, and other signaling molecules, such as in a signal transduction pathway.

A CSR isoform can interact directly or indirectly with a cell surface receptor to cause or participate in a biological effect, such as by modulating a biological activity of the cell surface receptor (e.g., in the instant case, the IR). A CSR isoform also can interact independently of a cell surface receptor to cause a biological effect, such as by initiating or inhibiting a signal transduction pathway. For example, a CSR isoform can initiate a signal transduction pathway and enhance or promote cellular metabolism. In another example, a CSR isoform can interact with the cell surface receptor as a ligand, causing a biological effect for example by inhibiting a signal transduction pathway that can promote or alter a cellular response to insulin. Hence, the isoforms provided herein can function as cell surface receptor ligands in that they interact with

the targeted receptor in the same manner that a cognate ligand interacts with and alters receptor activity. The isoforms can bind as a ligand, but not necessarily to the ligand binding site, and can serve to block receptor dimerization. They act as ligands in the sense that they interact with the receptor. The CSR isoforms also can act by binding to ligands for the receptor and/or by preventing receptor activities, such as dimerization.

For example, a CSR isoform can compete with a CSR for ligand binding. A CSR isoform can act as a dominant negative inhibitor, for example, when complexed with a CSR. A CSR isoform can act as a dominant negative inhibitor or as a competitive inhibitor of a CSR, for example, by complexing with a CSR isoform and altering the ability of the CSR to multimerize (e.g., dimerize or trimerize) with other CSRs. A CSR isoform can compete with a CSR for interactions with other polypeptides and cofactors in a signal transduction pathway.

The cell surface isoforms and families of isoforms provided herein include, for example, isoforms of the HER-2 receptor (e.g., Herstatin), IR, etc. Pharmaceutical compositions containing one or more different CSR isoforms are provided. Also provided are methods of treatment of diseases and conditions by administering the pharmaceutical compositions or delivering a CSR isoform, such by administering the isoform protein (polypeptide, etc), and/or by administration of a vector that encodes the isoform. Administration, by either means, can be effected *in vivo* or *ex vivo*. Also provided are methods for expressing, isolating and formulating CSR isoforms.

Herstatin and/or RBD Int8 polypeptides and therapeutic agents

In preferred aspects, the present invention provides for Herstatin (e.g., the sequences of SEQ ID NO:2) and polypeptides thereof that bind to a *insulin receptor* (IR) as a target receptor (specifically, or in addition to the known targets: EGFR, HER-2, HER-3, DEGRF, HER-4 and IGF-IR). Also provided are RBD Int8 polypeptides (e.g., the sequences of SEQ ID NO:1) and receptor-binding polypeptides thereof that bind to a *insulin receptor* as a target receptor (specifically, or in addition to the known targets EGFR, HER-2, HER-3, DEGRF, HER-4 and IGF-IR).

Preferably, the Herstatin and/or RBD Int8 polypeptides comprise an amino acid sequence of SEQ ID NO:1 (or of SEQ ID NO:1 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions), or a fragment of a sequence of SEQ ID NO:1 (or a fragment of SEQ ID NO:1 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions) of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the extracellular domain (ECD) of a target receptor (e.g.,

EGFR, HER-2, HER-3, DEGFR, HER-4, IGF-IR and IR (as disclosed herein)) with an affinity binding constant of at least 10^7 M^{-1} , at least $5 \times 10^7 \text{ M}^{-1}$, or at least 10^8 M^{-1} . Preferably, the Herstatin and/or RBD Int8 polypeptide is from about 69 to 79 contiguous residues in length, with a IR affinity binding constant of at least 10^7 M^{-1} , at least $5 \times 10^7 \text{ M}^{-1}$, or at least 10^8 M^{-1} (similar to the respective binding constants associated with the known EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR target receptors). Preferably, Herstatin and/or RBD Int8 polypeptide comprises a sequence of SEQ ID NO:1, or a conservative amino acid substitution variant thereof. In particular aspects, the Int8 RBD polypeptide, or a variant thereof, comprises a sequence selected from the group consisting of SEQ ID NOS:21-31. Preferably, the Int8 RBD polypeptide or variant thereof comprises SEQ ID NO:21. Preferably, the Int8 RBD polypeptide or variant thereof consists of SEQ ID NO:21.

Preferably, the Herstatin and/or RBD Int8 polypeptides comprise an amino acid sequence of SEQ ID NO:2 (or of SEQ ID NO:2 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions), or a fragment of a sequence of SEQ ID NO:2 (or a fragment of SEQ ID NO:2 having from 1, to about 3, to about 5, to about 10, or to about 20 conservative amino acid substitutions) of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, and wherein the polypeptide binds to the extracellular domain (ECD) of a IR with an affinity binding constant of at least 10^7 M^{-1} , at least $5 \times 10^7 \text{ M}^{-1}$, or at least 10^8 M^{-1} (similar to the respective binding constants associated with the known EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR target receptors). Preferably, the Herstatin and/or RBD Int8 polypeptide is from about 350 to 419 contiguous residues in length, wherein the polypeptide binds to the extracellular domain (ECD) of a IR with an affinity binding constant of at least 10^7 M^{-1} , at least $5 \times 10^7 \text{ M}^{-1}$, or at least 10^8 M^{-1} (similar to the respective binding constants associated with the known EGFR, HER-2, HER-3, DEGFR, HER-4 and IGF-IR target receptors). Preferably, comprises a sequence of SEQ ID NO:2, or a conservative amino acid substitution variant thereof. In particular aspects, the Herstatin, or variant thereof, comprises a sequence selected from the group consisting of SEQ ID NOS:32-42. Preferably, the Herstatin or variant thereof comprises SEQ ID NO:32. Preferably, the Herstatin or variant thereof consists of SEQ ID NO:32.

Biologically Active Variants

Variants of Herstatin and/or RBD Int8 polypeptide have substantial utility in various aspects of the present invention. Variants can be naturally or non-naturally occurring. Naturally occurring variants are found in humans or other species and comprise amino acid sequences

which are substantially identical to the amino acid sequences shown in SEQ ID NO:1 or SEQ ID NO:2, and include natural sequence polymorphisms. Species homologs of the protein can be obtained using subgenomic polynucleotides of the invention, as described below, to make suitable probes or primers for screening cDNA expression libraries from other species, such as mice, monkeys, yeast, or bacteria, identifying cDNAs which encode homologs of the protein, and expressing the cDNAs as is known in the art.

Non-naturally occurring variants which retain substantially the same biological activities as naturally occurring protein variants, including the target RBD activity and the modulation of target receptor signaling activity, are also included here. Preferably, naturally or non-naturally occurring variants have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequence shown in SEQ ID NOS:1 or 2. More preferably, the molecules are at least 98% or 99% identical. Percent identity is determined using any method known in the art. A non-limiting example is the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1. The Smith-Waterman homology search algorithm is taught in Smith and Waterman, *Adv. Appl. Math.* 2:482-489, 1981.

As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are generally in the "L" isomeric form. Residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property is retained by the polypeptide. NH₂ refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in *J. Biol. Chem.*, 243:3552-59 (1969) and adopted at 37 C.F.R., §§.1.821-1.822, abbreviations for amino acid residues are shown in Table 1:

TABLE 1 – Table of Correspondence

SYMBOL		AMINO ACID
1-Letter	3-Letter	
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine

SYMBOL		
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	Proline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	aspartic acid
N	Asn	Asparagine
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

It should be noted that all amino acid residue sequences represented herein by a formula have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase "amino acid residue" is defined to include the amino acids listed in the Table of Correspondence and modified and unusual amino acids, such as those referred to in 37 C.F.R., §§ 1.821-1.822, and incorporated herein by reference. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues or to an amino-terminal group such as NH₂ or to a carboxyl-terminal group such as COOH.

Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity can be found using computer programs well known in the art, such as DNASTARTM software. Preferably, amino acid changes in the protein variants disclosed herein are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change

involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

In a peptide or protein, suitable conservative substitutions of amino acids are known to those of skill in this art and generally can be made without altering a biological activity of a resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, *e.g.*, Watson *et al. Molecular Biology of the Gene*, 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p.224).

Such substitutions may be made in accordance with those set forth in TABLE 2 as follows:

TABLE 2

Original residue	Conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Other substitutions also are permissible and can be determined empirically or in accord with other known conservative (or non-conservative) substitutions.

5 Variants of the Herstatin and/or RBD Int8 polypeptide disclosed herein include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (*e.g.*, pegylated molecules). Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art. Variants also include allelic variants, species variants, and muteins. Truncations or deletions of regions which do not affect functional activity of the
10 proteins are also variants.

A subset of mutants, called muteins, is a group of polypeptides in which neutral amino acids, such as serines, are substituted for cysteine residues which do not participate in disulfide bonds. These mutants may be stable over a broader temperature range than native secreted proteins (Mark *et al.*, United States Patent 4,959,314).

15 Preferably, amino acid changes in the Herstatin and/or RBD Int8 polypeptide variants are conservative amino acid changes, *i.e.*, substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains. Naturally occurring amino acids are generally divided into four families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar
20 (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cystine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids.

It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or
25 valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting secreted protein or polypeptide variant. Properties and functions of Herstatin and/or RBD Int8 polypeptide protein or polypeptide variants are of the same type as a protein comprising the amino acid sequence encoded by the nucleotide sequences shown in SEQ
30 ID NO:1 or 2, although the properties and functions of variants can differ in degree.

Herstatin and/or RBD Int8 polypeptide variants include glycosylated forms, aggregative conjugates with other molecules, and covalent conjugates with unrelated chemical moieties (*e.g.*, pegylated molecules). Herstatin and/or RBD Int8 polypeptide variants also include allelic variants (*e.g.*, polymorphisms), species variants, and muteins. Truncations or deletions of

regions which do not preclude functional activity of the proteins are also variants. Covalent variants can be prepared by linking functionalities to groups which are found in the amino acid chain or at the N- or C-terminal residue, as is known in the art.

It will be recognized in the art that some amino acid sequence of the Herstatin and/or RBD Int8 polypeptides of the invention can be varied without significant effect on the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there are critical areas on the protein which determine activity. In general, it is possible to replace residues that form the tertiary structure, provided that residues performing a similar function are used. In other instances, the type of residue may be completely unimportant if the alteration occurs at a non-critical region of the protein. The replacement of amino acids can also change the selectivity of binding to cell surface receptors (Ostade et al., *Nature* 361:266-268, 1993). Thus, the Herstatin and/or RBD Int8 polypeptides of the present invention may include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the disclosed protein. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic (Pinckard et al., *Clin. Exp. Immunol.* 2:331-340, 1967; Robbins et al., *Diabetes* 36:838-845, 1987; Cleland et al., *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377, 1993).

Amino acids in the Herstatin and/or RBD Int8 polypeptides of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085, 1989). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as binding to a natural or synthetic binding partner. Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol.* 224:899-904, 1992 and de Vos et al. *Science* 255:306-312, 1992).

As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein. Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors,

including those described above. Generally speaking, the number of substitutions for any given Herstatin and/or RBD Int8 polypeptide will not be more than 50, 40, 30, 25, 20, 15, 10, 5 or 3.

In addition, pegylation of Herstatin and/or RBD Int8 polypeptides and/or muteins is expected to provide such improved properties as increased half-life, solubility, and protease resistance. Pegylation is well known in the art.

Fusion Proteins

Fusion proteins comprising proteins or polypeptide fragments of Herstatin and/or RBD Int8 polypeptide can also be constructed. Fusion proteins are useful for generating antibodies against amino acid sequences and for use in various targeting and assay systems. For example, fusion proteins can be used to identify proteins which interact with a Herstatin and/or RBD Int8 polypeptide of the invention or which interfere with its biological function. Physical methods, such as protein affinity chromatography, or library-based assays for protein-protein interactions, such as the yeast two-hybrid or phage display systems, can also be used for this purpose. Such methods are well known in the art and can also be used as drug screens. Fusion proteins comprising a signal sequence can be used.

A fusion protein comprises two protein segments fused together by means of a peptide bond. Amino acid sequences for use in fusion proteins of the invention can be utilize the amino acid sequence shown in SEQ ID NOS:1 or 2 or can be prepared from biologically active variants of SEQ ID NOS:1 or 2, such as those described above. The first protein segment can include of a full-length Herstatin and/or RBD Int8 polypeptide.

Other first protein segments can consist of about 50 to about 79 contiguous amino acids from SEQ ID NO:1, or, with respect to SEQ ID NO:2, from about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids of SEQ ID NO:2 are present, or from about 350 to 419 contiguous residues in length wherein the C-terminal 79 contiguous amino acids of SEQ ID NO:2 are present.

The second protein segment can be a full-length protein or a polypeptide fragment. Proteins commonly used in fusion protein construction include β -galactosidase, β -glucuronidase, green fluorescent protein (GFP), autofluorescent proteins, including blue fluorescent protein (BFP), glutathione-S-transferase (GST), luciferase, horseradish peroxidase (HRP), and chloramphenicol acetyltransferase (CAT). Additionally, epitope tags can be used in fusion protein constructions, including histidine (His) tags, FLAG tags, influenza hemagglutinin (HA) tags, Myc tags, VSV-G tags, and thioredoxin (Trx) tags. Other fusion constructions can

include maltose binding protein (MBP), S-tag, Lex a DNA binding domain (DBD) fusions, GAL4 DNA binding domain fusions, and herpes simplex virus (HSV) BP16 protein fusions.

These fusions can be made, for example, by covalently linking two protein segments or by standard procedures in the art of molecular biology. Recombinant DNA methods can be used to prepare fusion proteins, for example, by making a DNA construct which comprises a coding region for the protein sequence of SEQ ID NOS:1 or 2 in proper reading frame with a nucleotide encoding the second protein segment and expressing the DNA construct in a host cell, as is known in the art. Many kits for constructing fusion proteins are available from companies that supply research labs with tools for experiments, including, for example, Promega Corporation (Madison, WI), Stratagene (La Jolla, CA), Clontech (Mountain View, CA), Santa Cruz Biotechnology (Santa Cruz, CA), MBL International Corporation (MIC; Watertown, MA), and Quantum Biotechnologies (Montreal, Canada; 1-888-DNA-KITS).

Cell Targeting

According to additional preferred aspects of the present invention, cell surface receptor isoforms such as Herstatin- and/or RBD Int8 polypeptide-based agents can be used to target insulin receptor (IR) on cells (*e.g.*, insulin-resistant cells, IR-expressing cells involved with some aspect of glucose regulation or metabolism, cancer cells, etc.). Herstatin- and/or RBD Int8 polypeptide-based agents can be used to deliver a locally acting biological agent that will affect the targeted cell.

IR, in the context of the inventive targeting, is expressed on the surface of cells and is accessible (specifically, or in addition to at least one of the other known Herstatin targets: EGFR; HER-2; HER-3; HER-4, Δ EGFR and IGF-IR) to exogenous molecules. For example, where IR is present at higher levels on particular IR-bearing cells (*e.g.*, adipocytes, hepatocytes, skeletal muscle cells, pancreatic beta cells, brain/nerve cells, etc) as compared to other cells, they can be utilized as preferential targets for systemic Herstatin- and/or RBD Int8 polypeptide-based agents and therapies. The differential expression of the target receptor (*e.g.*, IR) enables the specificity of Herstatin- and/or RBD Int8 polypeptide-based agents-based therapy. Herstatin- and/or RBD Int8 polypeptide-based agents (*e.g.*, drugs, cytotoxic agents, labeling agents, etc.) directed against the target receptor preferentially affect the targeted cell over normal tissue. For example, a Herstatin- or RBD Int8 polypeptide-drug conjugate that binds a IR present predominantly on particular cells (*e.g.*, adipocytes, hepatocytes, skeletal muscle cells, pancreatic beta cells, brain/nerve cells, etc) would be expected to selectively affect those cells within a treated individual. Preferably, the target receptor is accessible to the Herstatin- and/or

RBD Int8 polypeptide-based agent, and is found in substantially greater concentrations on the targeted cells (*e.g.*, adipocytes, hepatocytes, skeletal muscle cells, pancreatic beta cells, brain/nerve cells, etc) relative to other cells that don't express IR or that express IR at relatively low levels.

5 Therefore, the present invention includes Herstatin- and/or RBD Int8 polypeptide-based agents specific to one or more of the target receptors (*e.g.*, IR) that will enable or facilitate therapeutic treatments relating to, for example, adipocytes, hepatocytes, skeletal muscle cells, pancreatic beta cells, brain cells, etc.

10 In particular aspects, Herstatin- and/or RBD Int8 polypeptides are conjugated or coupled to drugs, or to toxins.

 In alternate embodiments, Herstatin- and/or RBD Int8 polypeptides are conjugated or coupled to radionuclides.

 Additional embodiments provide for Herstatin- and/or RBD Int8 polypeptide-coated liposomes that contain one or more biologically active compounds.

15 In preferred embodiments, Herstatin-mediated targeting is used to deliver drugs or other agents to adipocytes, hepatocytes, skeletal muscle cells, pancreatic beta cells, brain cells, and combinations thereof.

 In alternate aspects, targeted binding of an Herstatin- and/or RBD Int8 polypeptide-agent to a cell is sufficient to modulate IR-mediated signaling, inhibit or alter growth (*e.g.*, cytostatic effects) or even kill the target cell (cytotoxic effects) if so desired. The mechanism of these activities may vary, but may involve Herstatin- and/or RBD Int8 polypeptide-dependent receptor activation, changes in receptor expression, cell-mediated cytotoxicity, activation of apoptosis, inhibition of ligand-receptor function, or provide a signal for complement fixation. In fact, Herstatin- and/or RBD Int8 polypeptide-agents may exhibit one or several such activities. In particular aspects, Herstatin- and/or RBD Int8 polypeptide-agents are cytostatic, but not cytotoxic. In particular embodiments, Herstatin- and/or RBD Int8 polypeptide-agents bind to target receptors (*e.g.*, IR, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), Δ EGFR or IGF-IR), and modulate signaling and cellular metabolism, or are either cytotoxic or cytostatic, etc.

30 In additional embodiments, Herstatin- and/or RBD Int8 polypeptide-agents are conjugated or coupled to a diverse array of compounds which include, but are not limited to proteins, drugs, toxins or cytotoxic agents, cytostatic agents, radionuclides, apoptotic factors (Wuest et al. 2002), anti-angiogenic compounds or other biologically active compounds which will affect cellular signaling or metabolism, inhibit the growth of or even kill the target cell or

tissue. For example, cytotoxic or cytostatic agents include, but are not limited to, diphtheria toxin and Pseudomonas exotoxin (Kreitman 2001 a; Kreitman 2001 b), ricin (Kreitman 2001 a), gelonin, doxorubicin (Ajani et al. 2000) and its derivatives, iodine-131, yttrium-90 (Witzig 2001), indium-111 (Witzig 2001), RNase (Newton and Ryback 2001), calicheamicin (Bernstein 2000), apoptotic agents, and antiangiogenic agents (Frankel et al. 2000; Brinkmann et al. 2001; Garnett 2001). According to particular aspects of the present invention, Herstatin- and/or RBD Int8 polypeptides coupled to these compounds are used to adversely affect cells displaying one or more target receptors (*e.g.*, IR, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-IR).

Toxins can also be targeted to specific cells by incorporation of the toxin into Herstatin- and/or RBD Int8 polypeptide-coated liposomes. The Herstatin- and/or RBD Int8 polypeptide-based agent directs the liposome to the target cell where the bioactive compound is released. For example, cytotoxins in Herstatin- and/or RBD Int8 polypeptide-coated liposomes are used to treat cancer. In alternate embodiments, these targeted liposomes are loaded with DNA encoding bioactive polypeptides (*e.g.*, inducible nitric oxide synthase; Khare et al. 2001).

Prodrugs or enzymes can also be delivered to targeted cells by specific Herstatin- and/or RBD Int8 polypeptide-agents. In this case the Herstatin conjugate consists of a Herstatin- and/or RBD Int8 polypeptide-based agent coupled to a drug that can be activated once the polypeptide agent binds the target cell. Examples of this strategy using antibodies have been reviewed (Denny 2001; Xu and McLeod 2001).

Therefore, in particular embodiments, Herstatin- and/or RBD Int8 polypeptide-prodrug/enzyme conjugates targeted to one or more target receptors (*e.g.*, IR, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-IR) have utility for the treatment of, for example, cancer and other treatable conditions discussed herein.

The specificity and high affinity of the Herstatin- and/or RBD Int8 polypeptide-based agents makes them ideal candidates for delivery of toxic agents to a specific subset of cellular targets. Preferably, one or more target receptors (*e.g.*, IR, EGFR (HER-1, erbB-1); HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), ΔEGFR or IGF-IR) are present at higher levels on the target cells (*e.g.*, cancer, tumor cells) than on non-cancer cells.

As used herein, a composition refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

As used herein, a combination refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two

collections, can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

As used herein, a pharmaceutical effect refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

As used herein therapeutic effect means an effect resulting from treatment of a subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

In particular aspects, a therapeutic effect may also encompass prophylaxis of symptoms of a condition.

As used herein, the term "subject" refers to animals, including mammals, such as human beings. As used herein, a patient refers to a human subject.

As used herein, the phrase "associated with" or "characterized by" refers to certain biological aspects such as expression of a receptor or signaling by a receptor that occurs in the context of a disease or condition. Such biological aspects may or may not be causative or integral to the disease or condition but merely an aspect of the disease or condition.

As used herein, a biological activity refers to a function of a polypeptide including but not limited to complexation, dimerization, multimerization, receptor-associated kinase activity, receptor-associated protease activity, phosphorylation, dephosphorylation, autophosphorylation, ability to form complexes with other molecules, ligand binding, catalytic or enzymatic activity, activation including auto-activation and activation of other polypeptides, inhibition or modulation of another molecule's function, stimulation or inhibition of signal transduction and/or cellular responses such as cell proliferation, migration, differentiation, and growth, degradation, membrane localization, membrane binding, and oncogenesis. A biological activity can be assessed by assays described herein and by any suitable assays known to those of skill in the art, including, but not limited to *in vitro* assays, including cell-based assays, *in vivo* assays, including assays in animal models for particular diseases.

Pharmaceutical Compositions and Therapeutic Uses

Pharmaceutical compositions of the invention comprise a cell surface receptor isoform such as Herstatin and/or RBD Int8 polypeptides, or Herstatin- and/or RBD Int8 polypeptide-based agents of the claimed invention in a therapeutically effective amount. The term “therapeutically effective amount” as used herein refers to an amount of a therapeutic agent to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect. The effect can be detected by, for example, chemical markers or antigen levels. Therapeutic effects also include reduction in physical symptoms. The precise effective amount for a subject will depend upon the subject’s size and health, the nature and extent of the condition, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance. However, the effective amount for a given situation is determined by routine experimentation and is within the judgment of the clinician. For purposes of the present invention, an effective dose will generally be from about 0.01 mg/kg to 50 mg/kg or 0.05 mg/kg to about 10 mg/kg of the Herstatin and/or RBD Int8 polypeptide constructs in the individual to which it is administered. A non-limiting example of a pharmaceutical composition is a composition that either enhances or diminishes signaling mediated by the inventive target receptors (*e.g.*, IR, EGFR, HER-2, HER-3, ΔEGFR, HER-4 and IGF-IR). Where such signaling modulates a disease-related process, modulation of the signaling would be the goal of the therapy.

A pharmaceutical composition can also contain a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent, such as antibodies or a polypeptide, genes, and other therapeutic agents. The term refers to any pharmaceutical carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition, and which can be administered without undue toxicity. Suitable carriers can be large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Such carriers are well known to those of ordinary skill in the art. Pharmaceutically acceptable carriers in therapeutic compositions can include liquids such as water, saline, glycerol and ethanol. Auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, can also be present in such vehicles. Typically, the therapeutic compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. Liposomes are included within the definition of a pharmaceutically acceptable carrier. Pharmaceutically acceptable salts can also be present in the pharmaceutical composition, *e.g.*, mineral acid salts such as hydrochlorides, hydrobromides,

phosphates, sulfates, and the like; and the salts of organic acids such as acetates, propionates, malonates, benzoates, and the like. A thorough discussion of pharmaceutically acceptable excipients is available in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., New Jersey, 1991).

5

Delivery Methods

Once formulated, the compositions of the invention can be administered (as proteins/polypeptides, or in the context of expression vectors for gene therapy) directly to the subject or delivered *ex vivo*, to cells derived from the subject (*e.g.*, as in *ex vivo* gene therapy).

10 Direct delivery of the compositions will generally be accomplished by parenteral injection, *e.g.*, subcutaneously, intraperitoneally, intravenously or intramuscularly, myocardial, intratumoral, peritumoral, or to the interstitial space of a tissue. Other modes of administration include oral and pulmonary administration, suppositories, and transdermal applications, needles, and gene guns or hyposprays. Dosage treatment can be a single dose schedule or a multiple dose
15 schedule.

Methods for the *ex vivo* delivery and reimplantation of transformed cells into a subject are known in the art and described in, for example, International Publication No. WO 93/14778. Examples of cells useful in *ex vivo* applications include, for example, stem cells, particularly hematopoietic, lymph cells, macrophages, dendritic cells, or tumor cells. Generally, delivery of
20 nucleic acids for both *ex vivo* and *in vitro* applications can be accomplished by, for example, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, direct microinjection of the DNA into nuclei, and viral-mediated, such as adenovirus (and adeno-associated virus) or alphavirus, all well known in the art.

25 In a preferred embodiment, certain disorders (*e.g.*, of proliferation, such as cancer, etc), can be amenable to treatment by administration of a therapeutic agent based on the provided polynucleotide or corresponding polypeptide. The therapeutic agent can be administered in conjunction with one or more other agents including, but not limited to, receptor-specific antibodies and/or other agents (*e.g.*, insulin-sensitizing agents, chemotherapeutic agents, etc).
30 Administered "in conjunction" includes administration at the same time, or within 1 day, 12 hours, 6 hours, one hour, or less than one hour, as the other therapeutic agent(s). The compositions may be mixed for co-administration, or may be administered separately by the same or different routes.

The dose and the means of administration of the inventive pharmaceutical compositions are determined based on the specific qualities of the therapeutic composition, the condition, age, and weight of the patient, the progression of the disease, and other relevant factors. For example, administration of polynucleotide therapeutic compositions agents of the invention includes local or systemic administration, including injection, oral administration, particle gun or catheterized administration, and topical administration. The therapeutic polynucleotide composition can contain an expression construct comprising a promoter operably linked to a polynucleotide encoding, for example, about 80 to 419 (or about 350 to 419) contiguous amino acids of SEQ ID NO:2. Various methods can be used to administer the therapeutic composition directly to a specific site in the body. For example, an abnormal tissue, or small metastatic lesion is located and the therapeutic composition injected several times in several different locations within the body of the tissue, or tumor. Alternatively, arteries which serve a tissue or tumor are identified, and the therapeutic composition injected into such an artery, in order to deliver the composition directly into the tumor. A tissue or tumor that has a necrotic center is aspirated and the composition injected directly into the now empty center of the tissue or tumor. X-ray imaging is used to assist in certain of the above delivery methods.

Herstatin and/or RBD Int8 polypeptide-mediated targeted delivery of therapeutic agents to specific tissues can also be used. Receptor-mediated DNA delivery techniques are described in, for example, Findeis et al., *Trends Biotechnol.* (1993) 11:202; Chiou et al., *Gene Therapeutics: Methods And Applications Of Direct Gene Transfer* (J.A. Wolff, ed.) (1994); Wu et al., *J. Biol. Chem.* (1988) 263:621; Wu et al., *J. Biol. Chem.* (1994) 269:542; Zenke et al., *Proc. Natl. Acad. Sci. (USA)* (1990) 87:3655; Wu et al., *J. Biol. Chem.* (1991) 266:338.

For gene therapy, therapeutic compositions containing a polynucleotide are administered in a range of about 100 ng to about 200 mg of DNA for local administration in a gene therapy protocol. Concentration ranges of about 500 ng to about 50 mg, about 1 mg to about 2 mg, about 5 mg to about 500 mg, and about 20 mg to about 100 mg of DNA can also be used during a gene therapy protocol. Factors such as method of action (e.g., for enhancing or inhibiting levels of the encoded gene product) and efficacy of transformation and expression are considerations which will affect the dosage required for ultimate efficacy of the subgenomic polynucleotides. Where greater expression is desired over a larger area of tissue, larger amounts of subgenomic polynucleotides or the same amounts re-administered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions of, for example, a tumor site, may be required to affect a positive therapeutic outcome. In all cases,

routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.

The therapeutic polynucleotides and polypeptides of the present invention can be delivered using gene delivery vehicles. The gene delivery vehicle can be of viral or non-viral origin (see generally, Jolly, *Cancer Gene Therapy* (1994) 1:51; Kimura, *Human Gene Therapy* (1994) 5:845; Connelly, *Human Gene Therapy* (1995) 1:185; and Kaplitt, *Nature Genetics* (1994) 6:148). Expression of such coding sequences can be induced using endogenous mammalian or heterologous promoters. Expression of the coding sequence can be either constitutive or regulated.

Viral-based vectors for delivery of a desired polynucleotide and expression in a desired cell are well known in the art. Exemplary viral-based vehicles include, but are not limited to, recombinant retroviruses (see, e.g., WO 90/07936; WO 94/03622; WO 93/25698; WO 93/25234; U.S. Patent No. 5, 219,740; WO 93/11230; WO 93/10218; U.S. Patent No. 4,777,127; GB Patent No. 2,200,651; EP 0 345 242; and WO 91/02805), alphavirus-based vectors (e.g., Sindbis virus vectors, Semliki forest virus (ATCC VR-67; ATCC VR-1247), Ross River virus (ATCC VR-373; ATCC VR-1246) and Venezuelan equine encephalitis virus (ATCC VR-923; ATCC VR-1250; ATCC VR 1249; ATCC VR-532), and adeno-associated virus (AAV) vectors (see, e.g., WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and WO 95/00655). Administration of DNA linked to killed adenovirus as described in Curiel, *Hum. Gene Ther.* (1992) 3:147 can also be employed.

Non-viral delivery vehicles and methods can also be employed, including, but not limited to, polycationic condensed DNA linked or unlinked to killed adenovirus alone (see, e.g., Curiel, *Hum. Gene Ther.* (1992) 3:147); ligand-linked DNA (see, e.g., Wu, *J. Biol. Chem.* 264:16985 (1989)); eukaryotic cell delivery vehicles cells (see, e.g., U.S. Patent No. 5,814,482; WO 95/07994; WO 96/17072; WO 95/30763; and WO 97/42338) and nucleic charge neutralization or fusion with cell membranes. Naked DNA can also be employed. Exemplary naked DNA introduction methods are described in WO 90/11092 and U.S. Patent No. 5,580,859. Liposomes that can act as gene delivery vehicles are described in U.S. Patent No. 5,422,120; WO 95/13796; WO 94/23697; WO 91/14445; and EP 0524968. Additional approaches are described in Philip, *Mol. Cell Biol.* 14:2411 (1994), and in Woffendin, *Proc. Natl. Acad. Sci.* (1994) 91:11581-11585.

Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in Woffendin et al., *Proc. Natl. Acad. Sci. USA* 91(24):11581 (1994). Moreover, the coding sequence and the product of expression of such can be delivered through

deposition of photopolymerized hydrogel materials or use of ionizing radiation (see, *e.g.*, U.S. Patent No. 5,206,152 and WO 92/11033). Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun (see, *e.g.*, U.S. Patent No. 5,149,655); use of ionizing radiation for activating transferred gene (see, *e.g.*, U.S. Patent No. 5,206,152 and WO 92/11033).

Conditions Treatable

Particular aspects of the present invention, for the first time, disclose that Herstatin or Int8 RBD polypeptides, and variants thereof, can not only modulate the expression/level of cellular insulin receptors (IR) (both pro-IR and IR), but also modulate IR-mediated signal transduction (*e.g.*, ERK pathway). According to particular aspects, Herstatin or Int8 RBD polypeptides, and variants thereof can be used in therapeutic methods and pharmaceutical compositions to treat a variety of conditions having an aspect related to, or associated with altered IR expression or altered IR-mediated signaling at a cellular level. Such methods comprising administering to a subject having such a condition, a therapeutically effective amount of a Herstatin or Int8 RBD polypeptide, or a variant thereof, that binds to the extracellular domain of cellular target insulin receptor. Such methods also encompass gene delivery-related methods.

IR is well known in the art to be involved with, *inter alia*, glycemic control (*e.g.*, hyper- and hypo-glycemia) and glucose metabolism. Accordingly, conditions having an aspect related to, or associated with altered glycemic control and/or glucose metabolism are within the scope of treatable conditions according to the present invention. Such conditions include, but are not limited to insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and combinations thereof.

Insulin resistance syndrome has become the major health problem of our times, and is associated with obesity, dyslipidemia, atherosclerosis, hypertension, and type-2 diabetes shorten life spans, and hyperandrogenism with polycystic ovarian syndrome affect quality of life and fertility in increasing numbers of women (see, *e.g.*, Ten & Maclaren, *J. Clin Endocrinol Metab.*, 89:2526-2539, 2004; and see Le Roith & Zick, *Diabetes Care* 24:588-597, 2001; both incorporated herein by reference). In particular preferred aspects, Herstatin or Int8 RBD polypeptide, or variants thereof can be used to treat insulin resistance syndrome.

Insulin resistance and associated abnormalities are believed to have a role in pregnancy induced hypertension (new-onset hypertension), and many features of the insulin resistance syndrome are associated with this condition (see, *e.g.*, Seely & Solomon, *J. Clin. Endocrinol. Metab.*, 88:2393-2398, 2003; incorporated herein by reference). According to the present invention, Herstatin or Int8 RBD polypeptide, or variants thereof can be used to treat hypertension and new-onset hypertension.

In prolonged critical illness neuroendocrine changes lead to more extensive metabolic changes. For example, insulin resistance and hyperglycemia are associated with critical illness (*e.g.*, in surgically critically ill populations with or without diabetes, post-myocardial infarction in patients with diabetes, etc.) (see, *e.g.*, Ronbinson & H. van Soeren, *AACN Clinical Issues*, 15:45-62, 2004; incorporated herein by reference). According to the present invention, Herstatin or Int8 RBD polypeptide, or variants thereof can be used to treat critical illness.

Significantly, impairment of insulin signaling in the brain has been linked, on the basis of studies using IR-knockout (NIRKO) mice, to neurodegenerative diseases. NIRKO mice exhibit a complete loss of insulin-mediated activation of phosphatidylinositol 3-kinase and insulin-mediated inhibition of neuronal apoptosis, resulting in markedly reduced phosphorylation of Akt and GSK3 β and leading to a substantially increased phosphorylation of the microtubule-associated protein Tau, a hallmark of neurodegenerative diseases (*e.g.*, Alzheimer's disease) (see, *e.g.*, Schubert et al., *PNAS* 101:3100-3105, 2004, incorporated herein by reference). According to the present invention, Herstatin or Int8 RBD polypeptide, or variants thereof can be used to treat neurodegenerative diseases (*e.g.*, Alzheimer's disease).

Combination Therapies

According to additional preferred aspects of the invention, Herstatin-related treatment of conditions having an aspect related to, or characterized by altered glycemic control and/or glucose metabolism, including, but not limited to insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, and combinations thereof, may further comprise administration of another therapeutic agent.

For example, the inventive treatment methods may further comprise administering a therapeutically effective amount of a receptor-specific antibody that binds to the extracellular domain of a target receptor selected from the group consisting of: IR, EGFR (HER-1, erbB-1); $\square$ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-IR.

Alternatively, the inventive treatment methods may further comprise administering a therapeutically effective amount of an agent selected from the group consisting of: insulin, insulin-sensitizing agents, insulin secretagogues, and combinations thereof. Preferably, the insulin-sensitizing agent is selected from the group consisting of biguanides, metformin, thiazolidinediones (glitazones), and combinations thereof. Preferably, the insulin secretagogue is selected from the group consisting of sulfonylureas, meglitinides, and combinations thereof (see, *e.g.*, Zangeneh et al., *Mayo Clin Proc.*, 78:471-479, 2003, incorporated by reference herein).

The present invention will now be illustrated by reference to the following examples which set forth particularly advantageous embodiments. However, it should be noted that these embodiments are illustrative and are not to be construed as restricting the claimed invention in any way.

EXAMPLE I

(Materials and Methods)

Cell lines, transfections, expression vectors, western blots and antibodies

Cell lines. IRA-3T3 (3T3 cells transfected with a human insulin receptor cDNA have been previously described (Faria et al., *J. Biol. Chem.* 269:13922-13928 (1994)), and Herstatin-expressing MCF-7 cell clones were obtained using previously described methods (Shamieh et al., *FEBS Letters*, 568:163-166, 2004).

Transfections. For transient transfections, 2 μ g of empty vector or 2 μ g expression vector are added with Lipofectamine™ (GIBCO-BRL) to cells in 6 cm plates.

Western blot analysis, and antibodies. For Western blot analyses, whole-cell lysates or immunoprecipitated proteins were resolved by SDS-PAGE and transferred onto nitrocellulose membranes (BioRad, Hercules, CA). Blots were blocked in 5% milk and incubated with primary antibody overnight at 4°C. The antibodies included anti-insulin receptor (IR; against the β subunit), anti-IGF-IR, anti-IRS-1, anti-IRS-2, anti-phosphotyrosine, anti-phospho-Akt, anti-Akt, anti-phospho-ERK, anti-ERK, and anti-Shc antibodies (Santa Cruz Biotechnology, Transduction Laboratories, Cell Signaling Technologies, Upstate Laboratories, or Biosource). After washing, the blots were incubated with secondary antibody conjugated to HRP for 30 min (BioRad, Hercules, CA). The membranes were developed with SuperSignal™ West Dura (Pierce, Rockford, IL) and exposed to x-ray film.

Expression and purification of intron 8-encoded peptide (Int8) and Herstatin:

Receptor binding domain (RBD). Intron 8 cDNA, in the pET 30 bacterial expression vector (Novagen, Madison, WI), is expressed in bacteria (BL-21), and purified by nickel affinity chromatography as described (Doherty et al., *supra*).

Herstatin. For purification of insect Herstatin, S2 insect cells, stably transfected with 6xHis tagged-Herstatin in the pMT/BiP expression plasmid (Invitrogen, Carlsbad, CA), were induced with 100 μ M cupric sulfate for about 16hrs. Herstatin was purified to about 90% purity by Ni-NTA (Qiagen, Valencia, CA) affinity chromatography as previously described (Jhabvala-Romero et al. *Supra*).

10 *Cell binding studies:*

ELISA. Monolayer cultures of $\sim 2 \times 10^6$ cells were plated in 6-well tissue culture plates, and were incubated with purified Herstatin for 2 hours at 4°C in serum-free DMEM. Cells were washed with Phosphate Buffered Saline (PBS) and extracted in 50mM Tris-HCl, pH 7.0, 1.0% NP-40. Herstatin bound to cells were quantified using a sandwich Herstatin ELISA per manufacturer's instructions (Upstate Biotechnology, Lake Placid, NY).

The dissociation constant (K_D) and maximal binding (B_{max}) of Herstatin were determined by nonlinear regression analysis of the plot of pmol of bound *versus* nM of Herstatin added. Statistical comparisons between different binding curves were performed by extra sums-of-squares F-test nonlinear regression coefficients. All tests were performed ($\alpha = 0.05$) using GraphPadTM Prism 4TM software (GraphPadTM Software, 1994-2003).

Pull-down assays with int8 peptide immobilized on protein S agarose:

About 100 μ l of a 50% suspension of S-protein agarose (Novagen) is incubated with or without 100 μ g of int8 peptide with an S-protein tag, at room temperature for 1hr, and then washed twice with 500 μ l PBS. The agarose samples are then incubated at room temperature for 1 hr with 200 μ g of transfected cell extract, then washed twice with 500 μ l of PBS with 1% NP40. The proteins associated with the resin are eluted at 92°C for 2 min in 40 μ l of SDS-sample buffer, and analyzed as a Western blot.

30 *Growth assays:*

Cells (4×10^4) were plated in quadruplicate in 24-well plates, incubated in serum-free DMEM for 24 hours, and treated with either 10 nM insulin (Sigma) or an equivalent volume of vehicle (25 mM HEPES). At the indicated time points, cell monolayers were washed with PBS and incubated for 30 minutes at 37°C with 30 μ l of MTS reagent [3-(4,5-dimethylthiazol-2-yl)-

5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl-2H-tetrazolium) inner salt Aqueous One Solution (Promega; Madison, WI) dissolved in 270 ml PBS] per well. Absorbance at 490 nm was determined a Bio-Tek plate reader.

5 *EGFR inhibitor studies*

Control MCF-7 cells were serum-starved overnight and treated with the EGFR kinase inhibitor AG1478 (Sigma) or vehicle (DMSO) for 5 minutes prior to the addition of 14 nM EGF or 10 nM insulin (Sigma). After growth factor treatment, cell lysates were prepared and analyzed for ERK and Akt/PKB activation as described above. The 24-hour treatment was done
10 in regular growth medium.

EXAMPLE II

(Herstatin was shown to bind specifically to insulin receptor (IR) with nM binding affinity)

The interaction of Herstatin with IR in transfected 3T3 cells (IRA-3T3) was investigated.
15 Herstatin bound specifically to IR at nM concentrations, and IR was thus shown herein to be a target of Herstatin.

Methods. Cell lines, expression vectors, protein purification, pull down assays, antibodies, Western blot analysis and ELISA assays were as described under EXAMPLE I, herein above.

20 *Results.* The interaction between Herstatin and IR was investigated. FIGURE 1 shows that Herstatin, purified from transfected S2 insect cells, exhibited dose-dependent binding to IR at nM concentrations. Increasing concentrations of Herstatin, expressed and purified from stably-transfected S2 insect cells, were added to 3T3 parental cells (filled triangles; "NIH-3T3") or 3T3 cells transfected with a human IR cDNA (filled squares; "IRA-3T3") as previously
25 described (Shamieh et al., *FEBS Letters*, 568:163-166, 2004). After incubation for 2hrs on ice, the cells were washed twice with PBS, and the bound Herstatin was quantified using a Herstatin ELISA (Upstate). The data are plotted as Herstatin ELISA units versus concentration added. The results indicate that Herstatin binds at nM concentrations to cells expressing IR, but not to 3T3 parental cells.

30 These results demonstrate that Herstatin binds specifically to IR with nM binding affinity and that IGF-IR is a target of Herstatin.

EXAMPLE III

(Herstatin up-regulated insulin receptor (IR) expression, and activation)

of IR by insulin in MCF-7 cells)

According to particular embodiments of the present invention, Herstatin not only up-regulates IR expression, but also up-regulates activation of IR by insulin (FIGURE 2).

Methods. Cell lines, expression vectors, protein purification, pull down assays, antibodies, Western blot analysis and ELISA assays were as described under EXAMPLE I, herein above. Insulin was added either to MCF-7 breast carcinoma cells, or to an MCF-7 cell line stably transfected with a Herstatin expression vector, to determine whether Herstatin expression affects IR expression, and/or insulin-stimulated IR signal transduction.

Results. FIGURE 2 shows that Herstatin expression not only up-regulated IR expression (including pro-IR), but also up-regulated IR activation (and thus signaling) in MCF-7 cells. Control and Herstatin-expressing MCF-7 cells were grown in complete medium prior to an overnight incubation in serum-free medium. Insulin was then added to the control and Herstatin-expressing cells and whole-cell lysates were prepared at the indicated times and processed directly for Western immunoblots with anti-insulin receptor (IR), phospho-Akt, Akt, phospho-ERK, and ERK antibodies, or first immunoprecipitated with anti-IR antibody and immunoprecipitates (IP) then analyzed by Western immunoblotting with anti-phosphotyrosine and anti-IR antibodies after transfer to nitrocellulose membranes. Following incubation of blots with primary antibodies, immunoreactive proteins were detected by enhanced chemiluminescence after a secondary incubation with HRP-conjugated secondary antisera. Similar results were obtained with a second Herstatin-expressing MCF-7 clone.

These results demonstrate that Herstatin not only up-regulates IR expression (including pro-IR), but also modulates IR-mediated signaling.

Additionally, as shown in FIGURE 2 (see also FIGURE 3 below), Herstatin up-regulated insulin-stimulated ERK activation (increased phospho-ERK).

EXAMPLE IV

(Herstatin expression amplified insulin-stimulated ERK activation in MCF-7 cells)

The effect of Herstatin expression on insulin-stimulated ERK activation/signaling was further investigated.

Methods. Methods were as described above under EXAMPLE III herein above.

Results. FIGURE 3 shows, in MCF-7 cells, that Herstatin expression amplified insulin-stimulated ERK activation. Control and Herstatin-expressing MCF-7 cells were treated and analyzed as those of Figure 2. Film exposures of enhanced chemiluminescence signals were

quantified by scanning densitometry, and the values for the phospho-ERK signals were normalized to the ERK signals to determine the relative level of ERK phosphorylation as a measure of activation.

Herstatin expression substantially amplified insulin-stimulated ERK activation in MCF-7
5 cells.

According to particular aspects of the present invention, this result supports a substantial utility for Herstatin in treating insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia),
10 obesity, critical illness, neurodegenerative disorders, and combinations thereof.

This is because the MEK (MAPK kinase)-ERK pathway has been shown to be significantly involved in glucose transport (*e.g.*, Harmon et al., *Am. J. Physiol. Endocrinol. Metab.*, 287:E758-E766, 2004). Specifically, Harmon et al show specific inhibition of MAPK kinase (MEK) by the inhibitors PD-98059 and U-0216, resulting in significant inhibition of
15 insulin-stimulated glucose uptake. The data support the importance of MEK for activation of GLUT4, and further, since the only target of MEK is ERK, the importance of the MEK (MAPK kinase)-ERK pathway for glucose transport.

EXAMPLE V

(Herstatin altered the expression of an array of proteins that are directly involved in insulin
20 action.)

In addition to the regulation of insulin receptor protein, the regulation of the IRS-1 and IRS-2 proteins and Shc (that function as adapter proteins linking the activated insulin receptor to some of its downstream pathways), the expression of ERK and Akt/PKB, and the regulation of
25 the IGF-IR (which may contribute to enhanced insulin receptor activation by decreasing the proportion of insulin receptor/IGF-I receptor hybrids, which do not respond to insulin) was investigated.

Methods. Cell lines, expression vectors, protein purification, antibodies and ELISA assays were as described under EXAMPLE I, herein above.

Results. Figure 4 shows that Herstatin altered the expression of an array of proteins that are directly involved in insulin action. Lysates from control and Herstatin-expressing MCF-7 cells were prepared from respective untreated (no insulin) cells following overnight incubation in serum-free media, and processed directly or (in the case of the IR) also immunoprecipitated prior to Western immunoblot analysis as described in relation to Figure 2.
30

These data illustrate that Herstatin: up-regulates insulin receptor protein as assessed by direct Western immunoblot and following immunoprecipitation; mediates the apparent phosphorylation state of the IRS-1 and IRS-2 (differentially down-regulated compared with IRS-1) proteins that function as adapter proteins linking the activated insulin receptor to some of its downstream pathways (see, *e.g.*, Le Roith & Zick, *Diabetes Care* 24:588-597, 2001, discussing role of IRS (IR substrate) proteins in IR-mediated signal transduction); elicits a slight decrease in IRS-2 expression; alters the relative expression of Shc isoforms expressed; increases the relative expression ratio of ERK1 and ERK2; and down-regulates the IGF-IR, which may contribute to enhanced insulin receptor activation by decreasing the proportion of IR/IGF-IR hybrids, which do not respond to insulin.

EXAMPLE VI

(The EGFR inhibitor AS1478 does not affect insulin signaling or lead to an increase in IR)

Figure 5 shows, according to particular aspects, that the EGFR inhibitor AS1478 did not affect insulin signaling.

Figure 6 shows, according to particular aspects, that inhibition of the EGF receptor with an EGF receptor-specific inhibitor did not lead to an increase in insulin receptor.

Other references of interest:

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- 5 Filmus, J., M. N. Pollak, R. Cailleau, and R. N. Buick, 1985, MDA-468, a human breast cancer cell line with a high number of epidermal growth factor (EGF) receptors, has an amplified EGF receptor gene and is growth inhibited by EGF: *Biochem Biophys Res Commun*, v. 128, p. 898-905.

CLAIMS

1. A method for treating a condition associated with altered insulin receptor expression or altered insulin receptor-mediated signaling, said method comprising administering to a subject in need thereof, a therapeutically effective amount of Herstatin, or a variant thereof,
5 that binds to the insulin receptor.

2. A method for treating a condition associated with altered insulin receptor expression or altered insulin receptor-mediated signaling, comprising administering to a subject in need thereof, a therapeutically effective amount of a Int8 RBD polypeptide, or a variant thereof, that binds to the insulin receptor.

10 3. The method of any one of claims 1 or 2, wherein the condition is at least one selected from the group consisting of insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, and neurodegenerative disorders.

15 4. The method of any one of claims 1 or 2, wherein the cell further expresses at least one target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4); and IGF-IR.

5. The method of claim 1, wherein the Herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2
20 of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, wherein at least one N-linked glycosylation site is present, and wherein the polypeptide binds to the insulin receptor.

6. The method of claim 1, wherein the Herstatin, or variant thereof, comprises a sequence selected from the group consisting of SEQ ID NOS:32-42.

25 7. The method of claim 1, wherein the Herstatin, or variant thereof, comprises SEQ ID NO:32.

8. The method of claim 2, wherein the Int8 RBD polypeptide, or a variant thereof comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the insulin receptor.

5 9. The method of claim 2, wherein the Int8 RBD polypeptide, or a variant thereof, comprises a sequence selected from the group consisting of SEQ ID NOS:21-31,

10. The method of claim 2, wherein the Int8 RBD polypeptide, or a variant thereof, comprises SEQ ID NO:21.

11. The method of any one of claims 1 or 2, further comprising administering a
10 therapeutically effective amount of a receptor-specific antibody that binds to a target receptor selected from the group consisting of: insulin receptor (IR), EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4), and IGF-IR.

12. The method of any one of claims 1 or 2, further comprising administration of a
15 therapeutically effective amount of an agent selected from the group consisting of: insulin, insulin-sensitizing agents, insulin secretagogues, and combinations thereof.

13. The method of claim 12, wherein the insulin-sensitizing agent is selected from the group consisting of biguanides, metformin, thiazolidinediones (glitazones), and combinations thereof.

14. The method of claim 12, wherein the insulin secretagogue is selected from the
20 group consisting of sulfonylureas, meglitinides, and combinations thereof.

15. A pharmaceutical composition for treating a condition associated with altered insulin receptor expression or altered insulin receptor-mediated signaling, comprising, Herstatin, or a variant thereof, that binds to the insulin receptor and a pharmaceutically acceptable carrier or excipient.

25 16. A pharmaceutical composition for treating a condition associated with altered insulin receptor expression or altered insulin receptor-mediated signaling, comprising, a Int8

RBD polypeptide, or a variant thereof, that binds to the insulin receptor and a pharmaceutically acceptable carrier or excipient.

17. The pharmaceutical composition of any one of claims 15 or 16, wherein the condition is selected from the group consisting of insulin resistance syndrome, pre-diabetic conditions, metabolic syndrome, type 1 and type 2 diabetes, cardiac disease, diabetes-associated vascular disease, atherosclerosis, hypertension, diabetes-associated lipid metabolism disorders (dyslipidemia), obesity, critical illness, neurodegenerative disorders, and combinations thereof.

18. The pharmaceutical composition of claim 15, wherein the Herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of SEQ ID NO:2 of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, wherein at least one N-linked glycosylation site is present, and wherein the polypeptide binds to the insulin receptor.

19. The pharmaceutical composition of claim 16, wherein the Int8 RBD polypeptide, or a variant thereof comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of SEQ ID NO:1 of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the insulin receptor.

20. The pharmaceutical composition of any one of claims 15 or 16, further comprising an agent selected from the group consisting of: insulin, insulin-sensitizing agents, insulin secretagogues, and combinations thereof.

21. The pharmaceutical composition of claim 20, wherein the insulin-sensitizing agent is selected from the group consisting of biguanides, metformin, thiazolidinediones (glitazones), and combinations thereof.

22. The pharmaceutical composition of claim 20, wherein the insulin secretagogue is selected from the group consisting of sulfonylureas, meglitinides, and combinations thereof..

23. A method for targeting a therapeutic agent to a cell expressing insulin receptor, comprising attaching the therapeutic agent to Herstatin, or to a variant thereof, that binds to the extracellular domain of a cellular target insulin receptor.

24. A method for targeting a therapeutic agent to a cell expressing insulin receptor, comprising attaching the therapeutic agent to a Int8 RBD polypeptide, or a variant thereof, that binds to the cellular target insulin receptor.

25. The method of any one of claims 23 or 24, wherein the cell further expresses a
5 target receptor selected from the group consisting of: EGFR (HER-1, erbB-1); Δ EGFR; HER-2 (erbB-2); HER-3 (erbB-3); HER-4 (erbB-4); IGF-IR, and combinations thereof.

26. The method of claim 23, wherein the wherein the Herstatin, or variant thereof, comprises a polypeptide selected from the group consisting of SEQ ID NO:2, or a fragment of
10 SEQ ID NO:2 of about 80 to 419 contiguous residues in length, wherein the C-terminal 79 contiguous amino acids are present, wherein at least one N-linked glycosylation site is present, and wherein the polypeptide binds to the insulin receptor.

27. The method of claim 24, wherein the Int8 RBD polypeptide, or a variant thereof comprises a polypeptide selected from the group consisting of SEQ ID NO:1, or a fragment of
15 SEQ ID NO:1 of about 50 to 79 contiguous residues in length, wherein the polypeptide binds to the insulin receptor.

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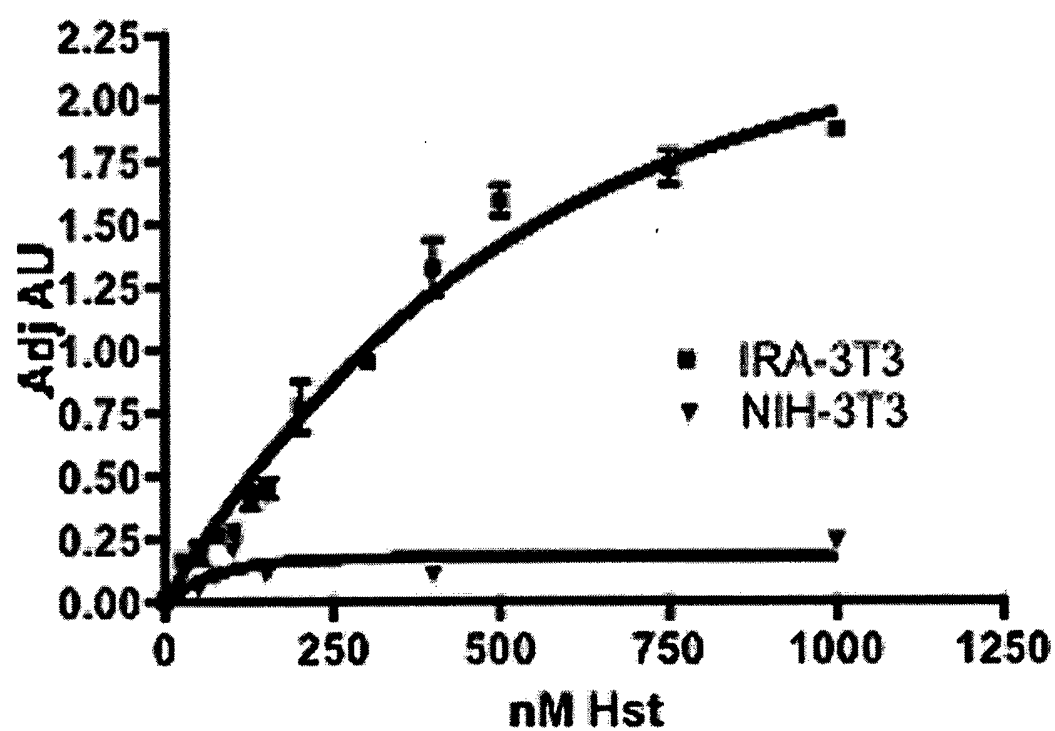


FIG. 1

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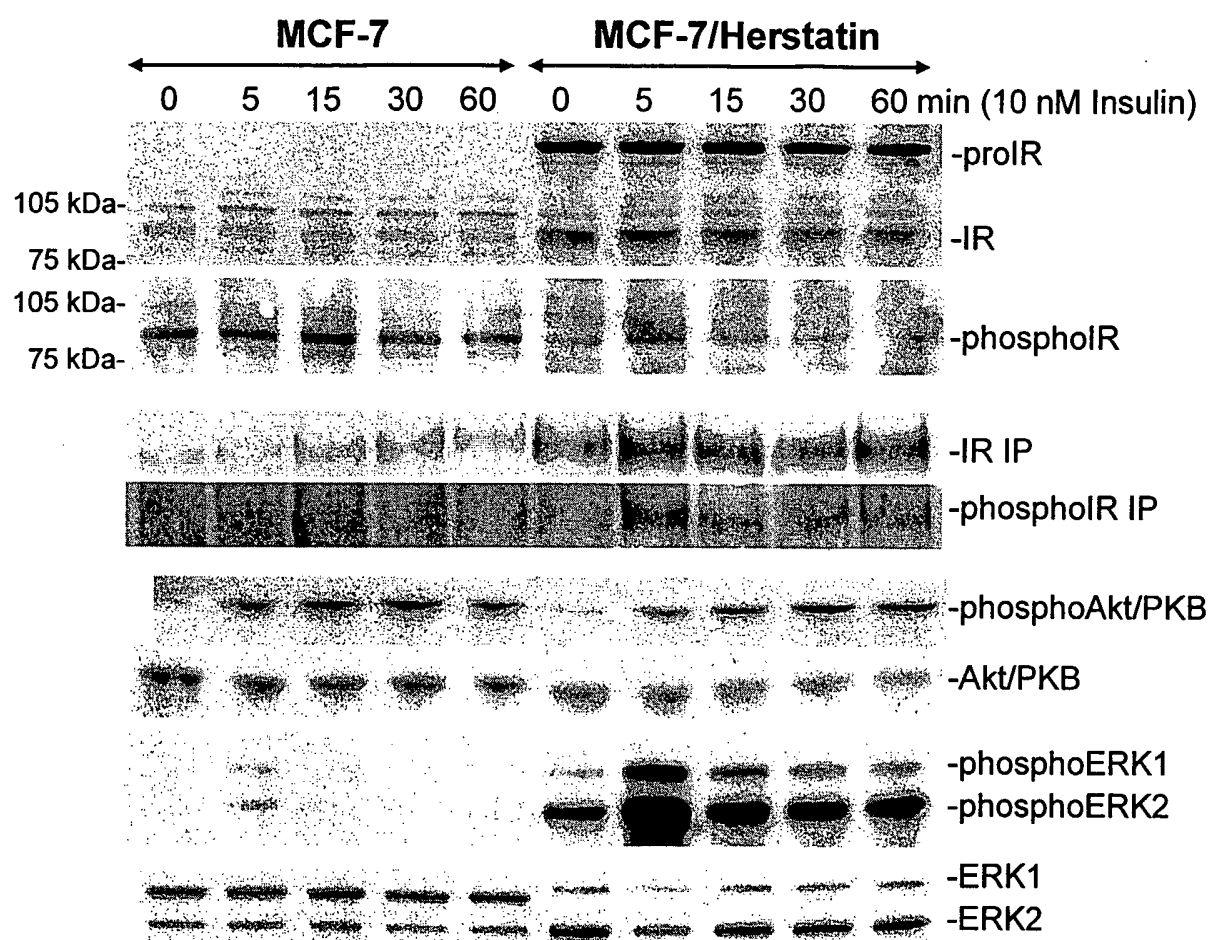


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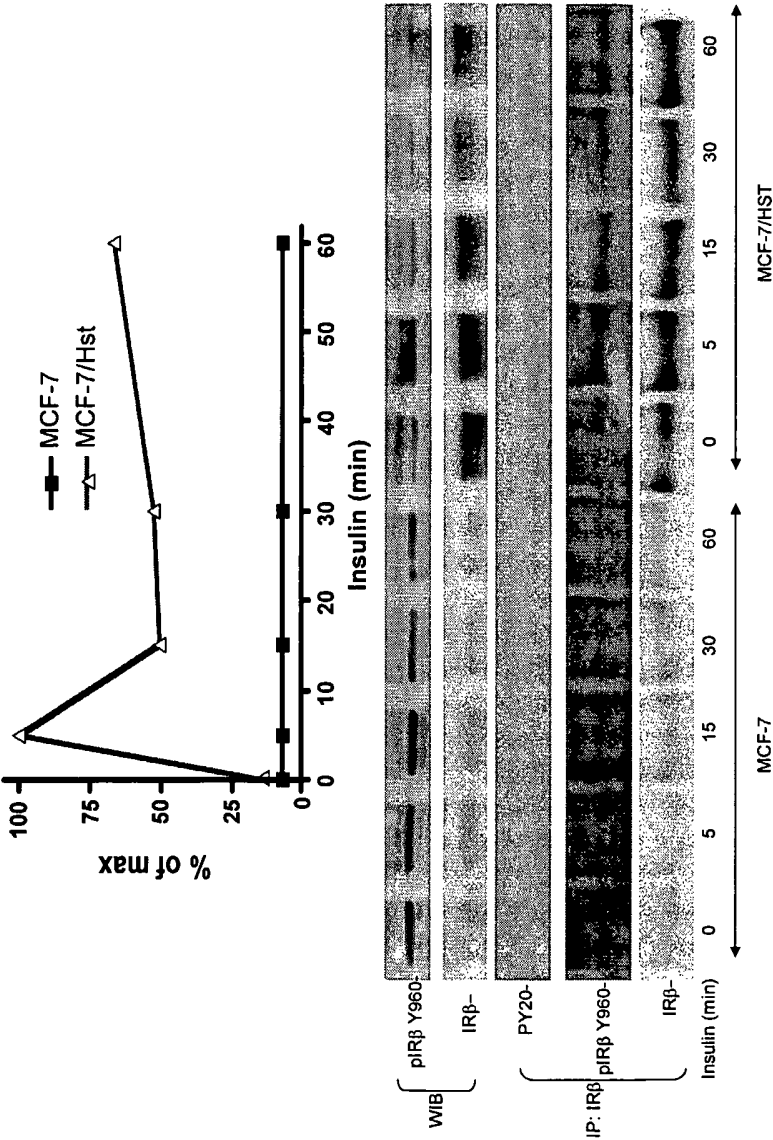


FIG. 2B

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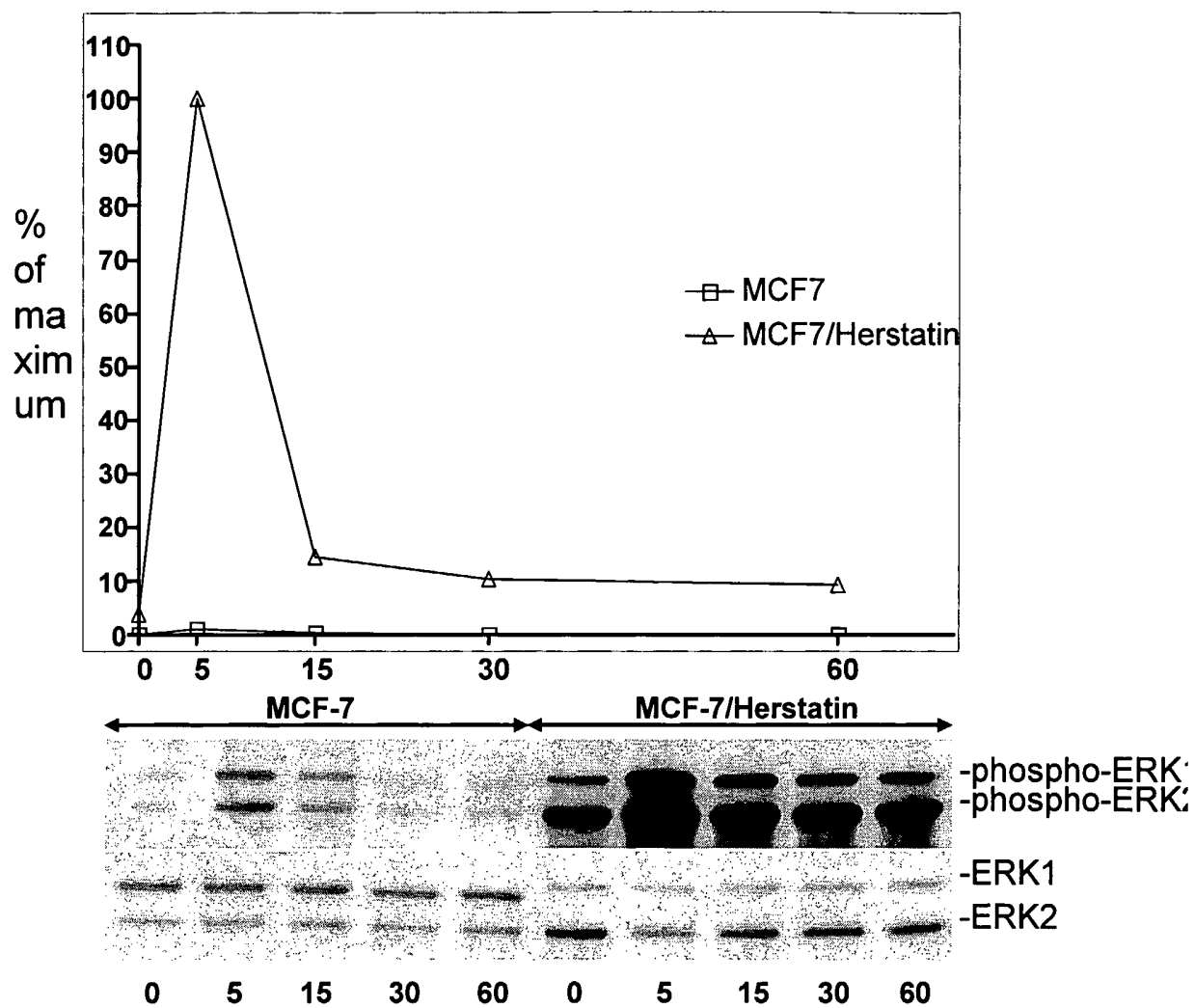


FIG. 3A

5/11

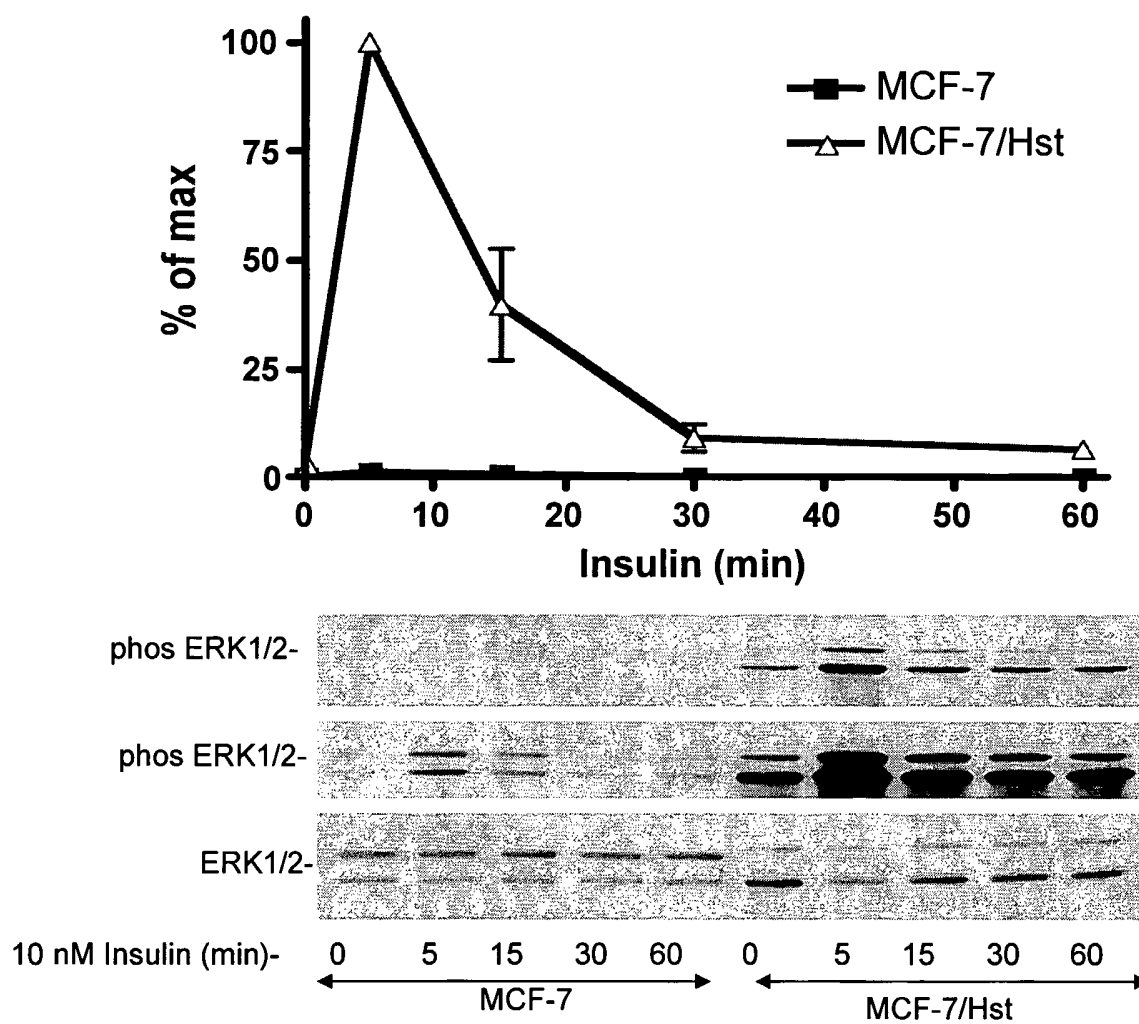


FIG. 3B

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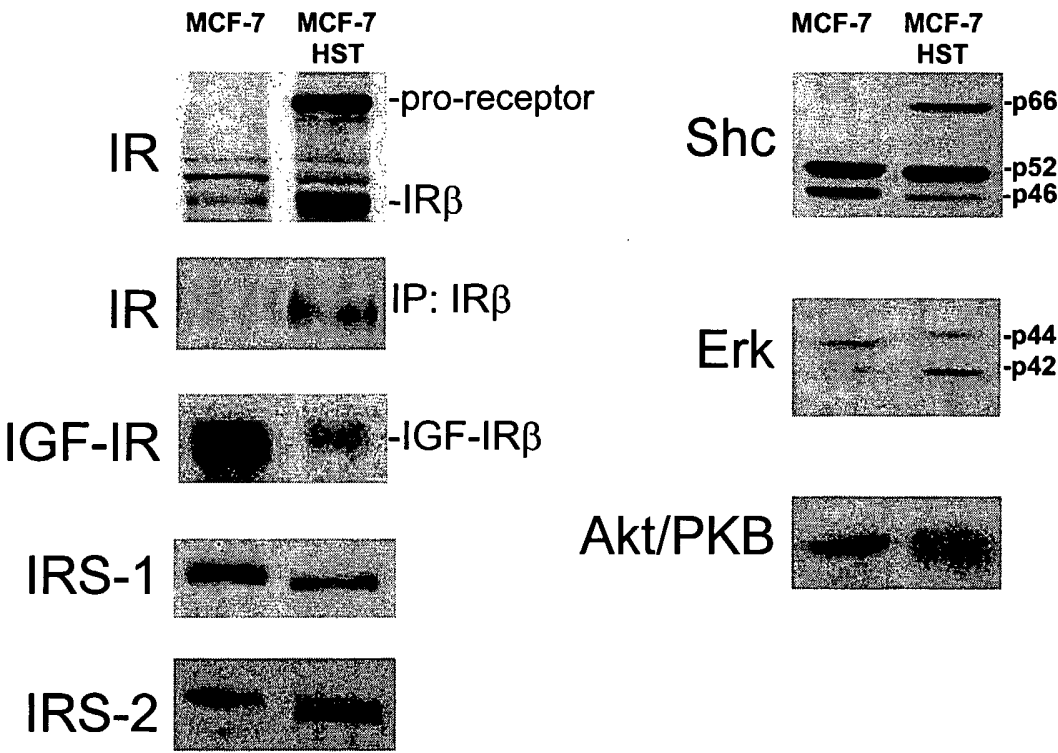


FIG. 4A

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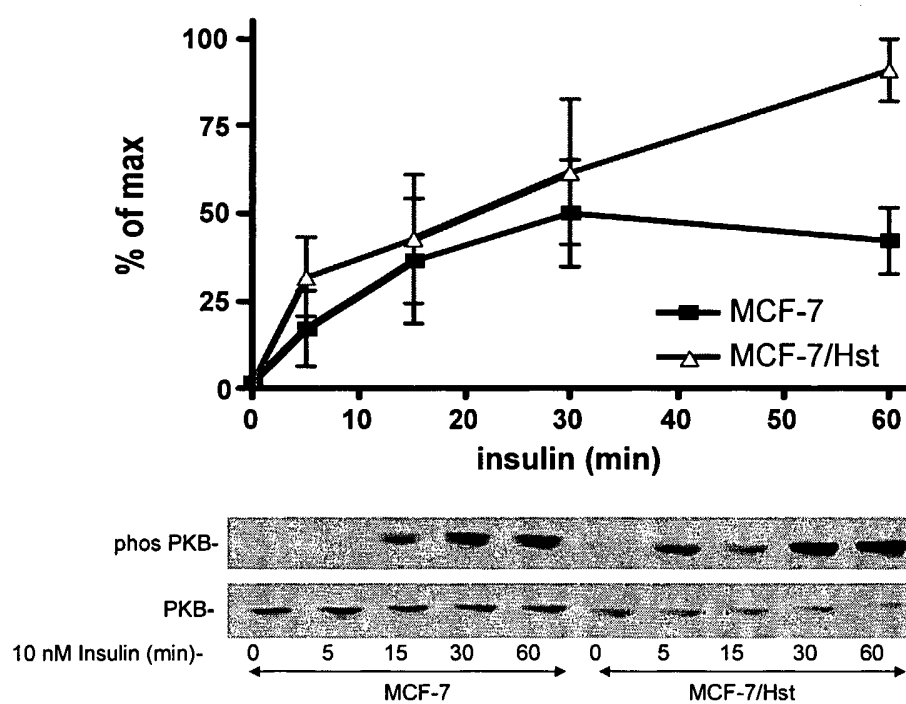
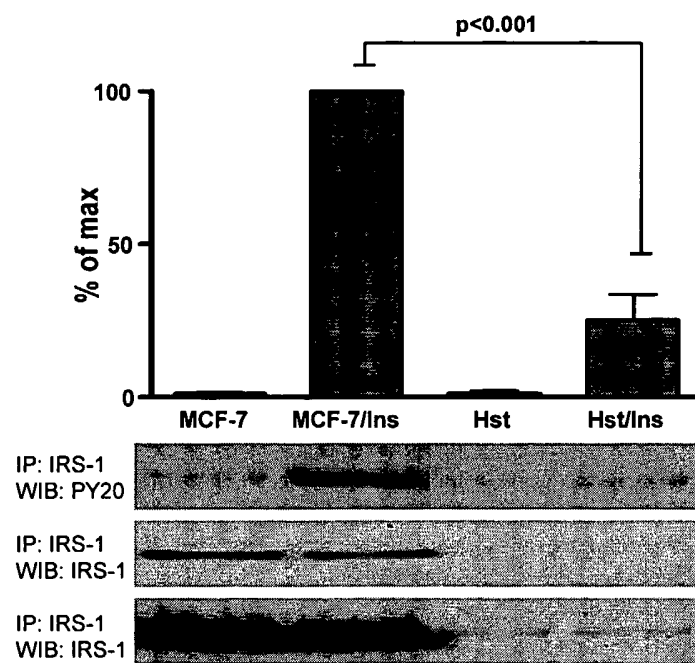


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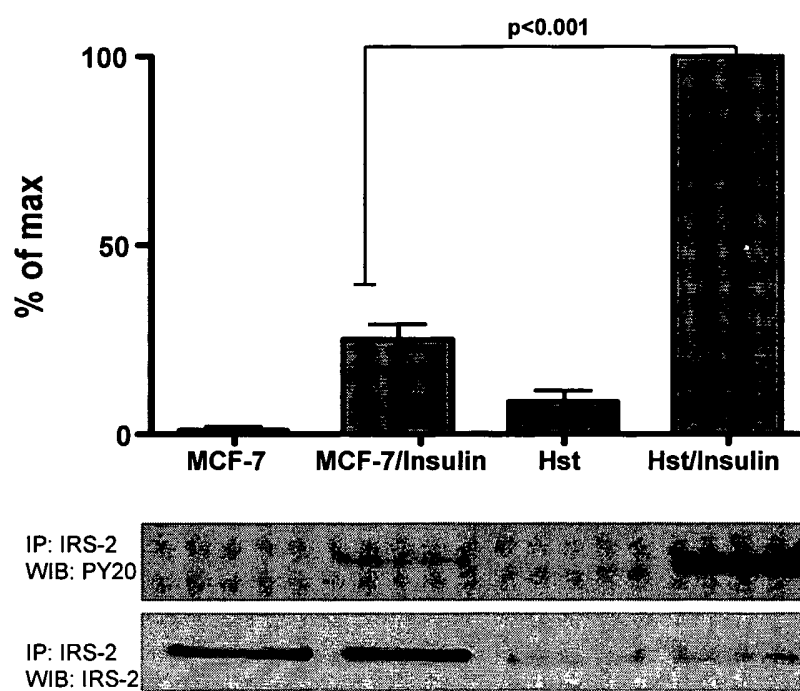
8/11



* Not corrected for differences in total IRS-1 between cell lines

FIG. 4C

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* Not corrected for differences in total IRS-2 between cell lines

FIG. 4D

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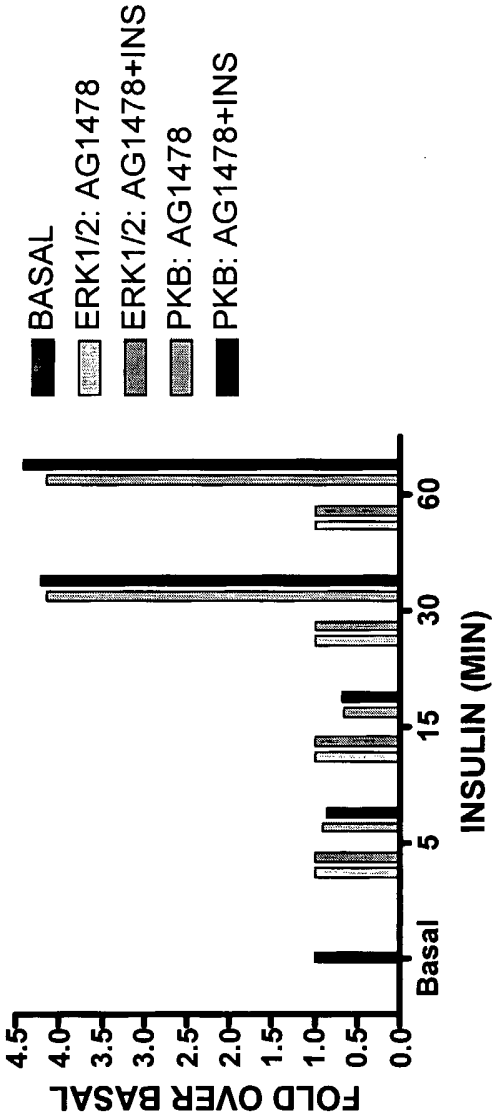


FIG. 5

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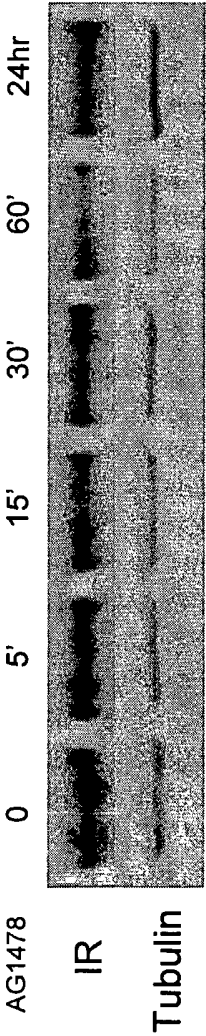


FIG. 6

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 tgc caa ggc acg agt aac aag ctc acg cag ttg ggc act ttt gaa gat 384
 Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp
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Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser			
335	340	345	350
ata aat gct acg aat att aaa cac ttc aaa aac tgc acc tcc atc agt			1344
Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser			
355	360	365	
ggc gat ctc cac atc ctg ccg gtg gca ttt agg ggt gac tcc ttc aca			1392
Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr			

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370	375	380	
cat act cct cct ctg gat cca cag gaa ctg gat att ctg aaa acc gta			1440
His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val			
385	390	395	
aag gaa atc aca ggg ttt ttg ctg att cag gct tgg cct gaa aac agg			1488
Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg			
400	405	410	
acg gac ctc cat gcc ttt gag aac cta gaa atc ata cgc ggc agg acc			1536
Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr			
415	420	425	430
aag caa cat ggt cag ttt tct ctt gca gtc gtc agc ctg aac ata aca			1584
Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr			
435	440	445	
tcc ttg gga tta cgc tcc ctc aag gag ata agt gat gga gat gtg ata			1632
Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile			
450	455	460	
att tca gga aac aaa aat ttg tgc tat gca aat aca ata aac tgg aaa			1680
Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys			
465	470	475	
aaa ctg ttt ggg acc tcc ggt cag aaa acc aaa att ata agc aac aga			1728
Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg			
480	485	490	
ggt gaa aac agc tgc aag gcc aca ggc cag gtc tgc cat gcc ttg tgc			1776
Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys			
495	500	505	510
tcc ccc gag ggc tgc tgg ggc ccg gag ccc agg gac tgc gtc tct tgc			1824
Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys			
515	520	525	
cgg aat gtc agc cga ggc agg gaa tgc gtc gac aag tgc aac ctt ctg			1872
Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu			
530	535	540	
gag ggt gag cca agg gag ttt gtg gag aac tct gag tgc ata cag tgc			1920
Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys			
545	550	555	
cac cca gag tgc ctg cct cag gcc atg aac atc acc tgc aca gga cgg			1968
His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg			
560	565	570	
gga cca gac aac tgt atc cag tgt gcc cac tac att gac ggc ccc cac			2016
Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His			
575	580	585	590
tgc gtc aag acc tgc ccg gca gga gtc atg gga gaa aac aac acc ctg			2064
Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu			
595	600	605	
gtc tgg aag tac gca gac gcc ggc cat gtg tgc cac ctg tgc cat cca			2112
Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro			
610	615	620	
aac tgc acc tac gga tgc act ggg cca ggt ctt gaa ggc tgt cca acg			2160
Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr			

49321-146.ST25.txt

625	630	635	
aat ggg cct aag atc ccg tcc atc gcc act ggg atg gtg ggg gcc ctc Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu 640 645 650			2208
ctc ttg ctg ctg gtg gtg gcc ctg ggg atc ggc ctc ttc atg cga agg Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg 655 660 665 670			2256
cgc cac atc gtt cgg aag cgc acg ctg cgg agg ctg ctg cag gag agg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg 675 680 685			2304
gag ctt gtg gag cct ctt aca ccc agt gga gaa gct ccc aac caa gct Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala 690 695 700			2352
ctc ttg agg atc ttg aag gaa act gaa ttc aaa aag atc aaa gtg ctg Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu 705 710 715			2400
ggc tcc ggt gcg ttc ggc acg gtg tat aag gga ctc tgg atc cca gaa Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu 720 725 730			2448
ggt gag aaa gtt aaa att ccc gtc gct atc aag gaa tta aga gaa gca Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala 735 740 745 750			2496
aca tct ccg aaa gcc aac aag gaa atc ctc gat gaa gcc tac gtg atg Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met 755 760 765			2544
gcc agc gtg gac aac ccc cac gtg tgc cgc ctg ctg ggc atc tgc ctc Ala Ser Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu 770 775 780			2592
acc tcc acc gtg cag ctc atc acg cag ctc atg ccc ttc ggc tgc ctc Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu 785 790 795			2640
ctg gac tat gtc cgg gaa cac aaa gac aat att ggc tcc cag tac ctg Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu 800 805 810			2688
ctc aac tgg tgt gtg cag atc gca aag ggc atg aac tac ttg gag gac Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp 815 820 825 830			2736
cgt cgc ttg gtg cac cgc gac ctg gca gcc agg aac gta ctg gtg aaa Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys 835 840 845			2784
aca ccg cag cat gtc aag atc aca gat ttt ggg ctg gcc aaa ctg ctg Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu 850 855 860			2832
ggt gcg gaa gag aaa gaa tac cat gca gaa gga ggc aaa gtg cct atc Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile 865 870 875			2880
aag tgg atg gca ttg gaa tca att tta cac aga atc tat acc cac cag Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln 880 885 890			2928

49321-146.ST25.txt

880	885	890	
agt gat gtc tgg agc tac ggg gtg acc gtt tgg gag ttg atg acc ttt			2976
Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe			
895	900	905	910
gga tcc aag cca tat gac gga atc cct gcc agc gag atc tcc tcc atc			3024
Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile			
	915	920	925
ctg gag aaa gga gaa cgc ctc cct cag cca ccc ata tgt acc atc gat			3072
Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp			
	930	935	940
gtc tac atg atc atg gtc aag tgc tgg atg ata gac gca gat agt cgc			3120
Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg			
	945	950	955
cca aag ttc cgt gag ttg atc atc gaa ttc tcc aaa atg gcc cga gac			3168
Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp			
	960	965	970
ccc cag cgc tac ctt gtc att cag ggg gat gaa aga atg cat ttg cca			3216
Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro			
	975	980	985
agt cct aca gac tcc aac ttc tac cgt gcc ctg atg gat gaa gaa gac			3264
Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp			
	995	1000	1005
atg gac gac gtg gtg gat gcc gac gag tac ctc atc cca cag cag			3309
Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln			
	1010	1015	1020
ggc ttc ttc agc agc ccc tcc acg tca cgg act ccc ctc ctg agc			3354
Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser			
	1025	1030	1035
tct ctg agt gca acc agc aac aat tcc acc gtg gct tgc att gat			3399
Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp			
	1040	1045	1050
aga aat ggg ctg caa agc tgt ccc atc aag gaa gac agc ttc ttg			3444
Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu			
	1055	1060	1065
cag cga tac agc tca gac ccc aca ggc gcc ttg act gag gac agc			3489
Gln Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser			
	1070	1075	1080
ata gac gac acc ttc ctc cca gtg cct gaa tac ata aac cag tcc			3534
Ile Asp Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser			
	1085	1090	1095
gtt ccc aaa agg ccc gct ggc tct gtg cag aat cct gtc tat cac			3579
Val Pro Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His			
	1100	1105	1110
aat cag cct ctg aac ccc gcg ccc agc aga gac cca cac tac cag			3624
Asn Gln Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln			
	1115	1120	1125
gac ccc cac agc act gca gtg ggc aac ccc gag tat ctc aac act			3669
Asp Pro His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr			

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1130	1135	1140	
gtc cag ccc acc tgt gtc aac agc aca ttc gac agc cct gcc cac			3714
Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His			
1145	1150	1155	
tgg gcc cag aaa ggc agc cac caa att agc ctg gac aac cct gac			3759
Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp			
1160	1165	1170	
tac cag cag gac ttc ttt ccc aag gaa gcc aag cca aat ggc atc			3804
Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile			
1175	1180	1185	
ttt aag ggc tcc aca gct gaa aat gca gaa tac cta agg gtc gcg			3849
Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val Ala			
1190	1195	1200	
cca caa agc agt gaa ttt att gga gca tga ccacggagga tagtatgagc			3899
Pro Gln Ser Ser Glu Phe Ile Gly Ala			
1205	1210		
cctaaaaatc cagactcttt cgatacccag gaccaagcca cagcaggtcc tccatcccaa			3959
cagccatgcc cgcattagct cttagaccca cagactgggt ttgcaacgtt tacaccgact			4019
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acttactccc cactgatgga ccagtgggtt ccagtcatga gcgttagact gacttgtttg			4619
tcttccattc cattgttttg aaactcagta tgctgcccct gtcttgctgt catgaaatca			4679
gcaagagagg atgacacatc aaataataac tcggattcca gccacattg gattcatcag			4739
catttggaac aatagcccac agctgagaat gtggaatacc taaggatagc accgcttttg			4799
ttctcgcaaa aacgtatctc ctaatttgag gctcagatga aatgcatcag gtcctttggg			4859
gcatagatca gaagactaca aaaatgaagc tgctctgaaa tctccttttag ccatcaccac			4919
aaccccccaa aattagtttg tgttacttat ggaagatagt tttctccttt tacttcactt			4979
caaaagcttt ttactcaaag agtatatggt cctccagggt cagctgcccc caaacccct			5039
ccttacgctt tgtcacacaa aaagtgtctc tgccttgagt catctattca agcacttaca			5099
gctctggcca caacagggca ttttacagggt gcgaatgaca gtagcattat gagtagtgtg			5159

49321-146.ST25.txt

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gaattcaggt agtaaatatg aaactagggt ttgaaattga taatgctttc acaacatttg 5219
cagatgtttt agaaggaaaa aagttccttc ctaaaataat ttctctacaa ttggaagatt 5279
ggaagattca gctagttagg agcccacctt ttttcctaata ctgtgtgtgc cctgtaacct 5339
gactgggttaa cagcagtcct ttgtaaacag tgttttaaac tctcctagtc aatatccacc 5399
ccatccaatt tatcaaggaa gaaatgggtc agaaaatatt ttcagcctac agttatgttc 5459
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<210> 6
<211> 1210
<212> PRT
<213> Homo sapiens

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<400> 6

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Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
1          5          10          15

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Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
20          25          30

```

```

Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
35          40          45

```

```

Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
50          55          60

```

```

Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys
65          70          75          80

```

```

Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
85          90          95

```

```

Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
100         105         110

```

```

Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
115         120         125

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Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
130         135         140

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His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
145         150         155         160

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49321-146.ST25.txt

Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
 165 170 175

Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
 180 185 190

Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
 195 200 205

Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
 210 215 220

Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
 225 230 235 240

Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
 245 250 255

Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
 260 265 270

Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
 275 280 285

Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
 290 295 300

Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
 305 310 315 320

Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val
 325 330 335

Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
 340 345 350

Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
 355 360 365

Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr
 370 375 380

Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu
 385 390 395 400

Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
 405 410 415

49321-146.ST25.txt

Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln
 420 425 430

His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
 435 440 445

Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
 450 455 460

Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
 465 470 475 480

Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
 485 490 495

Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
 500 505 510

Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
 515 520 525

Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
 530 535 540

Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro
 545 550 555 560

Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
 565 570 575

Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
 580 585 590

Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
 595 600 605

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
 610 615 620

Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
 625 630 635 640

Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
 645 650 655

Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
 660 665 670

49321-146.ST25.txt

Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
 675 680 685

Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
 690 695 700

Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
 705 710 715 720

Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
 725 730 735

Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
 740 745 750

Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
 755 760 765

Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
 770 775 780

Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
 785 790 795 800

Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
 805 810 815

Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
 820 825 830

Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro
 835 840 845

Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala
 850 855 860

Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
 865 870 875 880

Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
 885 890 895

Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
 900 905 910

Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
 915 920 925

49321-146.ST25.txt

Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
 930 935 940

Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
 945 950 955 960

Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
 965 970 975

Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
 980 985 990

Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
 995 1000 1005

Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe
 1010 1015 1020

Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu
 1025 1030 1035

Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn
 1040 1045 1050

Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg
 1055 1060 1065

Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
 1070 1075 1080

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro
 1085 1090 1095

Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
 1100 1105 1110

Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro
 1115 1120 1125

His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln
 1130 1135 1140

Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala
 1145 1150 1155

Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln
 1160 1165 1170

49321-146.ST25.txt

Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys
 1175 1180 1185

Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val Ala Pro Gln
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Ser Ser Glu Phe Ile Gly Ala
 1205 1210

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 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (247)..(3078)
 <223> delta EGFR coding sequence [represents in-frame deletion of 801 bp (275-1027) of the ECD of EGFR corresponding to exons 2-7 of the gene]

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 gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgagc tcttcgggga 240
 gcagcg atg cga ccc tcc ggg acg gcc ggg gca gtg gat gtg aac ccc 288
 Met Arg Pro Ser Gly Thr Ala Gly Ala Val Asp Val Asn Pro
 1 5 10

gag ggc aaa tac agc ttt ggt gcc acc tgc gtg aag aag tgt ccc cgt 336
 Glu Gly Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg
 15 20 25 30

aat tat gtg gtg aca gat cac ggc tcg tgc gtc cga gcc tgt ggg gcc 384
 Asn Tyr Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala
 35 40 45

gac agc tat gag atg gag gaa gac ggc gtc cgc aag tgt aag aag tgc 432
 Asp Ser Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys
 50 55 60

gaa ggg cct tgc cgc aaa gtg tgt aac gga ata ggt att ggt gaa ttt 480
 Glu Gly Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe
 65 70 75

aaa gac tca ctc tcc ata aat gct acg aat att aaa cac ttc aaa aac 528
 Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn
 80 85 90

tgc acc tcc atc agt ggc gat ctc cac atc ctg ccg gtg gca ttt agg 576
 Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg
 95 100 105 110

ggt gac tcc ttc aca cat act cct cct ctg gat cca cag gaa ctg gat 624
 Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp

49321-146.ST25.txt

115	120	125	
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ata cgc ggc agg acc aag caa cat ggt cag ttt tct ctt gca gtc gtc Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val	160 165	170	768
agc ctg aac ata aca tcc ttg gga tta cgc tcc ctc aag gag ata agt Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser	175 180	185 190	816
gat gga gat gtg ata att tca gga aac aaa aat ttg tgc tat gca aat Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn	195	200 205	864
aca ata aac tgg aaa aaa ctg ttt ggg acc tcc ggt cag aaa acc aaa Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys	210	215 220	912
att ata agc aac aga ggt gaa aac agc tgc aag gcc aca ggc cag gtc Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val	225	230 235	960
tgc cat gcc ttg tgc tcc ccc gag ggc tgc tgg ggc ccg gag ccc agg Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg	240 245	250	1008
gac tgc gtc tct tgc cgg aat gtc agc cga ggc agg gaa tgc gtg gac Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp	255 260	265 270	1056
aag tgc aac ctt ctg gag ggt gag cca agg gag ttt gtg gag aac tct Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser	275	280 285	1104
gag tgc ata cag tgc cac cca gag tgc ctg cct cag gcc atg aac atc Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile	290	295 300	1152
acc tgc aca gga cgg gga cca gac aac tgt atc cag tgt gcc cac tac Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr	305	310 315	1200
att gac ggc ccc cac tgc gtc aag acc tgc ccg gca gga gtc atg gga Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly	320 325	330	1248
gaa aac aac acc ctg gtc tgg aag tac gca gac gcc ggc cat gtg tgc Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys	335 340	345 350	1296
cac ctg tgc cat cca aac tgc acc tac gga tgc act ggg cca ggt ctt His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu	355	360 365	1344
gaa ggc tgt cca acg aat ggg cct aag atc ccg tcc atc gcc act ggg Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly			1392

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370	375	380	
atg gtg ggg gcc ctc ctc ttg ctg ctg gtg gtg gcc ctg ggg atc ggc			1440
Met Val Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly			
385	390	395	
ctc ttc atg cga agg cgc cac atc gtt cgg aag cgc acg ctg cgg agg			1488
Leu Phe Met Arg Arg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg			
400	405	410	
ctg ctg cag gag agg gag ctt gtg gag cct ctt aca ccc agt gga gaa			1536
Leu Leu Gln Glu Arg Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu			
415	420	425	430
gct ccc aac caa gct ctc ttg agg atc ttg aag gaa act gaa ttc aaa			1584
Ala Pro Asn Gln Ala Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys			
435	440	445	
aag atc aaa gtg ctg ggc tcc ggt gcg ttc ggc acg gtg tat aag gga			1632
Lys Ile Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly			
450	455	460	
ctc tgg atc cca gaa ggt gag aaa gtt aaa att ccc gtc gct atc aag			1680
Leu Trp Ile Pro Glu Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys			
465	470	475	
gaa tta aga gaa gca aca tct ccg aaa gcc aac aag gaa atc ctc gat			1728
Glu Leu Arg Glu Ala Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp			
480	485	490	
gaa gcc tac gtg atg gcc agc gtg gac aac ccc cac gtg tgc cgc ctg			1776
Glu Ala Tyr Val Met Ala Ser Val Asp Asn Pro His Val Cys Arg Leu			
495	500	505	510
ctg ggc atc tgc ctc acc tcc acc gtg cag ctc atc acg cag ctc atg			1824
Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met			
515	520	525	
ccc ttc ggc tgc ctc ctg gac tat gtc cgg gaa cac aaa gac aat att			1872
Pro Phe Gly Cys Leu Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile			
530	535	540	
ggc tcc cag tac ctg ctc aac tgg tgt gtg cag atc gca aag ggc atg			1920
Gly Ser Gln Tyr Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met			
545	550	555	
aac tac ttg gag gac cgt cgc ttg gtg cac cgc gac ctg gca gcc agg			1968
Asn Tyr Leu Glu Asp Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg			
560	565	570	
aac gta ctg gtg aaa aca ccg cag cat gtc aag atc aca gat ttt ggg			2016
Asn Val Leu Val Lys Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly			
575	580	585	590
ctg gcc aaa ctg ctg ggt gcg gaa gag aaa gaa tac cat gca gaa gga			2064
Leu Ala Lys Leu Leu Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly			
595	600	605	
ggc aaa gtg cct atc aag tgg atg gca ttg gaa tca att tta cac aga			2112
Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg			
610	615	620	
atc tat acc cac cag agt gat gtc tgg agc tac ggg gtg acc gtt tgg			2160
Ile Tyr Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp			

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625	630	635	
gag ttg atg acc ttt gga tcc aag cca tat gac gga atc cct gcc agc			2208
Glu Leu Met Thr Phe Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser			
640	645	650	
gag atc tcc tcc atc ctg gag aaa gga gaa cgc ctc cct cag cca ccc			2256
Glu Ile Ser Ser Ile Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro			
655	660	665	670
ata tgt acc atc gat gtc tac atg atc atg gtc aag tgc tgg atg ata			2304
Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile			
675	680	685	
gac gca gat agt cgc cca aag ttc cgt gag ttg atc atc gaa ttc tcc			2352
Asp Ala Asp Ser Arg Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser			
690	695	700	
aaa atg gcc cga gac ccc cag cgc tac ctt gtc att cag ggg gat gaa			2400
Lys Met Ala Arg Asp Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu			
705	710	715	
aga atg cat ttg cca agt cct aca gac tcc aac ttc tac cgt gcc ctg			2448
Arg Met His Leu Pro Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu			
720	725	730	
atg gat gaa gaa gac atg gac gac gtg gtg gat gcc gac gag tac ctc			2496
Met Asp Glu Glu Asp Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu			
735	740	745	750
atc cca cag cag ggc ttc ttc agc agc ccc tcc acg tca cgg act ccc			2544
Ile Pro Gln Gln Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro			
755	760	765	
ctc ctg agc tct ctg agt gca acc agc aac aat tcc acc gtg gct tgc			2592
Leu Leu Ser Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys			
770	775	780	
att gat aga aat ggg ctg caa agc tgt ccc atc aag gaa gac agc ttc			2640
Ile Asp Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe			
785	790	795	
ttg cag cga tac agc tca gac ccc aca ggc gcc ttg act gag gac agc			2688
Leu Gln Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser			
800	805	810	
ata gac gac acc ttc ctc cca gtg cct gaa tac ata aac cag tcc gtt			2736
Ile Asp Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val			
815	820	825	830
ccc aaa agg ccc gct ggc tct gtg cag aat cct gtc tat cac aat cag			2784
Pro Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln			
835	840	845	
cct ctg aac ccc gcg ccc agc aga gac cca cac tac cag gac ccc cac			2832
Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His			
850	855	860	
agc act gca gtg ggc aac ccc gag tat ctc aac act gtc cag ccc acc			2880
Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr			
865	870	875	
tgt gtc aac agc aca ttc gac agc cct gcc cac tgg gcc cag aaa ggc			2928
Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala Gln Lys Gly			

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880	885	890	
agc cac caa att agc ctg gac aac cct gac tac cag cag gac ttc ttt			2976
Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln Gln Asp Phe Phe			
895	900	905	910
ccc aag gaa gcc aag cca aat ggc atc ttt aag ggc tcc aca gct gaa			3024
Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys Gly Ser Thr Ala Glu			
	915	920	925
aat gca gaa tac cta agg gtc gcg cca caa agc agt gaa ttt att gga			3072
Asn Ala Glu Tyr Leu Arg Val Ala Pro Gln Ser Ser Glu Phe Ile Gly			
	930	935	940
gca tga ccacggagga tagtatgagc cctaaaaatc cagactcttt cgataccag			3128
Ala			
gaccaagcca cagcaggtcc tccatcccaa cagccatgcc cgcattagct cttagaccca			3188
cagactgggtt ttgcaacgtt tacaccgact agccaggaag tacttccacc tcgggcacat			3248
tttgggaagt tgcattcctt tgtcttcaaa ctgtgaagca tttacagaaa cgcattccagc			3308
aagaatattg tccctttgag cagaaattta tctttcaaag aggtatattt gaaaaaaaa			3368
aaaagtatat gtgaggattt ttattgattg gggatcttgg agtttttcat tgtcgctatt			3428
gatttttact tcaatgggct cttccaacaa ggaagaagct tgctggtagc acttgctacc			3488
ctgagttcat ccaggcccaa ctgtgagcaa ggagcacaag ccacaagtct tccagaggat			3548
gcttgattcc agtggttctg cttcaaggct tccactgcaa aacactaaag atccaagaag			3608
gccttcatgg cccagcagg ccggatcggg actgtatcaa gtcattggcag gtacagtagg			3668
ataagccact ctgtcccttc ctgggcaaag aagaaacgga ggggatggaa ttcttcctta			3728
gacttacttt tgtaaaaatg tccccacggg acttactccc cactgatgga ccagtggttt			3788
ccagtcatga gcgtagact gacttgtttg tcttccattc cattgttttg aaactcagta			3848
tgctgcccct gtcttgctgt catgaaatca gcaagagagg atgacacatc aaataataac			3908
tcggattcca gccacattg gattcatcag catttggaac aatagccac agctgagaat			3968
gtggaatacc taaggatagc accgcttttg ttctcgcaaa aacgtatctc ctaatttgag			4028
gctcagatga aatgcatcag gtcctttggg gcatagatca gaagactaca aaaatgaagc			4088
tgctctgaaa tctcctttag ccatcacccc aaccccccaa aattagtttg tgttacttat			4148
ggaagatagt tttctccttt tacttcactt caaaagcttt ttactcaaag agtatatgtt			4208
ccctccagggt cagctgcccc caaacccctt ccttacgctt tgtcacacaa aaagtgtctc			4268
tgcttgagct catctattca agcacttaca gctctggcca caacagggca ttttacagggt			4328
gcgaatgaca gtagcattat gagtagtggt gaattcagggt agtaaatatg aaactagggt			4388
ttgaaattga taatgctttc acaacatttg cagatgtttt agaaggaaaa aagttccttc			4448
ctaaaataat ttctctacaa ttggaagatt ggaagattca gctagttagg agcccacctt			4508

49321-146.ST25.txt

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ttttcctaatt ctgtgtgtgc cctgtaacct gactgggttaa cagcagtcct ttgtaaacag 4568
tggttttaaac tctcctagtc aatatccacc ccattccaatt tatcaaggaa gaaatgggttc 4628
agaaaatatt ttcagcctac agttatgttc agtcacacac acatacaaaa tggttcctttt 4688
gctttttaag taatttttga ctcccagatc agtcagagcc cctacagcat tggttaagaaa 4748
gtatttgatt tttgtctcaa tgaaaataaa actatatattca tttccactct aaaaaaaaaa 4808
aaaaaaa 4815

```

```

<210> 8
<211> 943
<212> PRT
<213> Homo sapiens

```

```

<400> 8

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```

Met Arg Pro Ser Gly Thr Ala Gly Ala Val Asp Val Asn Pro Glu Gly
1          5          10          15

```

```

Lys Tyr Ser Phe Gly Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr
          20          25          30

```

```

Val Val Thr Asp His Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser
          35          40          45

```

```

Tyr Glu Met Glu Glu Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly
50          55          60

```

```

Pro Cys Arg Lys Val Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp
65          70          75          80

```

```

Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr
          85          90          95

```

```

Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp
          100          105          110

```

```

Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu
          115          120          125

```

```

Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro
          130          135          140

```

```

Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg
          145          150          155          160

```

```

Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala Val Val Ser Leu
          165          170          175

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49321-146.ST25.txt

Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly
180 185 190

Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile
195 200 205

Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile
210 215 220

Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His
225 230 235 240

Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys
245 250 255

Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys
260 265 270

Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys
275 280 285

Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys
290 295 300

Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp
305 310 315 320

Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn
325 330 335

Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His Val Cys His Leu
340 345 350

Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly
355 360 365

Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val
370 375 380

Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe
385 390 395 400

Met Arg Arg Arg His Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu
405 410 415

Gln Glu Arg Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro
420 425 430

49321-146.ST25.txt

Asn Gln Ala Leu Leu Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile
 435 440 445

Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp
 450 455 460

Ile Pro Glu Gly Glu Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu
 465 470 475 480

Arg Glu Ala Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala
 485 490 495

Tyr Val Met Ala Ser Val Asp Asn Pro His Val Cys Arg Leu Leu Gly
 500 505 510

Ile Cys Leu Thr Ser Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe
 515 520 525

Gly Cys Leu Leu Asp Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser
 530 535 540

Gln Tyr Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr
 545 550 555 560

Leu Glu Asp Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn Val
 565 570 575

Leu Val Lys Thr Pro Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala
 580 585 590

Lys Leu Leu Gly Ala Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys
 595 600 605

Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr
 610 615 620

Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu
 625 630 635 640

Met Thr Phe Gly Ser Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile
 645 650 655

Ser Ser Ile Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys
 660 665 670

Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ala
 675 680 685

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Asp Ser Arg Pro Lys Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met
 690 695 700

Ala Arg Asp Pro Gln Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met
 705 710 715 720

His Leu Pro Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp
 725 730 735

Glu Glu Asp Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro
 740 745 750

Gln Gln Gly Phe Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu
 755 760 765

Ser Ser Leu Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp
 770 775 780

Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln
 785 790 795 800

Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
 805 810 815

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys
 820 825 830

Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu
 835 840 845

Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr
 850 855 860

Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val
 865 870 875 880

Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala Gln Lys Gly Ser His
 885 890 895

Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys
 900 905 910

Glu Ala Lys Pro Asn Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala
 915 920 925

Glu Tyr Leu Arg Val Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala
 930 935 940

49321-146.ST25.txt

```

<210> 9
<211> 4530
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (151)..(3918)
<223> HER-2 coding sequence

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cccgggccccc acccctcgca gcaccccgcg ccccgcgccc tcccagccgg gtccagccgg      120
agccatgggg cggagccgc agtgagcacc atg gag ctg gcg gcc ttg tgc cgc      174
                               Met Glu Leu Ala Ala Leu Cys Arg
                               1                               5

tgg ggg ctc ctc ctc gcc ctc ttg ccc ccc gga gcc gcg agc acc caa      222
Trp Gly Leu Leu Leu Ala Leu Leu Pro Pro Gly Ala Ala Ser Thr Gln
   10                               15                               20

gtg tgc acc ggc aca gac atg aag ctg cgg ctc cct gcc agt ccc gag      270
Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser Pro Glu
   25                               30                               35                               40

acc cac ctg gac atg ctc cgc cac ctc tac cag ggc tgc cag gtg gtg      318
Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln Val Val
                               45                               50                               55

cag gga aac ctg gaa ctc acc tac ctg ccc acc aat gcc agc ctg tcc      366
Gln Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser Leu Ser
                               60                               65                               70

ttc ctg cag gat atc cag gag gtg cag ggc tac gtg ctc atc gct cac      414
Phe Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile Ala His
   75                               80                               85

aac caa gtg agg cag gtc cca ctg cag agg ctg cgg att gtg cga ggc      462
Asn Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val Arg Gly
   90                               95                               100

acc cag ctc ttt gag gac aac tat gcc ctg gcc gtg cta gac aat gga      510
Thr Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp Asn Gly
  105                               110                               115                               120

gac ccg ctg aac aat acc acc cct gtc aca ggg gcc tcc cca gga ggc      558
Asp Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro Gly Gly
                               125                               130                               135

ctg cgg gag ctg cag ctt cga agc ctc aca gag atc ttg aaa gga ggg      606
Leu Arg Glu Leu Gln Leu Arg Ser Leu Thr Glu Ile Leu Lys Gly Gly
                               140                               145                               150

gtc ttg atc cag cgg aac ccc cag ctc tgc tac cag gac acg att ttg      654
Val Leu Ile Gln Arg Asn Pro Gln Leu Cys Tyr Gln Asp Thr Ile Leu
                               155                               160                               165

tgg aag gac atc ttc cac aag aac aac cag ctg gct ctc aca ctg ata      702
Trp Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr Leu Ile
   170                               175                               180

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gac acc aac cgc tct cgg gcc tgc cac ccc tgt tct ccg atg tgt aag	750
Asp Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Met Cys Lys	
185 190 195 200	
ggc tcc cgc tgc tgg gga gag agt tct gag gat tgt cag agc ctg acg	798
Gly Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser Leu Thr	
205 210 215	
cgc act gtc tgt gcc ggt ggc tgt gcc cgc tgc aag ggg cca ctg ccc	846
Arg Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro Leu Pro	
220 225 230	
act gac tgc tgc cat gag cag tgt gct gcc ggc tgc acg ggc ccc aag	894
Thr Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly Pro Lys	
235 240 245	
cac tct gac tgc ctg gcc tgc ctc cac ttc aac cac agt ggc atc tgt	942
His Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly Ile Cys	
250 255 260	
gag ctg cac tgc cca gcc ctg gtc acc tac aac aca gac acg ttt gag	990
Glu Leu His Cys Pro Ala Leu Val Thr Tyr Asn Thr Asp Thr Phe Glu	
265 270 275 280	
tcc atg ccc aat ccc gag ggc cgg tat aca ttc ggc gcc agc tgt gtg	1038
Ser Met Pro Asn Pro Glu Gly Arg Tyr Thr Phe Gly Ala Ser Cys Val	
285 290 295	
act gcc tgt ccc tac aac tac ctt tct acg gac gtg gga tcc tgc acc	1086
Thr Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser Cys Thr	
300 305 310	
ctc gtc tgc ccc ctg cac aac caa gag gtg aca gca gag gat gga aca	1134
Leu Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp Gly Thr	
315 320 325	
cag cgg tgt gag aag tgc agc aag ccc tgt gcc cga gtg tgc tat ggt	1182
Gln Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys Tyr Gly	
330 335 340	
ctg ggc atg gag cac ttg cga gag gtg agg gca gtt acc agt gcc aat	1230
Leu Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser Ala Asn	
345 350 355 360	
atc cag gag ttt gct ggc tgc aag aag atc ttt ggg agc ctg gca ttt	1278
Ile Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu Ala Phe	
365 370 375	
ctg ccg gag agc ttt gat ggg gac cca gcc tcc aac act gcc ccg ctc	1326
Leu Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala Pro Leu	
380 385 390	
cag cca gag cag ctc caa gtg ttt gag act ctg gaa gag atc aca ggt	1374
Gln Pro Glu Gln Leu Gln Val Phe Glu Thr Leu Glu Glu Ile Thr Gly	
395 400 405	
tac cta tac atc tca gca tgg ccg gac agc ctg cct gac ctc agc gtc	1422
Tyr Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu Ser Val	
410 415 420	
ttc cag aac ctg caa gta atc cgg gga cga att ctg cac aat ggc gcc	1470
Phe Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn Gly Ala	
425 430 435 440	

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Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
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 420 425 430

Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu
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Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly
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Cys	Gln	Pro	Met	Gly	Gly	Thr	Ala	Thr	Cys	Asn	Gly	Ser	Gly	Ser	Asp		
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 Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr
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 450 455 460
 His His Ser Leu Asn Trp Thr Lys Val Leu Arg Gly Pro Thr Glu Glu
 465 470 475 480
 Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg Asp Cys Val Ala Glu
 485 490 495
 Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro
 500 505 510
 Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Gly Gly Val
 515 520 525
 Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu Pro Arg Glu Phe Ala
 530 535 540

49321-146.ST25.txt

His Glu Ala Glu Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Gly
 545 550 555 560

Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp Thr Cys Ala Gln Cys
 565 570 575

Ala His Phe Arg Asp Gly Pro His Cys Val Ser Ser Cys Pro His Gly
 580 585 590

Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Val Gln Asn
 595 600 605

Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro
 610 615 620

Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val Leu Ile Gly Lys Thr
 625 630 635 640

His Leu Thr Met Ala Leu Thr Val Ile Ala Gly Leu Val Val Ile Phe
 645 650 655

Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln
 660 665 670

Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu
 675 680 685

Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe
 690 695 700

Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe
 705 710 715 720

Gly Thr Val His Lys Gly Val Trp Ile Pro Glu Gly Glu Ser Ile Lys
 725 730 735

Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser
 740 745 750

Phe Gln Ala Val Thr Asp His Met Leu Ala Ile Gly Ser Leu Asp His
 755 760 765

Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln
 770 775 780

Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg
 785 790 795 800

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Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val
 805 810 815

Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Gly Met Val His
 820 825 830

Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys Ser Pro Ser Gln Val
 835 840 845

Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys
 850 855 860

Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu
 865 870 875 880

Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser
 885 890 895

Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr
 900 905 910

Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu Leu Glu Lys Gly Glu
 915 920 925

Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met
 930 935 940

Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu
 945 950 955 960

Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu
 965 970 975

Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro
 980 985 990

His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val Glu Leu Glu Pro Glu
 995 1000 1005

Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn Leu Ala
 1010 1015 1020

Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu Pro Val Gly Thr Leu
 1025 1030 1035

Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser Ser Gly
 1040 1045 1050

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Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Gly Ser Cys Gln Glu
 1055 1060 1065

 Ser Ala Val Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro Val Ser
 1070 1075 1080

 Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu
 1085 1090 1095

 Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser
 1100 1105 1110

 Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly
 1115 1120 1125

 Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val
 1130 1135 1140

 Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly
 1145 1150 1155

 Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg
 1160 1165 1170

 Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr
 1175 1180 1185

 Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg
 1190 1195 1200

 Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu
 1205 1210 1215

 Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala
 1220 1225 1230

 Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile
 1235 1240 1245

 Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met
 1250 1255 1260

 Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala
 1265 1270 1275

 Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg
 1280 1285 1290

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Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala
1295 1300 1305

Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe
1310 1315 1320

Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn
1325 1330 1335

Ala Gln Arg Thr
1340

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<211> 4975
<212> DNA
<213> Homo sapiens
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<221> CDS
<222> (199)..(4227)
<223> HER-3 mutant coding sequence
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<220>
<221> mutation
<222> (1877)..(1877)
<223> mutation, comprising substitution of "a" instead of "g" at this
      position
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[illegible]

49321-146.ST25.txt

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Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly	
95 100 105	
acc cag gtc tac gat ggg aag ttt gcc atc ttc gtc atg ttg aac tat	567
Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr	
110 115 120	
aac acc aac tcc agc cac gct ctg cgc cag ctc cgc ttg act cag ctc	615
Asn Thr Asn Ser Ser His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu	
125 130 135	
acc gag att ctg tca ggg ggt gtt tat att gag aag aac gat aag ctt	663
Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu	
140 145 150 155	
tgt cac atg gac aca att gac tgg agg gac atc gtg agg gac cga gat	711
Cys His Met Asp Thr Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp	
160 165 170	
gct gag ata gtg gtg aag gac aat ggc aga agc tgt ccc ccc tgt cat	759
Ala Glu Ile Val Val Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His	
175 180 185	
gag gtt tgc aag ggg cga tgc tgg ggt cct gga tca gaa gac tgc cag	807
Glu Val Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln	
190 195 200	
aca ttg acc aag acc atc tgt gct cct cag tgt aat ggt cac tgc ttt	855
Thr Leu Thr Lys Thr Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe	
205 210 215	
ggg ccc aac ccc aac cag tgc tgc cat gat gag tgt gcc ggg ggc tgc	903
Gly Pro Asn Pro Asn Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys	
220 225 230 235	
tca ggc cct cag gac aca gac tgc ttt gcc tgc cgg cac ttc aat gac	951
Ser Gly Pro Gln Asp Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp	
240 245 250	
agt gga gcc tgt gta cct cgc tgt cca cag cct ctt gtc tac aac aag	999
Ser Gly Ala Cys Val Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys	
255 260 265	
cta act ttc cag ctg gaa ccc aat ccc cac acc aag tat cag tat gga	1047
Leu Thr Phe Gln Leu Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly	
270 275 280	
gga gtt tgt gta gcc agc tgt ccc cat aac ttt gtg gtg gat caa aca	1095
Gly Val Cys Val Ala Ser Cys Pro His Asn Phe Val Val Asp Gln Thr	
285 290 295	
tcc tgt gtc agg gcc tgt cct cct gac aag atg gaa gta gat aaa aat	1143
Ser Cys Val Arg Ala Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn	
300 305 310 315	
ggg ctc aag atg tgt gag cct tgt ggg gga cta tgt ccc aaa gcc tgt	1191
Gly Leu Lys Met Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys	
320 325 330	
gag gga aca ggc tct ggg agc cgc ttc cag act gtg gac tcg agc aac	1239
Glu Gly Thr Gly Ser Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn	
335 340 345	

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att gat gga ttt gtg aac tgc acc aag atc ctg ggc aac ctg gac ttt	1287
Ile Asp Gly Phe Val Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe	
350 355 360	
ctg atc acc ggc ctc aat gga gac ccc tgg cac aag atc cct gcc ctg	1335
Leu Ile Thr Gly Leu Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu	
365 370 375	
gac cca gag aag ctc aat gtc ttc cgg aca gta cgg gag atc aca ggt	1383
Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly	
380 385 390 395	
tac ctg aac atc cag tcc tgg ccg ccc cac atg cac aac ttc agt gtt	1431
Tyr Leu Asn Ile Gln Ser Trp Pro Pro His Met His Asn Phe Ser Val	
400 405 410	
ttt tcc aat ttg aca acc att gga ggc aga agc ctc tac aac cgg ggc	1479
Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly	
415 420 425	
ttc tca ttg ttg atc atg aag aac ttg aat gtc aca tct ctg ggc ttc	1527
Phe Ser Leu Leu Ile Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe	
430 435 440	
cga tcc ctg aag gaa att agt gct ggg cgt atc tat ata agt gcc aat	1575
Arg Ser Leu Lys Glu Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn	
445 450 455	
agg cag ctc tgc tac cac cac tct ttg aac tgg acc aag gtg ctt cgg	1623
Arg Gln Leu Cys Tyr His His Ser Leu Asn Trp Thr Lys Val Leu Arg	
460 465 470 475	
ggg cct acg gaa gag cga cta gac atc aag cat aat cgg ccg cgc aga	1671
Gly Pro Thr Glu Glu Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg	
480 485 490	
gac tgc gtg gca gag ggc aaa gtg tgt gac cca ctg tgc tcc tct ggg	1719
Asp Cys Val Ala Glu Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly	
495 500 505	
gga tgc tgg ggc cca ggc cct ggt cag tgc ttg tcc tgt cga aat tat	1767
Gly Cys Trp Gly Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr	
510 515 520	
agc cga gga ggt gtc tgt gtg acc cac tgc aac ttt ctg aat ggg gag	1815
Ser Arg Gly Gly Val Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu	
525 530 535	
cct cga gaa ttt gcc cat gag gcc gaa tgc ttc tcc tgc cac ccg gaa	1863
Pro Arg Glu Phe Ala His Glu Ala Glu Cys Phe Ser Cys His Pro Glu	
540 545 550 555	
tgc caa ccc atg gag ggc act gcc aca tgc aat ggc tcg ggc tct gat	1911
Cys Gln Pro Met Glu Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp	
560 565 570	
act tgt gct caa tgt gcc cat ttt cga gat ggg ccc cac tgt gtg agc	1959
Thr Cys Ala Gln Cys Ala His Phe Arg Asp Gly Pro His Cys Val Ser	
575 580 585	
agc tgc ccc cat gga gtc cta ggt gcc aag ggc cca atc tac aag tac	2007
Ser Cys Pro His Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr	
590 595 600	

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cca gat gtt cag aat gaa tgt cgg ccc tgc cat gag aac tgc acc cag	2055
Pro Asp Val Gln Asn Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln	
605 610 615	
ggg tgt aaa gga cca gag ctt caa gac tgt tta gga caa aca ctg gtg	2103
Gly Cys Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val	
620 625 630 635	
ctg atc ggc aaa acc cat ctg aca atg gct ttg aca gtg ata gca gga	2151
Leu Ile Gly Lys Thr His Leu Thr Met Ala Leu Thr Val Ile Ala Gly	
640 645 650	
ttg gta gtg att ttc atg atg ctg ggc ggc act ttt ctc tac tgg cgt	2199
Leu Val Val Ile Phe Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg	
655 660 665	
ggg cgc cgg att cag aat aaa agg gct atg agg cga tac ttg gaa cgg	2247
Gly Arg Arg Ile Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg	
670 675 680	
ggg gag agc ata gag cct ctg gac ccc agt gag aag gct aac aaa gtc	2295
Gly Glu Ser Ile Glu Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val	
685 690 695	
ttg gcc aga atc ttc aaa gag aca gag cta agg aag ctt aaa gtg ctt	2343
Leu Ala Arg Ile Phe Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu	
700 705 710 715	
ggc tcg ggt gtc ttt gga act gtg cac aaa gga gtg tgg atc cct gag	2391
Gly Ser Gly Val Phe Gly Thr Val His Lys Gly Val Trp Ile Pro Glu	
720 725 730	
ggg gaa tca atc aag att cca gtc tgc att aaa gtc att gag gac aag	2439
Gly Glu Ser Ile Lys Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys	
735 740 745	
agt gga cgg cag agt ttt caa gct gtg aca gat cat atg ctg gcc att	2487
Ser Gly Arg Gln Ser Phe Gln Ala Val Thr Asp His Met Leu Ala Ile	
750 755 760	
ggc agc ctg gac cat gcc cac att gta agg ctg ctg gga cta tgc cca	2535
Gly Ser Leu Asp His Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro	
765 770 775	
ggg tca tct ctg cag ctt gtc act caa tat ttg cct ctg ggt tct ctg	2583
Gly Ser Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu	
780 785 790 795	
ctg gat cat gtg aga caa cac cgg ggg gca ctg ggg cca cag ctg ctg	2631
Leu Asp His Val Arg Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu	
800 805 810	
ctc aac tgg gga gta caa att gcc aag gga atg tac tac ctt gag gaa	2679
Leu Asn Trp Gly Val Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu	
815 820 825	
cat ggt atg gtg cat aga aac ctg gct gcc cga aac gtg cta ctc aag	2727
His Gly Met Val His Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys	
830 835 840	
tca ccc agt cag gtt cag gtg gca gat ttt ggt gtg gct gac ctg ctg	2775
Ser Pro Ser Gln Val Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu	
845 850 855	

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cct cct gat gat aag cag ctg cta tac agt gag gcc aag act cca att	2823
Pro Pro Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile	
860 865 870 875	
aag tgg atg gcc ctt gag agt atc cac ttt ggg aaa tac aca cac cag	2871
Lys Trp Met Ala Leu Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln	
880 885 890	
agt gat gtc tgg agc tat ggt gtg aca gtt tgg gag ttg atg acc ttc	2919
Ser Asp Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe	
895 900 905	
ggg gca gag ccc tat gca ggg cta cga ttg gct gaa gta cca gac ctg	2967
Gly Ala Glu Pro Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu	
910 915 920	
cta gag aag ggg gag cgg ttg gca cag ccc cag atc tgc aca att gat	3015
Leu Glu Lys Gly Glu Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp	
925 930 935	
gtc tac atg gtg atg gtc aag tgt tgg atg att gat gag aac att cgc	3063
Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg	
940 945 950 955	
cca acc ttt aaa gaa cta gcc aat gag ttc acc agg atg gcc cga gac	3111
Pro Thr Phe Lys Glu Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp	
960 965 970	
cca cca cgg tat ctg gtc ata aag aga gag agt ggg cct gga ata gcc	3159
Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala	
975 980 985	
cct ggg cca gag ccc cat ggt ctg aca aac aag aag cta gag gaa gta	3207
Pro Gly Pro Glu Pro His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val	
990 995 1000	
gag ctg gag cca gaa cta gac cta gac cta gac ttg gaa gca gag	3252
Glu Leu Glu Pro Glu Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu	
1005 1010 1015	
gag gac aac ctg gca acc acc aca ctg ggc tcc gcc ctc agc cta	3297
Glu Asp Asn Leu Ala Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu	
1020 1025 1030	
cca gtt gga aca ctt aat cgg cca cgt ggg agc cag agc ctt tta	3342
Pro Val Gly Thr Leu Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu	
1035 1040 1045	
agt cca tca tct gga tac atg ccc atg aac cag ggt aat ctt ggg	3387
Ser Pro Ser Ser Gly Tyr Met Pro Met Asn Gln Gly Asn Leu Gly	
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Gly Ser Cys Gln Glu Ser Ala Val Ser Gly Ser Ser Glu Arg Cys	
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ccc cgt cca gtc tct cta cac cca atg cca cgg gga tgc ctg gca	3477
Pro Arg Pro Val Ser Leu His Pro Met Pro Arg Gly Cys Leu Ala	
1080 1085 1090	
tca gag tca tca gag ggg cat gta aca ggc tct gag gct gag ctc	3522
Ser Glu Ser Ser Glu Gly His Val Thr Gly Ser Glu Ala Glu Leu	
1095 1100 1105	

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cag gag	aaa gtg	tca atg	tgt	aga agc	cgg agc	agg	agc cgg	agc	3567
Gln Glu	Lys Val	Ser Met	Cys	Arg Ser	Arg Ser	Arg	Ser Arg	Ser	
1110			1115			1120			
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Pro Arg	Pro Arg	Gly Asp	Ser	Ala Tyr	His Ser	Gln	Arg His	Ser	
1125			1130			1135			
ctg ctg	act cct	gtt acc	cca	ctc tcc	cca ccc	ggg	tta gag	gaa	3657
Leu Leu	Thr Pro	Val Thr	Pro	Leu Ser	Pro Pro	Gly	Leu Glu	Glu	
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gag gat	gtc aac	ggg tat	gtc	atg cca	gat aca	cac	ctc aaa	ggg	3702
Glu Asp	Val Asn	Gly Tyr	Val	Met Pro	Asp Thr	His	Leu Lys	Gly	
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act ccc	tcc tcc	cgg gaa	ggc	acc ctt	tct tca	gtg	ggg ctc	agt	3747
Thr Pro	Ser Ser	Arg Glu	Gly	Thr Leu	Ser Ser	Val	Gly Leu	Ser	
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tct gtc	ctg ggt	act gaa	gaa	gaa gat	gaa gat	gag	gag tat	gaa	3792
Ser Val	Leu Gly	Thr Glu	Glu	Glu Asp	Glu Asp	Glu	Glu Tyr	Glu	
1185			1190			1195			
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Tyr Met	Asn Arg	Arg Arg	Arg	His Ser	Pro Pro	His	Pro Pro	Arg	
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Pro Ser	Ser Leu	Glu Glu	Leu	Gly Tyr	Glu Tyr	Met	Asp Val	Gly	
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tca gac	ctc agt	gcc tct	ctg	ggc agc	aca cag	agt	tgc cca	ctc	3927
Ser Asp	Leu Ser	Ala Ser	Leu	Gly Ser	Thr Gln	Ser	Cys Pro	Leu	
1230			1235			1240			
cac cct	gta ccc	atc atg	ccc	act gca	ggc aca	act	cca gat	gaa	3972
His Pro	Val Pro	Ile Met	Pro	Thr Ala	Gly Thr	Thr	Pro Asp	Glu	
1245			1250			1255			
gac tat	gaa tat	atg aat	cgg	caa cga	gat gga	ggg	ggg cct	ggg	4017
Asp Tyr	Glu Tyr	Met Asn	Arg	Gln Arg	Asp Gly	Gly	Gly Pro	Gly	
1260			1265			1270			
ggg gat	tat gca	gcc atg	ggg	gcc tgc	cca gca	tct	gag caa	ggg	4062
Gly Asp	Tyr Ala	Ala Met	Gly	Ala Cys	Pro Ala	Ser	Glu Gln	Gly	
1275			1280			1285			
tat gaa	gag atg	aga gct	ttt	cag ggg	cct gga	cat	cag gcc	ccc	4107
Tyr Glu	Glu Met	Arg Ala	Phe	Gln Gly	Pro Gly	His	Gln Ala	Pro	
1290			1295			1300			
cat gtc	cat tat	gcc cgc	cta	aaa act	cta cgt	agc	tta gag	gct	4152
His Val	His Tyr	Ala Arg	Leu	Lys Thr	Leu Arg	Ser	Leu Glu	Ala	
1305			1310			1315			
aca gac	tct gcc	ttt gat	aac	cct gat	tac tgg	cat	agc agg	ctt	4197
Thr Asp	Ser Ala	Phe Asp	Asn	Pro Asp	Tyr Trp	His	Ser Arg	Leu	
1320			1325			1330			
ttc ccc	aag gct	aat gcc	cag	aga acg	taa ctctgtctcc	ctgtggcact			4247
Phe Pro	Lys Ala	Asn Ala	Gln	Arg Thr					
1335			1340						

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 cccatctc 4975

<210> 14
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 <212> PRT
 <213> Homo sapiens

<400> 14

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Ala Arg Gly Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr
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35 40 45

Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu
50 55 60

Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile
65 70 75 80

Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr
85 90 95

Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp
100 105 110

Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser
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```

115                               120                               125

His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser
130                               135                               140

Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr
145                               150                               155                               160

Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val
165                               170                               175

Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly
180                               185                               190

Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr
195                               200                               205

Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn
210                               215                               220

Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp
225                               230                               235                               240

Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val
245                               250                               255

Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu
260                               265                               270

Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala
275                               280                               285

Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala
290                               295                               300

Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys
305                               310                               315                               320

Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser
325                               330                               335

Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val
340                               345                               350

Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gly Leu
355                               360                               365

Asn Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu
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370 375 380
 Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly Tyr Leu Asn Ile Gln
 385 390 395 400
 Ser Trp Pro Pro His Met His Asn Phe Ser Val Phe Ser Asn Leu Thr
 405 410 415
 Thr Ile Gly Gly Arg Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu Ile
 420 425 430
 Met Lys Asn Leu Asn Val Thr Ser Leu Gly Phe Arg Ser Leu Lys Glu
 435 440 445
 Ile Ser Ala Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln Leu Cys Tyr
 450 455 460
 His His Ser Leu Asn Trp Thr Lys Val Leu Arg Gly Pro Thr Glu Glu
 465 470 475 480
 Arg Leu Asp Ile Lys His Asn Arg Pro Arg Arg Asp Cys Val Ala Glu
 485 490 495
 Gly Lys Val Cys Asp Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly Pro
 500 505 510
 Gly Pro Gly Gln Cys Leu Ser Cys Arg Asn Tyr Ser Arg Gly Gly Val
 515 520 525
 Cys Val Thr His Cys Asn Phe Leu Asn Gly Glu Pro Arg Glu Phe Ala
 530 535 540
 His Glu Ala Glu Cys Phe Ser Cys His Pro Glu Cys Gln Pro Met Glu
 545 550 555 560
 Gly Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp Thr Cys Ala Gln Cys
 565 570 575
 Ala His Phe Arg Asp Gly Pro His Cys Val Ser Ser Cys Pro His Gly
 580 585 590
 Val Leu Gly Ala Lys Gly Pro Ile Tyr Lys Tyr Pro Asp Val Gln Asn
 595 600 605
 Glu Cys Arg Pro Cys His Glu Asn Cys Thr Gln Gly Cys Lys Gly Pro
 610 615 620
 Glu Leu Gln Asp Cys Leu Gly Gln Thr Leu Val Leu Ile Gly Lys Thr
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625 630 635 640
 His Leu Thr Met Ala Leu Thr Val Ile Ala Gly Leu Val Val Ile Phe
 645 650 655
 Met Met Leu Gly Gly Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile Gln
 660 665 670
 Asn Lys Arg Ala Met Arg Arg Tyr Leu Glu Arg Gly Glu Ser Ile Glu
 675 680 685
 Pro Leu Asp Pro Ser Glu Lys Ala Asn Lys Val Leu Ala Arg Ile Phe
 690 695 700
 Lys Glu Thr Glu Leu Arg Lys Leu Lys Val Leu Gly Ser Gly Val Phe
 705 710 715 720
 Gly Thr Val His Lys Gly Val Trp Ile Pro Glu Gly Glu Ser Ile Lys
 725 730 735
 Ile Pro Val Cys Ile Lys Val Ile Glu Asp Lys Ser Gly Arg Gln Ser
 740 745 750
 Phe Gln Ala Val Thr Asp His Met Leu Ala Ile Gly Ser Leu Asp His
 755 760 765
 Ala His Ile Val Arg Leu Leu Gly Leu Cys Pro Gly Ser Ser Leu Gln
 770 775 780
 Leu Val Thr Gln Tyr Leu Pro Leu Gly Ser Leu Leu Asp His Val Arg
 785 790 795 800
 Gln His Arg Gly Ala Leu Gly Pro Gln Leu Leu Leu Asn Trp Gly Val
 805 810 815
 Gln Ile Ala Lys Gly Met Tyr Tyr Leu Glu Glu His Gly Met Val His
 820 825 830
 Arg Asn Leu Ala Ala Arg Asn Val Leu Leu Lys Ser Pro Ser Gln Val
 835 840 845
 Gln Val Ala Asp Phe Gly Val Ala Asp Leu Leu Pro Pro Asp Asp Lys
 850 855 860
 Gln Leu Leu Tyr Ser Glu Ala Lys Thr Pro Ile Lys Trp Met Ala Leu
 865 870 875 880
 Glu Ser Ile His Phe Gly Lys Tyr Thr His Gln Ser Asp Val Trp Ser
 890 895 900
 Page 60

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885

890

895

Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ala Glu Pro Tyr
 900 905 910

Ala Gly Leu Arg Leu Ala Glu Val Pro Asp Leu Leu Glu Lys Gly Glu
 915 920 925

Arg Leu Ala Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr Met Val Met
 930 935 940

Val Lys Cys Trp Met Ile Asp Glu Asn Ile Arg Pro Thr Phe Lys Glu
 945 950 955 960

Leu Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu
 965 970 975

Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro
 980 985 990

His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val Glu Leu Glu Pro Glu
 995 1000 1005

Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn Leu Ala
 1010 1015 1020

Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu Pro Val Gly Thr Leu
 1025 1030 1035

Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser Ser Gly
 1040 1045 1050

Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Gly Ser Cys Gln Glu
 1055 1060 1065

Ser Ala Val Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro Val Ser
 1070 1075 1080

Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu
 1085 1090 1095

Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser
 1100 1105 1110

Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly
 1115 1120 1125

Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val
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1130 1135 1140
 Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly
 1145 1150 1155
 Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg
 1160 1165 1170
 Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr
 1175 1180 1185
 Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg
 1190 1195 1200
 Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu
 1205 1210 1215
 Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala
 1220 1225 1230
 Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile
 1235 1240 1245
 Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met
 1250 1255 1260
 Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala
 1265 1270 1275
 Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg
 1280 1285 1290
 Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala
 1295 1300 1305
 Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe
 1310 1315 1320
 Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn
 1325 1330 1335
 Ala Gln Arg Thr
 1340

<210> 15
 <211> 5484
 <212> DNA
 <213> Homo sapiens

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<220>
<221> CDS
<222> (34)..(3960)
<223> HER-4 coding sequence

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                               Met Lys Pro Ala Thr Gly Leu
                               1                               5

tgg gtc tgg gtg agc ctt ctc gtg gcg gcg ggg acc gtc cag ccc agc      102
Trp Val Trp Val Ser Leu Leu Val Ala Ala Gly Thr Val Gln Pro Ser
          10                               15                               20

gat tct cag tca gtg tgt gca gga acg gag aat aaa ctg agc tct ctc      150
Asp Ser Gln Ser Val Cys Ala Gly Thr Glu Asn Lys Leu Ser Ser Leu
          25                               30                               35

tct gac ctg gaa cag cag tac cga gcc ttg cgc aag tac tat gaa aac      198
Ser Asp Leu Glu Gln Gln Tyr Arg Ala Leu Arg Lys Tyr Tyr Glu Asn
          40                               45                               50                               55

tgt gag gtt gtc atg ggc aac ctg gag ata acc agc att gag cac aac      246
Cys Glu Val Val Met Gly Asn Leu Glu Ile Thr Ser Ile Glu His Asn
          60                               65                               70

cgg gac ctc tcc ttc ctg cgg tct gtt cga gaa gtc aca ggc tac gtg      294
Arg Asp Leu Ser Phe Leu Arg Ser Val Arg Glu Val Thr Gly Tyr Val
          75                               80                               85

tta gtg gct ctt aat cag ttt cgt tac ctg cct ctg gag aat tta cgc      342
Leu Val Ala Leu Asn Gln Phe Arg Tyr Leu Pro Leu Glu Asn Leu Arg
          90                               95                               100

att att cgt ggg aca aaa ctt tat gag gat cga tat gcc ttg gca ata      390
Ile Ile Arg Gly Thr Lys Leu Tyr Glu Asp Arg Tyr Ala Leu Ala Ile
          105                               110                               115

ttt tta aac tac aga aaa gat gga aac ttt gga ctt caa gaa ctt gga      438
Phe Leu Asn Tyr Arg Lys Asp Gly Asn Phe Gly Leu Gln Glu Leu Gly
          120                               125                               130                               135

tta aag aac ttg aca gaa atc cta aat ggt gga gtc tat gta gac cag      486
Leu Lys Asn Leu Thr Glu Ile Leu Asn Gly Gly Val Tyr Val Asp Gln
          140                               145                               150

aac aaa ttc ctt tgt tat gca gac acc att cat tgg caa gat att gtt      534
Asn Lys Phe Leu Cys Tyr Ala Asp Thr Ile His Trp Gln Asp Ile Val
          155                               160                               165

cgg aac cca tgg cct tcc aac ttg act ctt gtg tca aca aat ggt agt      582
Arg Asn Pro Trp Pro Ser Asn Leu Thr Leu Val Ser Thr Asn Gly Ser
          170                               175                               180

tca gga tgt gga cgt tgc cat aag tcc tgt act ggc cgt tgc tgg gga      630
Ser Gly Cys Gly Arg Cys His Lys Ser Cys Thr Gly Arg Cys Trp Gly
          185                               190                               195

ccc aca gaa aat cat tgc cag act ttg aca agg acg gtg tgt gca gaa      678
Pro Thr Glu Asn His Cys Gln Thr Leu Thr Arg Thr Val Cys Ala Glu
          200                               205                               210                               215

caa tgt gac ggc aga tgc tac gga cct tac gtc agt gac tgc tgc cat      726

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Gln	Cys	Asp	Gly	Arg	Cys	Tyr	Gly	Pro	Tyr	Val	Ser	Asp	Cys	Cys	His	
				220					225					230		
cga	gaa	tgt	gct	gga	ggc	tgc	tca	gga	cct	aag	gac	aca	gac	tgc	ttt	774
Arg	Glu	Cys	Ala	Gly	Gly	Cys	Ser	Gly	Pro	Lys	Asp	Thr	Asp	Cys	Phe	
			235					240					245			
gcc	tgc	atg	aat	ttc	aat	gac	agt	gga	gca	tgt	gtt	act	cag	tgt	ccc	822
Ala	Cys	Met	Asn	Phe	Asn	Asp	Ser	Gly	Ala	Cys	Val	Thr	Gln	Cys	Pro	
		250					255					260				
caa	acc	ttt	gtc	tac	aat	cca	acc	acc	ttt	caa	ctg	gag	cac	aat	ttc	870
Gln	Thr	Phe	Val	Tyr	Asn	Pro	Thr	Thr	Phe	Gln	Leu	Glu	His	Asn	Phe	
	265					270					275					
aat	gca	aag	tac	aca	tat	gga	gca	ttc	tgt	gtc	aag	aaa	tgt	cca	cat	918
Asn	Ala	Lys	Tyr	Thr	Tyr	Gly	Ala	Phe	Cys	Val	Lys	Lys	Cys	Pro	His	
280					285				290						295	
aac	ttt	gtg	gta	gat	tcc	agt	tct	tgt	gtg	cgt	gcc	tgc	cct	agt	tcc	966
Asn	Phe	Val	Val	Asp	Ser	Ser	Ser	Cys	Val	Arg	Ala	Cys	Pro	Ser	Ser	
				300					305					310		
aag	atg	gaa	gta	gaa	gaa	aat	ggg	att	aaa	atg	tgt	aaa	cct	tgc	act	1014
Lys	Met	Glu	Val	Glu	Glu	Asn	Gly	Ile	Lys	Met	Cys	Lys	Pro	Cys	Thr	
			315					320					325			
gac	att	tgc	cca	aaa	gct	tgt	gat	ggc	att	ggc	aca	gga	tca	ttg	atg	1062
Asp	Ile	Cys	Pro	Lys	Ala	Cys	Asp	Gly	Ile	Gly	Thr	Gly	Ser	Leu	Met	
		330					335					340				
tca	gct	cag	act	gtg	gat	tcc	agt	aac	att	gac	aaa	ttc	ata	aac	tgt	1110
Ser	Ala	Gln	Thr	Val	Asp	Ser	Ser	Asn	Ile	Asp	Lys	Phe	Ile	Asn	Cys	
	345					350					355					
acc	aag	atc	aat	ggg	aat	ttg	atc	ttt	cta	gtc	act	ggg	att	cat	ggg	1158
Thr	Lys	Ile	Asn	Gly	Asn	Leu	Ile	Phe	Leu	Val	Thr	Gly	Ile	His	Gly	
360					365				370						375	
gac	cct	tac	aat	gca	att	gaa	gcc	ata	gac	cca	gag	aaa	ctg	aac	gtc	1206
Asp	Pro	Tyr	Asn	Ala	Ile	Glu	Ala	Ile	Asp	Pro	Glu	Lys	Leu	Asn	Val	
				380					385					390		
ttt	cgg	aca	gtc	aga	gag	ata	aca	ggg	ttc	ctg	aac	ata	cag	tca	tgg	1254
Phe	Arg	Thr	Val	Arg	Glu	Ile	Thr	Gly	Phe	Leu	Asn	Ile	Gln	Ser	Trp	
			395					400					405			
cca	cca	aac	atg	act	gac	ttc	agt	gtt	ttt	tct	aac	ctg	gtg	acc	att	1302
Pro	Pro	Asn	Met	Thr	Asp	Phe	Ser	Val	Phe	Ser	Asn	Leu	Val	Thr	Ile	
		410					415					420				
ggg	gga	aga	gta	ctc	tat	agt	ggc	ctg	tcc	ttg	ctt	atc	ctc	aag	caa	1350
Gly	Gly	Arg	Val	Leu	Tyr	Ser	Gly	Leu	Ser	Leu	Leu	Ile	Leu	Lys	Gln	
	425					430					435					
cag	ggc	atc	acc	tct	cta	cag	ttc	cag	tcc	ctg	aag	gaa	atc	agc	gca	1398
Gln	Gly	Ile	Thr	Ser	Leu	Gln	Phe	Gln	Ser	Leu	Lys	Glu	Ile	Ser	Ala	
440					445				450						455	
gga	aac	atc	tat	att	act	gac	aac	agc	aac	ctg	tgt	tat	tat	cat	acc	1446
Gly	Asn	Ile	Tyr	Ile	Thr	Asp	Asn	Ser	Asn	Leu	Cys	Tyr	Tyr	His	Thr	
				460				465						470		
att	aac	tgg	aca	aca	ctc	ttc	agc	aca	atc	aac	cag	aga	ata	gta	atc	1494

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Ile	Asn	Trp	Thr	Thr	Leu	Phe	Ser	Thr	Ile	Asn	Gln	Arg	Ile	Val	Ile		
			475					480					485				
cg	g	a	a	a	g	g	a	a	t	t	g	a	g	a	t	g	1542
Arg	Asp	Asn	Arg	Lys	Ala	Glu	Asn	Cys	Thr	Ala	Glu	Gly	Met	Val	Cys		
		490					495					500					
aac	cat	ctg	tgt	tcc	agt	gat	ggc	tgt	tgg	gga	cct	ggg	cca	gac	caa	1590	
Asn	His	Leu	Cys	Ser	Ser	Asp	Gly	Cys	Trp	Gly	Pro	Gly	Pro	Asp	Gln		
	505					510					515						
tgt	ctg	tcg	tgt	cgc	cgc	ttc	agt	aga	gga	agg	atc	tgc	ata	gag	tct	1638	
Cys	Leu	Ser	Cys	Arg	Arg	Phe	Ser	Arg	Gly	Arg	Ile	Cys	Ile	Glu	Ser		
520					525					530					535		
tgt	aac	ctc	tat	gat	gg	g	tt	c	g	g	tt	g	a	g	t	1686	
Cys	Asn	Leu	Tyr	Asp	Gly	Glu	Phe	Arg	Glu	Phe	Glu	Asn	Gly	Ser	Ile		
				540					545					550			
tgt	gtg	gag	tgt	gac	ccc	cag	tgt	gag	aag	atg	gaa	gat	ggc	ctc	ctc	1734	
Cys	Val	Glu	Cys	Asp	Pro	Gln	Cys	Glu	Lys	Met	Glu	Asp	Gly	Leu	Leu		
			555					560					565				
aca	tgc	cat	gga	ccg	gg	c	g	a	t	g	a	a	t	g	t	1782	
Thr	Cys	His	Gly	Pro	Gly	Pro	Asp	Asn	Cys	Thr	Lys	Cys	Ser	His	Phe		
		570					575					580					
aaa	gat	ggc	cca	aac	tgt	gtg	gaa	aaa	tgt	cca	gat	ggc	tta	cag	ggg	1830	
Lys	Asp	Gly	Pro	Asn	Cys	Val	Glu	Lys	Cys	Pro	Asp	Gly	Leu	Gln	Gly		
	585					590					595						
gca	aac	agt	ttc	att	ttc	aag	tat	gct	gat	cca	gat	cgg	gag	tgc	cac	1878	
Ala	Asn	Ser	Phe	Ile	Phe	Lys	Tyr	Ala	Asp	Pro	Asp	Arg	Glu	Cys	His		
600					605					610					615		
cca	tgc	cat	cca	aac	tgc	acc	caa	ggg	tgt	aac	gg	ccc	act	agt	cat	1926	
Pro	Cys	His	Pro	Asn	Cys	Thr	Gln	Gly	Cys	Asn	Gly	Pro	Thr	Ser	His		
				620					625					630			
gac	tgc	att	tac	tac	cca	tgg	acg	ggc	cat	tcc	act	tta	cca	caa	cat	1974	
Asp	Cys	Ile	Tyr	Tyr	Pro	Trp	Thr	Gly	His	Ser	Thr	Leu	Pro	Gln	His		
			635					640					645				
gct	aga	act	ccc	ctg	att	gca	gct	gga	gta	att	gg	ggg	ctc	ttc	att	2022	
Ala	Arg	Thr	Pro	Leu	Ile	Ala	Ala	Gly	Val	Ile	Gly	Gly	Leu	Phe	Ile		
		650					655					660					
ctg	gtc	att	gtg	gg	ctg	aca	ttt	gct	gtt	tat	gtt	aga	agg	aag	agc	2070	
Leu	Val	Ile	Val	Gly	Leu	Thr	Phe	Ala	Val	Tyr	Val	Arg	Arg	Lys	Ser		
		665				670					675						
atc	aaa	aag	aaa	aga	gcc	ttg	aga	aga	ttc	ttg	gaa	aca	gag	ttg	gtg	2118	
Ile	Lys	Lys	Lys	Arg	Ala	Leu	Arg	Arg	Phe	Leu	Glu	Thr	Glu	Leu	Val		
680					685					690					695		
gaa	cca	tta	act	ccc	agt	ggc	aca	gca	ccc	aat	caa	gct	caa	ctt	cgt	2166	
Glu	Pro	Leu	Thr	Pro	Ser	Gly	Thr	Ala	Pro	Asn	Gln	Ala	Gln	Leu	Arg		
				700					705					710			
att	ttg	aaa	gaa	act	gag	ctg	aag	agg	gta	aaa	gtc	ctt	ggc	tca	gg	2214	
Ile	Leu	Lys	Glu	Thr	Glu	Leu	Lys	Arg	Val	Lys	Val	Leu	Gly	Ser	Gly		
			715					720					725				
gct	ttt	gga	acg	gtt	tat	aaa	gg	att	tgg	gta	cct	gaa	gga	gaa	act	2262	

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Ala	Phe	Gly	Thr	Val	Tyr	Lys	Gly	Ile	Trp	Val	Pro	Glu	Gly	Glu	Thr		
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gtg	aag	att	cct	gtg	gct	att	aag	att	ctt	aat	gag	aca	act	ggg	ccc	2310	
Val	Lys	Ile	Pro	Val	Ala	Ile	Lys	Ile	Leu	Asn	Glu	Thr	Thr	Gly	Pro		
	745					750				755							
aag	gca	aat	gtg	gag	ttc	atg	gat	gaa	gct	ctg	atc	atg	gca	agt	atg	2358	
Lys	Ala	Asn	Val	Glu	Phe	Met	Asp	Glu	Ala	Leu	Ile	Met	Ala	Ser	Met		
760					765				770						775		
gat	cat	cca	cac	cta	gtc	cgg	ttg	ctg	ggg	gtg	tgt	ctg	agc	cca	acc	2406	
Asp	His	Pro	His	Leu	Val	Arg	Leu	Leu	Gly	Val	Cys	Leu	Ser	Pro	Thr		
				780					785						790		
atc	cag	ctg	gtt	act	caa	ctt	atg	ccc	cat	ggc	tgc	ctg	ttg	gag	tat	2454	
Ile	Gln	Leu	Val	Thr	Gln	Leu	Met	Pro	His	Gly	Cys	Leu	Leu	Glu	Tyr		
			795					800					805				
gtc	cac	gag	cac	aag	gat	aac	att	gga	tca	caa	ctg	ctg	ctt	aac	tgg	2502	
Val	His	Glu	His	Lys	Asp	Asn	Ile	Gly	Ser	Gln	Leu	Leu	Leu	Asn	Trp		
		810					815					820					
tgt	gtc	cag	ata	gct	aag	gga	atg	atg	tac	ctg	gaa	gaa	aga	cga	ctc	2550	
Cys	Val	Gln	Ile	Ala	Lys	Gly	Met	Met	Tyr	Leu	Glu	Glu	Arg	Arg	Leu		
		825				830					835						
gtt	cat	cgg	gat	ttg	gca	gcc	cgt	aat	gtc	tta	gtg	aaa	tct	cca	aac	2598	
Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Val	Leu	Val	Lys	Ser	Pro	Asn		
					845					850					855		
cat	gtg	aaa	atc	aca	gat	ttt	ggg	cta	gcc	aga	ctc	ttg	gaa	gga	gat	2646	
His	Val	Lys	Ile	Thr	Asp	Phe	Gly	Leu	Ala	Arg	Leu	Leu	Glu	Gly	Asp		
				860					865						870		
gaa	aaa	gag	tac	aat	gct	gat	gga	gga	aag	atg	cca	att	aaa	tgg	atg	2694	
Glu	Lys	Glu	Tyr	Asn	Ala	Asp	Gly	Gly	Lys	Met	Pro	Ile	Lys	Trp	Met		
			875					880					885				
gct	ctg	gag	tgt	ata	cat	tac	agg	aaa	ttc	acc	cat	cag	agt	gac	gtt	2742	
Ala	Leu	Glu	Cys	Ile	His	Tyr	Arg	Lys	Phe	Thr	His	Gln	Ser	Asp	Val		
		890					895					900					
tgg	agc	tat	gga	gtt	act	ata	tgg	gaa	ctg	atg	acc	ttt	gga	gga	aaa	2790	
Trp	Ser	Tyr	Gly	Val	Thr	Ile	Trp	Glu	Leu	Met	Thr	Phe	Gly	Gly	Lys		
		905				910					915						
ccc	tat	gat	gga	att	cca	acg	cga	gaa	atc	cct	gat	tta	tta	gag	aaa	2838	
Pro	Tyr	Asp	Gly	Ile	Pro	Thr	Arg	Glu	Ile	Pro	Asp	Leu	Leu	Glu	Lys		
					925					930					935		
gga	gaa	cgt	ttg	cct	cag	cct	ccc	atc	tgc	act	att	gac	gtt	tac	atg	2886	
Gly	Glu	Arg	Leu	Pro	Gln	Pro	Pro	Ile	Cys	Thr	Ile	Asp	Val	Tyr	Met		
				940					945						950		
gtc	atg	gtc	aaa	tgt	tgg	atg	att	gat	gct	gac	agt	aga	cct	aaa	ttt	2934	
Val	Met	Val	Lys	Cys	Trp	Met	Ile	Asp	Ala	Asp	Ser	Arg	Pro	Lys	Phe		
			955					960					965				
aag	gaa	ctg	gct	gct	gag	ttt	tca	agg	atg	gct	cga	gac	cct	caa	aga	2982	
Lys	Glu	Leu	Ala	Ala	Glu	Phe	Ser	Arg	Met	Ala	Arg	Asp	Pro	Gln	Arg		
		970					975					980					
tac	cta	gtt	att	cag	ggg	gat	gat	cgt	atg	aag	ctt	ccc	agt	cca	aat	3030	

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Tyr	Leu	Val	Ile	Gln	Gly	Asp	Asp	Arg	Met	Lys	Leu	Pro	Ser	Pro	Asn	
985						990					995					
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Glu Asn Lys Leu Ser Ser Leu Ser Asp Leu Glu Gln Gln Tyr Arg Ala
 35 40 45

Leu Arg Lys Tyr Tyr Glu Asn Cys Glu Val Val Met Gly Asn Leu Glu
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Asp Arg Tyr Ala Leu Ala Ile Phe Leu Asn Tyr Arg Lys Asp Gly Asn
 115 120 125

Phe Gly Leu Gln Glu Leu Gly Leu Lys Asn Leu Thr Glu Ile Leu Asn
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Gly Gly Val Tyr Val Asp Gln Asn Lys Phe Leu Cys Tyr Ala Asp Thr
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Ile His Trp Gln Asp Ile Val Arg Asn Pro Trp Pro Ser Asn Leu Thr
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Leu Val Ser Thr Asn Gly Ser Ser Gly Cys Gly Arg Cys His Lys Ser
 Page 69

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185

180

190

Cys Thr Gly Arg Cys Trp Gly Pro Thr Glu Asn His Cys Gln Thr Leu
195 200 205

Thr Arg Thr Val Cys Ala Glu Gln Cys Asp Gly Arg Cys Tyr Gly Pro
210 215 220

Tyr Val Ser Asp Cys Cys His Arg Glu Cys Ala Gly Gly Cys Ser Gly
225 230 235 240

Pro Lys Asp Thr Asp Cys Phe Ala Cys Met Asn Phe Asn Asp Ser Gly
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260 265 270

Phe Gln Leu Glu His Asn Phe Asn Ala Lys Tyr Thr Tyr Gly Ala Phe
275 280 285

Cys Val Lys Lys Cys Pro His Asn Phe Val Val Asp Ser Ser Ser Cys
290 295 300

Val Arg Ala Cys Pro Ser Ser Lys Met Glu Val Glu Glu Asn Gly Ile
305 310 315 320

Lys Met Cys Lys Pro Cys Thr Asp Ile Cys Pro Lys Ala Cys Asp Gly
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340 345 350

Ile Asp Lys Phe Ile Asn Cys Thr Lys Ile Asn Gly Asn Leu Ile Phe
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Leu Val Thr Gly Ile His Gly Asp Pro Tyr Asn Ala Ile Glu Ala Ile
370 375 380

Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg Glu Ile Thr Gly
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Phe Leu Asn Ile Gln Ser Trp Pro Pro Asn Met Thr Asp Phe Ser Val
405 410 415

Phe Ser Asn Leu Val Thr Ile Gly Gly Arg Val Leu Tyr Ser Gly Leu
420 425 430

Ser Leu Leu Ile Leu Lys Gln Gln Gly Ile Thr Ser Leu Gln Phe Gln
Page 70

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435
 Ser Leu Lys Glu Ile Ser Ala Gly Asn Ile Tyr Ile Thr Asp Asn Ser
 450 455 460

Asn Leu Cys Tyr Tyr His Thr Ile Asn Trp Thr Thr Leu Phe Ser Thr
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Thr Ala Glu Gly Met Val Cys Asn His Leu Cys Ser Ser Asp Gly Cys
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Trp Gly Pro Gly Pro Asp Gln Cys Leu Ser Cys Arg Arg Phe Ser Arg
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Lys Met Glu Asp Gly Leu Leu Thr Cys His Gly Pro Gly Pro Asp Asn
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Cys Thr Lys Cys Ser His Phe Lys Asp Gly Pro Asn Cys Val Glu Lys
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Cys Pro Asp Gly Leu Gln Gly Ala Asn Ser Phe Ile Phe Lys Tyr Ala
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Cys Asn Gly Pro Thr Ser His Asp Cys Ile Tyr Tyr Pro Trp Thr Gly
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His Ser Thr Leu Pro Gln His Ala Arg Thr Pro Leu Ile Ala Ala Gly
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Val Ile Gly Gly Leu Phe Ile Leu Val Ile Val Gly Leu Thr Phe Ala
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Val Tyr Val Arg Arg Lys Ser Ile Lys Lys Lys Arg Ala Leu Arg Arg
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Phe Leu Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly Thr Ala

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725                                     730                                     735

Trp Val Pro Glu Gly Glu Thr Val Lys Ile Pro Val Ala Ile Lys Ile
740                                     745                                     750

Leu Asn Glu Thr Thr Gly Pro Lys Ala Asn Val Glu Phe Met Asp Glu
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Ala Leu Ile Met Ala Ser Met Asp His Pro His Leu Val Arg Leu Leu
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Gly Val Cys Leu Ser Pro Thr Ile Gln Leu Val Thr Gln Leu Met Pro
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His Gly Cys Leu Leu Glu Tyr Val His Glu His Lys Asp Asn Ile Gly
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Ser Gln Leu Leu Leu Asn Trp Cys Val Gln Ile Ala Lys Gly Met Met
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Tyr Leu Glu Glu Arg Arg Leu Val His Arg Asp Leu Ala Ala Arg Asn
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Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe Gly Leu
850                                     855                                     860

Ala Arg Leu Leu Glu Gly Asp Glu Lys Glu Tyr Asn Ala Asp Gly Gly
865                                     870                                     875                                     880

Lys Met Pro Ile Lys Trp Met Ala Leu Glu Cys Ile His Tyr Arg Lys
885                                     890                                     895

Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Ile Trp Glu
900                                     905                                     910

Leu Met Thr Phe Gly Gly Lys Pro Tyr Asp Gly Ile Pro Thr Arg Glu
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Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile
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Cys Thr Ile Asp Val Tyr Met Val Met Val Lys Cys Trp Met Ile Asp

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Lys Lys  Ala Phe Asp Asn Pro  Asp Tyr Trp Asn His  Ser Leu Pro
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Pro Arg  Ser Thr Leu Gln His  Pro Asp Tyr Leu Gln  Glu Tyr Ser
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Thr Lys  Tyr Phe Tyr Lys Gln  Asn Gly Arg Ile Arg  Pro Ile Val
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Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile Cys Gly Pro Gly
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Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg Leu Glu Asn Cys
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acg gtg atc gag ggc tac ctc cac atc ctg ctc atc tcc aag gcc gag      249
Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile Ser Lys Ala Glu
55                               60                               65

gac tac cgc agc tac cgc ttc ccc aag ctc acg gtc att acc gag tac      297
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Pro	Asn	Leu	Thr	Val	Ile	Arg	Gly	Trp	Lys	Leu	Phe	Tyr	Asn	Tyr	Ala	
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Lys	Leu	Cys	Val	Ser	Glu	Ile	Tyr	Arg	Met	Glu	Glu	Val	Thr	Gly	Thr	
		455					460					465				
aaa	ggg	cgc	caa	agc	aaa	ggg	gac	ata	aac	acc	agg	aac	aac	ggg	gag	1497
Lys	Gly	Arg	Gln	Ser	Lys	Gly	Asp	Ile	Asn	Thr	Arg	Asn	Asn	Gly	Glu	
	470					475					480					
aga	gcc	tcc	tgt	gaa	agt	gac	gtc	ctg	cat	ttc	acc	tcc	acc	acc	acg	1545
Arg	Ala	Ser	Cys	Glu	Ser	Asp	Val	Leu	His	Phe	Thr	Ser	Thr	Thr	Thr	
485					490					495					500	
tcg	aag	aat	cgc	atc	atc	ata	acc	tgg	cac	cgg	tac	cgg	ccc	cct	gac	1593
Ser	Lys	Asn	Arg	Ile	Ile	Ile	Thr	Trp	His	Arg	Tyr	Arg	Pro	Pro	Asp	
				505					510					515		
tac	agg	gat	ctc	atc	agc	ttc	acc	gtt	tac	tac	aag	gaa	gca	ccc	ttt	1641
Tyr	Arg	Asp	Leu	Ile	Ser	Phe	Thr	Val	Tyr	Tyr	Lys	Glu	Ala	Pro	Phe	
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Trp	Asn	Met	Val	Asp	Val	Asp	Leu	Pro	Pro	Asn	Lys	Asp	Val	Glu	Pro	
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Gly	Ile	Leu	Leu	His	Gly	Leu	Lys	Pro	Trp	Thr	Gln	Tyr	Ala	Val	Tyr	
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Ala	Lys	Ser	Glu	Ile	Leu	Tyr	Ile	Arg	Thr	Asn	Ala	Ser	Val	Pro	Ser	
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att	ccc	ttg	gac	gtt	ctt	tca	gca	tcg	aac	tcc	tct	tct	cag	tta	atc	1929
Ile	Pro	Leu	Asp	Val	Leu	Ser	Ala	Ser	Asn	Ser	Ser	Ser	Gln	Leu	Ile	
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gtg	aag	tgg	aac	cct	ccc	tct	ctg	ccc	aac	ggc	aac	ctg	agt	tac	tac	1977
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			630				635					640				
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Ile	Val	Arg	Trp	Gln	Arg	Gln	Pro	Gln	Asp	Gly	Tyr	Leu	Tyr	Arg	His	
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Asn	Tyr	Cys	Ser	Lys	Asp	Lys	Ile	Pro	Ile	Arg	Lys	Tyr	Ala	Asp	Gly	
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acc	atc	gac	att	gag	gag	gtc	aca	gag	aac	ccc	aag	act	gag	gtg	tgt	2121
Thr	Ile	Asp	Ile	Glu	Glu	Val	Thr	Glu	Asn	Pro	Lys	Thr	Glu	Val	Cys	
				680				685					690			
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Gly	Gly	Glu	Lys	Gly	Pro	Cys	Cys	Ala	Cys	Pro	Lys	Thr	Glu	Ala	Glu	
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Lys	Gln	Ala	Glu	Lys	Glu	Glu	Ala	Glu	Tyr	Arg	Lys	Val	Phe	Glu	Asn	
			710				715				720					
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Phe	Leu	His	Asn	Ser	Ile	Phe	Val	Pro	Arg	Pro	Glu	Arg	Lys	Arg	Arg	
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gat	gtc	atg	caa	gtg	gcc	aac	acc	acc	atg	tcc	agc	cga	agc	agg	aac	2313
Asp	Val	Met	Gln	Val	Ala	Asn	Thr	Thr	Met	Ser	Ser	Arg	Ser	Arg	Asn	
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			760					765					770			
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Thr	Glu	Tyr	Pro	Phe	Phe	Glu	Ser	Arg	Val	Asp	Asn	Lys	Glu	Arg	Thr	
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Val	Ile	Ser	Asn	Leu	Arg	Pro	Phe	Thr	Leu	Tyr	Arg	Ile	Asp	Ile	His	
			790			795					800					
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Ser	Cys	Asn	His	Glu	Ala	Glu	Lys	Leu	Gly	Cys	Ser	Ala	Ser	Asn	Phe	
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Val	Phe	Ala	Arg	Thr	Met	Pro	Ala	Glu	Gly	Ala	Asp	Asp	Ile	Pro	Gly	
				825					830					835		
cca	gtg	acc	tgg	gag	cca	agg	cct	gaa	aac	tcc	atc	ttt	tta	aag	tgg	2601

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Pro	Val	Thr	Trp	Glu	Pro	Arg	Pro	Glu	Asn	Ser	Ile	Phe	Leu	Lys	Trp	
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Pro	Glu	Pro	Glu	Asn	Pro	Asn	Gly	Leu	Ile	Leu	Met	Tyr	Glu	Ile	Lys	
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Tyr	Gly	Ser	Gln	Val	Glu	Asp	Gln	Arg	Glu	Cys	Val	Ser	Arg	Gln	Glu	
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Tyr	Arg	Lys	Tyr	Gly	Gly	Ala	Lys	Leu	Asn	Arg	Leu	Asn	Pro	Gly	Asn	
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Tyr	Thr	Ala	Arg	Ile	Gln	Ala	Thr	Ser	Leu	Ser	Gly	Asn	Gly	Ser	Trp	
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aca	gat	cct	gtg	ttc	ttc	tat	gtc	cag	gcc	aaa	aca	gga	tat	gaa	aac	2841
Thr	Asp	Pro	Val	Phe	Phe	Tyr	Val	Gln	Ala	Lys	Thr	Gly	Tyr	Glu	Asn	
			920					925					930			
ttc	atc	cat	ctg	atc	atc	gct	ctg	ccc	gtc	gct	gtc	ctg	ttg	atc	gtg	2889
Phe	Ile	His	Leu	Ile	Ile	Ala	Leu	Pro	Val	Ala	Val	Leu	Leu	Ile	Val	
		935					940					945				
gga	ggg	ttg	gtg	att	atg	ctg	tac	gtc	ttc	cat	aga	aag	aga	aat	aac	2937
Gly	Gly	Leu	Val	Ile	Met	Leu	Tyr	Val	Phe	His	Arg	Lys	Arg	Asn	Asn	
	950					955					960					
agc	agg	ctg	ggg	aat	gga	gtg	ctg	tat	gcc	tct	gtg	aac	ccg	gag	tac	2985
Ser	Arg	Leu	Gly	Asn	Gly	Val	Leu	Tyr	Ala	Ser	Val	Asn	Pro	Glu	Tyr	
965					970					975					980	
ttc	agc	gct	gct	gat	gtg	tac	gtt	cct	gat	gag	tgg	gag	gtg	gct	cgg	3033
Phe	Ser	Ala	Ala	Asp	Val	Tyr	Val	Pro	Asp	Glu	Trp	Glu	Val	Ala	Arg	
				985					990					995		
gag	aag	atc	acc	atg	agc	cgg	gaa	ctt	ggg	cag	ggg	tcg	ttt	ggg		3078
Glu	Lys	Ile	Thr	Met	Ser	Arg	Glu	Leu	Gly	Gln	Gly	Ser	Phe	Gly		
			1000					1005					1010			
atg	gtc	tat	gaa	gga	gtt	gcc	aag	ggt	gtg	gtg	aaa	gat	gaa	cct		3123
Met	Val	Tyr	Glu	Gly	Val	Ala	Lys	Gly	Val	Val	Lys	Asp	Glu	Pro		
			1015					1020					1025			
gaa	acc	aga	gtg	gcc	att	aaa	aca	gtg	aac	gag	gcc	gca	agc	atg		3168
Glu	Thr	Arg	Val	Ala	Ile	Lys	Thr	Val	Asn	Glu	Ala	Ala	Ser	Met		
			1030					1035					1040			
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Arg	Glu	Arg	Ile	Glu	Phe	Leu	Asn	Glu	Ala	Ser	Val	Met	Lys	Glu		
			1045					1050					1055			
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Phe	Asn	Cys	His	His	Val	Val	Arg	Leu	Leu	Gly	Val	Val	Ser	Gln		
			1060					1065					1070			
ggc	cag	cca	aca	ctg	gtc	atc	atg	gaa	ctg	atg	aca	cgg	ggc	gat		3303
Gly	Gln	Pro	Thr	Leu	Val	Ile	Met	Glu	Leu	Met	Thr	Arg	Gly	Asp		
			1075					1080					1085			
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Leu	Lys	Ser	Tyr	Leu	Arg	Ser	Leu	Arg	Pro	Glu	Met	Glu	Asn	Asn	
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cca	gtc	cta	gca	cct	cca	agc	ctg	agc	aag	atg	att	cag	atg	gcc	3393
Pro	Val	Leu	Ala	Pro	Pro	Ser	Leu	Ser	Lys	Met	Ile	Gln	Met	Ala	
			1105					1110					1115		
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Gly	Glu	Ile	Ala	Asp	Gly	Met	Ala	Tyr	Leu	Asn	Ala	Asn	Lys	Phe	
			1120					1125					1130		
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Val	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Cys	Met	Val	Ala	Glu	Asp	
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Phe	Thr	Val	Lys	Ile	Gly	Asp	Phe	Gly	Met	Thr	Arg	Asp	Ile	Tyr	
			1150					1155					1160		
gag	aca	gac	tat	tac	cgg	aaa	gga	ggc	aaa	ggg	ctg	ctg	ccc	gtg	3573
Glu	Thr	Asp	Tyr	Tyr	Arg	Lys	Gly	Gly	Lys	Gly	Leu	Leu	Pro	Val	
			1165					1170					1175		
cgc	tgg	atg	tct	cct	gag	tcc	ctc	aag	gat	gga	gtc	ttc	acc	act	3618
Arg	Trp	Met	Ser	Pro	Glu	Ser	Leu	Lys	Asp	Gly	Val	Phe	Thr	Thr	
			1180					1185					1190		
tac	tcg	gac	gtc	tgg	tcc	ttc	ggg	gtc	gtc	ctc	tgg	gag	atc	gcc	3663
Tyr	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Val	Leu	Trp	Glu	Ile	Ala	
			1195					1200					1205		
aca	ctg	gcc	gag	cag	ccc	tac	cag	ggc	ttg	tcc	aac	gag	caa	gtc	3708
Thr	Leu	Ala	Glu	Gln	Pro	Tyr	Gln	Gly	Leu	Ser	Asn	Glu	Gln	Val	
			1210					1215					1220		
ctt	cgc	ttc	gtc	atg	gag	ggc	ggc	ctt	ctg	gac	aag	cca	gac	aac	3753
Leu	Arg	Phe	Val	Met	Glu	Gly	Gly	Leu	Leu	Asp	Lys	Pro	Asp	Asn	
			1225					1230					1235		
tgt	cct	gac	atg	ctg	ttt	gaa	ctg	atg	cgc	atg	tgc	tgg	cag	tat	3798
Cys	Pro	Asp	Met	Leu	Phe	Glu	Leu	Met	Arg	Met	Cys	Trp	Gln	Tyr	
			1240					1245					1250		
aac	ccc	aag	atg	agg	cct	tcc	ttc	ctg	gag	atc	atc	agc	agc	atc	3843
Asn	Pro	Lys	Met	Arg	Pro	Ser	Phe	Leu	Glu	Ile	Ile	Ser	Ser	Ile	
			1255					1260					1265		
aaa	gag	gag	atg	gag	cct	ggc	ttc	cgg	gag	gtc	tcc	ttc	tac	tac	3888
Lys	Glu	Glu	Met	Glu	Pro	Gly	Phe	Arg	Glu	Val	Ser	Phe	Tyr	Tyr	
			1270					1275					1280		
agc	gag	gag	aac	aag	ctg	ccc	gag	ccg	gag	gag	ctg	gac	ctg	gag	3933
Ser	Glu	Glu	Asn	Lys	Leu	Pro	Glu	Pro	Glu	Glu	Leu	Asp	Leu	Glu	
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Pro	Glu	Asn	Met	Glu	Ser	Val	Pro	Leu	Asp	Pro	Ser	Ala	Ser	Ser	
			1300					1305					1310		
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Ser	Ser	Leu	Pro	Leu	Pro	Asp	Arg	His	Ser	Gly	His	Lys	Ala	Glu	
			1315					1320					1325		
aac	ggc	ccc	ggc	cct	ggg	gtg	ctg	gtc	ctc	cgc	gcc	agc	ttc	gac	4068

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Asn Gly Pro Gly Pro Gly Val Leu Val Leu Arg Ala Ser Phe Asp
 1330 1335 1340

gag aga cag cct tac gcc cac atg aac ggg ggc cgc aag aac gag 4113
 Glu Arg Gln Pro Tyr Ala His Met Asn Gly Gly Arg Lys Asn Glu
 1345 1350 1355

cgg gcc ttg ccg ctg ccc cag tct tgg acc tgc tga tccttggatc 4159
 Arg Ala Leu Pro Leu Pro Gln Ser Ser Thr Cys
 1360 1365

ctgaatctgt gcaaacagta acgtgtgcgc acgcgcagcg ggggtgggggg ggagagagag 4219

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gcccgcggga gacagcttct ctgcagtaaa acacatttgg gatgttcctt ttttcaatat 4339

gcaagcagct ttttattccc tgcccaaacc cttaactgac atgggccttt aagaacctta 4399

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cttccctggt ctccttttct ctctcctctc tgcttcataa cggaaaaata attgccacaa 4519

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 <212> PRT
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<400> 18

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Leu Phe Leu Ser Ala Ala Leu Ser Leu Trp Pro Thr Ser Gly Glu Ile
 20 25 30

Cys Gly Pro Gly Ile Asp Ile Arg Asn Asp Tyr Gln Gln Leu Lys Arg
 35 40 45

Leu Glu Asn Cys Thr Val Ile Glu Gly Tyr Leu His Ile Leu Leu Ile
 50 55 60

Ser Lys Ala Glu Asp Tyr Arg Ser Tyr Arg Phe Pro Lys Leu Thr Val
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65					70					75						80
Ile	Thr	Glu	Tyr	Leu 85	Leu	Leu	Phe	Arg	Val 90	Ala	Gly	Leu	Glu	Ser 95	Leu	
Gly	Asp	Leu	Phe 100	Pro	Asn	Leu	Thr	Val 105	Ile	Arg	Gly	Trp	Lys 110	Leu	Phe	
Tyr	Asn	Tyr 115	Ala	Leu	Val	Ile	Phe 120	Glu	Met	Thr	Asn	Leu 125	Lys	Asp	Ile	
Gly	Leu 130	Tyr	Asn	Leu	Arg	Asn 135	Ile	Thr	Arg	Gly	Ala 140	Ile	Arg	Ile	Glu	
Lys 145	Asn	Ala	Asp	Leu	Cys 150	Tyr	Leu	Ser	Thr	Val 155	Asp	Trp	Ser	Leu	Ile 160	
Leu	Asp	Ala	Val	Ser 165	Asn	Asn	Tyr	Ile	Val 170	Gly	Asn	Lys	Pro	Pro	Lys	
Glu	Cys	Gly	Asp 180	Leu	Cys	Pro	Gly	Thr 185	Met	Glu	Glu	Lys	Pro 190	Met	Cys	
Glu	Lys	Thr 195	Thr	Ile	Asn	Asn	Glu 200	Tyr	Asn	Tyr	Arg	Cys 205	Trp	Thr	Thr	
Asn	Arg 210	Cys	Gln	Lys	Met	Cys 215	Pro	Ser	Thr	Cys	Gly 220	Lys	Arg	Ala	Cys	
Thr 225	Glu	Asn	Asn	Glu	Cys 230	Cys	His	Pro	Glu	Cys 235	Leu	Gly	Ser	Cys	Ser 240	
Ala	Pro	Asp	Asn	Asp 245	Thr	Ala	Cys	Val	Ala 250	Cys	Arg	His	Tyr	Tyr 255	Tyr	
Ala	Gly	Val	Cys 260	Val	Pro	Ala	Cys	Pro 265	Pro	Asn	Thr	Tyr	Arg 270	Phe	Glu	
Gly	Trp	Arg 275	Cys	Val	Asp	Arg	Asp 280	Phe	Cys	Ala	Asn	Ile 285	Leu	Ser	Ala	
Glu	Ser 290	Ser	Asp	Ser	Glu	Gly 295	Phe	Val	Ile	His	Asp 300	Gly	Glu	Cys	Met	
Gln 305	Glu	Cys	Pro	Ser	Gly 310	Phe	Ile	Arg	Asn	Gly 315	Ser	Gln	Ser	Met	Tyr 320	
Cys	Ile	Pro	Cys	Glu	Gly	Pro	Cys	Pro	Lys	Val	Cys	Glu	Glu	Glu	Lys	

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325

330

335

Lys Thr Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Met Leu Gln Gly
 340 345 350

Cys Thr Ile Phe Lys Gly Asn Leu Leu Ile Asn Ile Arg Arg Gly Asn
 355 360 365

Asn Ile Ala Ser Glu Leu Glu Asn Phe Met Gly Leu Ile Glu Val Val
 370 375 380

Thr Gly Tyr Val Lys Ile Arg His Ser His Ala Leu Val Ser Leu Ser
 385 390 395 400

Phe Leu Lys Asn Leu Arg Leu Ile Leu Gly Glu Glu Gln Leu Glu Gly
 405 410 415

Asn Tyr Ser Phe Tyr Val Leu Asp Asn Gln Asn Leu Gln Gln Leu Trp
 420 425 430

Asp Trp Asp His Arg Asn Leu Thr Ile Lys Ala Gly Lys Met Tyr Phe
 435 440 445

Ala Phe Asn Pro Lys Leu Cys Val Ser Glu Ile Tyr Arg Met Glu Glu
 450 455 460

Val Thr Gly Thr Lys Gly Arg Gln Ser Lys Gly Asp Ile Asn Thr Arg
 465 470 475 480

Asn Asn Gly Glu Arg Ala Ser Cys Glu Ser Asp Val Leu His Phe Thr
 485 490 495

Ser Thr Thr Thr Ser Lys Asn Arg Ile Ile Ile Thr Trp His Arg Tyr
 500 505 510

Arg Pro Pro Asp Tyr Arg Asp Leu Ile Ser Phe Thr Val Tyr Tyr Lys
 515 520 525

Glu Ala Pro Phe Lys Asn Val Thr Glu Tyr Asp Gly Gln Asp Ala Cys
 530 535 540

Gly Ser Asn Ser Trp Asn Met Val Asp Val Asp Leu Pro Pro Asn Lys
 545 550 555 560

Asp Val Glu Pro Gly Ile Leu Leu His Gly Leu Lys Pro Trp Thr Gln
 565 570 575

Tyr Ala Val Tyr Val Lys Ala Val Thr Leu Thr Met Val Glu Asn Asp
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580

585

590

His Ile Arg Gly Ala Lys Ser Glu Ile Leu Tyr Ile Arg Thr Asn Ala
595 600 605

Ser Val Pro Ser Ile Pro Leu Asp Val Leu Ser Ala Ser Asn Ser Ser
610 615 620

Ser Gln Leu Ile Val Lys Trp Asn Pro Pro Ser Leu Pro Asn Gly Asn
625 630 635 640

Leu Ser Tyr Tyr Ile Val Arg Trp Gln Arg Gln Pro Gln Asp Gly Tyr
645 650 655

Leu Tyr Arg His Asn Tyr Cys Ser Lys Asp Lys Ile Pro Ile Arg Lys
660 665 670

Tyr Ala Asp Gly Thr Ile Asp Ile Glu Glu Val Thr Glu Asn Pro Lys
675 680 685

Thr Glu Val Cys Gly Gly Glu Lys Gly Pro Cys Cys Ala Cys Pro Lys
690 695 700

Thr Glu Ala Glu Lys Gln Ala Glu Lys Glu Glu Ala Glu Tyr Arg Lys
705 710 715 720

Val Phe Glu Asn Phe Leu His Asn Ser Ile Phe Val Pro Arg Pro Glu
725 730 735

Arg Lys Arg Arg Asp Val Met Gln Val Ala Asn Thr Thr Met Ser Ser
740 745 750

Arg Ser Arg Asn Thr Thr Ala Ala Asp Thr Tyr Asn Ile Thr Asp Pro
755 760 765

Glu Glu Leu Glu Thr Glu Tyr Pro Phe Phe Glu Ser Arg Val Asp Asn
770 775 780

Lys Glu Arg Thr Val Ile Ser Asn Leu Arg Pro Phe Thr Leu Tyr Arg
785 790 795 800

Ile Asp Ile His Ser Cys Asn His Glu Ala Glu Lys Leu Gly Cys Ser
805 810 815

Ala Ser Asn Phe Val Phe Ala Arg Thr Met Pro Ala Glu Gly Ala Asp
820 825 830

Asp Ile Pro Gly Pro Val Thr Trp Glu Pro Arg Pro Glu Asn Ser Ile
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835 840 845

Phe	Leu	Lys	Trp	Pro	Glu	Pro	Glu	Asn	Pro	Asn	Gly	Leu	Ile	Leu	Met
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Tyr	Glu	Ile	Lys	Tyr	Gly	Ser	Gln	Val	Glu	Asp	Gln	Arg	Glu	Cys	Val
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Ser	Arg	Gln	Glu	Tyr	Arg	Lys	Tyr	Gly	Gly	Ala	Lys	Leu	Asn	Arg	Leu
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Asn	Gly	Ser	Trp	Thr	Asp	Pro	Val	Phe	Phe	Tyr	Val	Gln	Ala	Lys	Thr
		915					920					925			
Gly	Tyr	Glu	Asn	Phe	Ile	His	Leu	Ile	Ile	Ala	Leu	Pro	Val	Ala	Val
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Leu	Leu	Ile	Val	Gly	Gly	Leu	Val	Ile	Met	Leu	Tyr	Val	Phe	His	Arg
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Lys	Arg	Asn	Asn	Ser	Arg	Leu	Gly	Asn	Gly	Val	Leu	Tyr	Ala	Ser	Val
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Gln Met Ala Gly Glu Ile Ala	Asp Gly Met Ala Tyr	Leu Asn Ala		
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Asn Lys Phe Val His Arg Asp	Leu Ala Ala Arg Asn	Cys Met Val		
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1145	1150	1155		
Asp Ile Tyr Glu Thr Asp Tyr	Tyr Arg Lys Gly Gly	Lys Gly Leu		
1160	1165	1170		
Leu Pro Val Arg Trp Met Ser	Pro Glu Ser Leu Lys	Asp Gly Val		
1175	1180	1185		
Phe Thr Thr Tyr Ser Asp Val	Trp Ser Phe Gly Val	Val Leu Trp		
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Glu Ile Ala Thr Leu Ala Glu	Gln Pro Tyr Gln Gly	Leu Ser Asn		
1205	1210	1215		
Glu Gln Val Leu Arg Phe Val	Met Glu Gly Gly Leu	Leu Asp Lys		
1220	1225	1230		
Pro Asp Asn Cys Pro Asp Met	Leu Phe Glu Leu Met	Arg Met Cys		
1235	1240	1245		
Trp Gln Tyr Asn Pro Lys Met	Arg Pro Ser Phe Leu	Glu Ile Ile		
1250	1255	1260		
Ser Ser Ile Lys Glu Glu Met	Glu Pro Gly Phe Arg	Glu Val Ser		
1265	1270	1275		
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Asp Leu Glu Pro Glu Asn Met	Glu Ser Val Pro Leu	Asp Pro Ser		
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Ala Ser Ser Ser Ser Leu Pro	Leu Pro Asp Arg His	Ser Gly His		
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Lys Ala Glu Asn Gly Pro Gly	Pro Gly Val Leu Val	Leu Arg Ala		

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1325

1330

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 Met Gly Thr
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 Gly Gly Arg Arg Gly Ala Ala Ala Pro Leu Leu Val Ala Val Ala
 5 10 15

gcg ctg cta ctg ggc gcc gcg ggc cac ctg tac ccc gga gag gtg tgt 211
 Ala Leu Leu Leu Gly Ala Ala Gly His Leu Tyr Pro Gly Glu Val Cys
 20 25 30 35

ccc ggc atg gat atc cgg aac aac ctc act agg ttg cat gag ctg gag 259
 Pro Gly Met Asp Ile Arg Asn Asn Leu Thr Arg Leu His Glu Leu Glu
 40 45 50

aat tgc tct gtc atc gaa gga cac ttg cag ata ctc ttg atg ttc aaa 307
 Asn Cys Ser Val Ile Glu Gly His Leu Gln Ile Leu Leu Met Phe Lys
 55 60 65

acg agg ccc gaa gat ttc cga gac ctc agt ttc ccc aaa ctc atc atg 355
 Thr Arg Pro Glu Asp Phe Arg Asp Leu Ser Phe Pro Lys Leu Ile Met
 70 75 80

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ttt aac tac gcg ctg gtc atc ttc gag atg gtt cac ctc aag gaa ctc Phe Asn Tyr Ala Leu Val Ile Phe Glu Met Val His Leu Lys Glu Leu 120 125 130	499
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 gag ctc cga gga tgc acc gtc atc aac ggg agt ctg atc atc aac att	1219
Glu Leu Arg Gly Cys Thr Val Ile Asn Gly Ser Leu Ile Ile Asn Ile	
360 365 370	
 cga gga ggc aac aat ctg gca gct gag cta gaa gcc aac ctc ggc ctc	1267
Arg Gly Gly Asn Asn Leu Ala Ala Glu Leu Glu Ala Asn Leu Gly Leu	
375 380 385	
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Ile Glu Glu Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser Tyr Ala Leu	
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Val Ser Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg Gly Glu Thr	
405 410 415	
 ttg gaa att ggg aac tac tcc ttc tat gcc ttg gac aac cag aac cta	1411
Leu Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn Gln Asn Leu	
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Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Thr Thr Gln Gly	
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Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser Glu Ile His	
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Ile Ala Leu Lys Thr Asn Gly Asp Lys Ala Ser Cys Glu Asn Glu Leu	
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Gln Asp Ala Cys Gly Ser Asn Ser Trp Thr Val Val Asp Ile Asp Pro	
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Pro Leu Arg Ser Asn Asp Pro Lys Ser Gln Asn His Pro Gly Trp Leu	
565 570 575	
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Met Arg Gly Leu Lys Pro Trp Thr Gln Tyr Ala Ile Phe Val Lys Thr	
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615 620 625	
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Pro Ile Ser Val Ser Asn Ser Ser Ser Gln Ile Ile Leu Lys Trp Lys	
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Tyr Glu Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu His Leu Cys	
885 890 895	
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Val Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg Leu Arg Gly	
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950 955 960	
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Ala	Ala	Arg	Asn	Cys	Met	Val	Ala	His	Asp	Phe	Thr	Val	Lys	Ile	
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Gly	Asp	Phe	Gly	Met	Thr	Arg	Asp	Ile	Tyr	Glu	Thr	Asp	Tyr	Tyr	
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Arg	Lys	Gly	Gly	Lys	Gly	Leu	Leu	Pro	Val	Arg	Trp	Met	Ala	Pro	
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Pro	Tyr	Gln	Gly	Leu	Ser	Asn	Glu	Gln	Val	Leu	Lys	Phe	Val	Met	
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Asp	Gly	Gly	Tyr	Leu	Asp	Gln	Pro	Asp	Asn	Cys	Pro	Glu	Arg	Val	
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Thr	Asp	Leu	Met	Arg	Met	Cys	Trp	Gln	Phe	Asn	Pro	Lys	Met	Arg	
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Pro	Thr	Phe	Leu	Glu	Ile	Val	Asn	Leu	Leu	Lys	Asp	Asp	Leu	His	
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Pro	Ser	Phe	Pro	Glu	Val	Ser	Phe	Phe	His	Ser	Glu	Glu	Asn	Lys	
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gct	ccc	gag	agt	gag	gag	ctg	gag	atg	gag	ttt	gag	gac	atg	gag	4081
Ala	Pro	Glu	Ser	Glu	Glu	Leu	Glu	Met	Glu	Phe	Glu	Asp	Met	Glu	
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aat	gtg	ccc	ctg	gac	cgt	tcc	tcg	cac	tgt	cag	agg	gag	gag	gcg	4126
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Glu Glu His Ile Pro Tyr Thr His Met Asn Gly Gly Lys Lys Asn
      1360                      1365                      1370

ggg cgg att ctg acc ttg cct cgg tcc aat cct tcc taa cagtgcctac    4265
Gly Arg Ile Leu Thr Leu Pro Arg Ser Asn Pro Ser
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aaactcagga ttctcacgac tctacatgt ccagtggagt tcagagatcg ttcctataca    4385

tttctgttca tcttaaggtg gactcgtttg gttaccaatt taactagtcc tgcagaggat    4445

ttaactgtga acctggaggg caaggggttt ccacagttgc tgctcctttg gggcaacgac    4505

ggtttcaaac caggatTTtg tgttttttcg ttccccccac ccgccccag cagatggaaa    4565

gaaagcacct gtttttacia attctttttt tttttttttt tttttttttt ttgctggtgt    4625

ctgagcttca gtataaaaga caaaacttcc tgtttgtgga acaaaatttc gaaagaaaaa    4685

accaaa                                                                4691

<210> 20
<211> 1382
<212> PRT
<213> Homo sapiens

<400> 20

Met Gly Thr Gly Gly Arg Arg Gly Ala Ala Ala Ala Pro Leu Leu Val
1                      5                      10                      15

Ala Val Ala Ala Leu Leu Leu Gly Ala Ala Gly His Leu Tyr Pro Gly
      20                      25                      30

Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn Leu Thr Arg Leu His
      35                      40                      45

Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His Leu Gln Ile Leu Leu
      50                      55                      60

Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp Leu Ser Phe Pro Lys
65                      70                      75                      80

Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu Phe Arg Val Tyr Gly Leu
      85                      90                      95

Glu Ser Leu Lys Asp Leu Phe Pro Asn Leu Thr Val Ile Arg Gly Ser
      100                      105                      110

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49321-146.ST25.txt

Arg Leu Phe Phe Asn Tyr Ala Leu Val Ile Phe Glu Met Val His Leu
 115 120 125

Lys Glu Leu Gly Leu Tyr Asn Leu Met Asn Ile Thr Arg Gly Ser Val
 130 135 140

Arg Ile Glu Lys Asn Asn Glu Leu Cys Tyr Leu Ala Thr Ile Asp Trp
 145 150 155 160

Ser Arg Ile Leu Asp Ser Val Glu Asp Asn His Ile Val Leu Asn Lys
 165 170 175

Asp Asp Asn Glu Glu Cys Gly Asp Ile Cys Pro Gly Thr Ala Lys Gly
 180 185 190

Lys Thr Asn Cys Pro Ala Thr Val Ile Asn Gly Gln Phe Val Glu Arg
 195 200 205

Cys Trp Thr His Ser His Cys Gln Lys Val Cys Pro Thr Ile Cys Lys
 210 215 220

Ser His Gly Cys Thr Ala Glu Gly Leu Cys Cys His Ser Glu Cys Leu
 225 230 235 240

Gly Asn Cys Ser Gln Pro Asp Asp Pro Thr Lys Cys Val Ala Cys Arg
 245 250 255

Asn Phe Tyr Leu Asp Gly Arg Cys Val Glu Thr Cys Pro Pro Pro Tyr
 260 265 270

Tyr His Phe Gln Asp Trp Arg Cys Val Asn Phe Ser Phe Cys Gln Asp
 275 280 285

Leu His His Lys Cys Lys Asn Ser Arg Arg Gln Gly Cys His Gln Tyr
 290 295 300

Val Ile His Asn Asn Lys Cys Ile Pro Glu Cys Pro Ser Gly Tyr Thr
 305 310 315 320

Met Asn Ser Ser Asn Leu Leu Cys Thr Pro Cys Leu Gly Pro Cys Pro
 325 330 335

Lys Val Cys His Leu Leu Glu Gly Glu Lys Thr Ile Asp Ser Val Thr
 340 345 350

Ser Ala Gln Glu Leu Arg Gly Cys Thr Val Ile Asn Gly Ser Leu Ile
 355 360 365

49321-146.ST25.txt

Ile Asn Ile Arg Gly Gly Asn Asn Leu Ala Ala Glu Leu Glu Ala Asn
 370 375 380

Leu Gly Leu Ile Glu Glu Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser
 385 390 395 400

Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg
 405 410 415

Gly Glu Thr Leu Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn
 420 425 430

Gln Asn Leu Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Thr
 435 440 445

Thr Gln Gly Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser
 450 455 460

Glu Ile His Lys Met Glu Glu Val Ser Gly Thr Lys Gly Arg Gln Glu
 465 470 475 480

Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Lys Ala Ser Cys Glu
 485 490 495

Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser Phe Asp Lys Ile
 500 505 510

Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe Arg Asp Leu Leu
 515 520 525

Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln Asn Val Thr Glu
 530 535 540

Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser Trp Thr Val Val Asp
 545 550 555 560

Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro Lys Ser Gln Asn His Pro
 565 570 575

Gly Trp Leu Met Arg Gly Leu Lys Pro Trp Thr Gln Tyr Ala Ile Phe
 580 585 590

Val Lys Thr Leu Val Thr Phe Ser Asp Glu Arg Arg Thr Tyr Gly Ala
 595 600 605

Lys Ser Asp Ile Ile Tyr Val Gln Thr Asp Ala Thr Asn Pro Ser Val
 610 615 620

49321-146.ST25.txt

Pro Leu Asp Pro Ile Ser Val Ser Asn Ser Ser Ser Gln Ile Ile Leu
 625 630 635 640

Lys Trp Lys Pro Pro Ser Asp Pro Asn Gly Asn Ile Thr His Tyr Leu
 645 650 655

Val Phe Trp Glu Arg Gln Ala Glu Asp Ser Glu Leu Phe Glu Leu Asp
 660 665 670

Tyr Cys Leu Lys Gly Leu Lys Leu Pro Ser Arg Thr Trp Ser Pro Pro
 675 680 685

Phe Glu Ser Glu Asp Ser Gln Lys His Asn Gln Ser Glu Tyr Glu Asp
 690 695 700

Ser Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile Leu
 705 710 715 720

Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe Glu Asp Tyr Leu
 725 730 735

His Asn Val Val Phe Val Pro Arg Lys Thr Ser Ser Gly Thr Gly Ala
 740 745 750

Glu Asp Pro Arg Pro Ser Arg Lys Arg Arg Ser Leu Gly Asp Val Gly
 755 760 765

Asn Val Thr Val Ala Val Pro Thr Val Ala Ala Phe Pro Asn Thr Ser
 770 775 780

Ser Thr Ser Val Pro Thr Ser Pro Glu Glu His Arg Pro Phe Glu Lys
 785 790 795 800

Val Val Asn Lys Glu Ser Leu Val Ile Ser Gly Leu Arg His Phe Thr
 805 810 815

Gly Tyr Arg Ile Glu Leu Gln Ala Cys Asn Gln Asp Thr Pro Glu Glu
 820 825 830

Arg Cys Ser Val Ala Ala Tyr Val Ser Ala Arg Thr Met Pro Glu Ala
 835 840 845

Lys Ala Asp Asp Ile Val Gly Pro Val Thr His Glu Ile Phe Glu Asn
 850 855 860

Asn Val Val His Leu Met Trp Gln Glu Pro Lys Glu Pro Asn Gly Leu
 865 870 875 880

49321-146.ST25.txt

Ile Val Leu Tyr Glu Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu
 885 890 895

His Leu Cys Val Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg
 900 905 910

Leu Arg Gly Leu Ser Pro Gly Asn Tyr Ser Val Arg Ile Arg Ala Thr
 915 920 925

Ser Leu Ala Gly Asn Gly Ser Trp Thr Glu Pro Thr Tyr Phe Tyr Val
 930 935 940

Thr Asp Tyr Leu Asp Val Pro Ser Asn Ile Ala Lys Ile Ile Ile Gly
 945 950 955 960

Pro Leu Ile Phe Val Phe Leu Phe Ser Val Val Ile Gly Ser Ile Tyr
 965 970 975

Leu Phe Leu Arg Lys Arg Gln Pro Asp Gly Pro Leu Gly Pro Leu Tyr
 980 985 990

Ala Ser Ser Asn Pro Glu Tyr Leu Ser Ala Ser Asp Val Phe Pro Cys
 995 1000 1005

Ser Val Tyr Val Pro Asp Glu Trp Glu Val Ser Arg Glu Lys Ile
 1010 1015 1020

Thr Leu Leu Arg Glu Leu Gly Gln Gly Ser Phe Gly Met Val Tyr
 1025 1030 1035

Glu Gly Asn Ala Arg Asp Ile Ile Lys Gly Glu Ala Glu Thr Arg
 1040 1045 1050

Val Ala Val Lys Thr Val Asn Glu Ser Ala Ser Leu Arg Glu Arg
 1055 1060 1065

Ile Glu Phe Leu Asn Glu Ala Ser Val Met Lys Gly Phe Thr Cys
 1070 1075 1080

His His Val Val Arg Leu Leu Gly Val Val Ser Lys Gly Gln Pro
 1085 1090 1095

Thr Leu Val Val Met Glu Leu Met Ala His Gly Asp Leu Lys Ser
 1100 1105 1110

Tyr Leu Arg Ser Leu Arg Pro Glu Ala Glu Asn Asn Pro Gly Arg
 1115 1120 1125

49321-146.ST25.txt

Pro	Pro	Pro	Thr	Leu	Gln	Glu	Met	Ile	Gln	Met	Ala	Ala	Glu	Ile
	1130					1135							1140	
Ala	Asp	Gly	Met	Ala	Tyr	Leu	Asn	Ala	Lys	Lys	Phe	Val	His	Arg
	1145					1150							1155	
Asp	Leu	Ala	Ala	Arg	Asn	Cys	Met	Val	Ala	His	Asp	Phe	Thr	Val
	1160					1165							1170	
Lys	Ile	Gly	Asp	Phe	Gly	Met	Thr	Arg	Asp	Ile	Tyr	Glu	Thr	Asp
	1175					1180							1185	
Tyr	Tyr	Arg	Lys	Gly	Gly	Lys	Gly	Leu	Leu	Pro	Val	Arg	Trp	Met
	1190					1195							1200	
Ala	Pro	Glu	Ser	Leu	Lys	Asp	Gly	Val	Phe	Thr	Thr	Ser	Ser	Asp
	1205					1210								
Met	Trp	Ser	Phe	Gly	Val	Val	Leu	Trp	Glu	Ile	Thr	Ser	Leu	Ala
	1220					1225								
Glu	Gln	Pro	Tyr	Gln	Gly	Leu	Ser	Asn	Glu	Gln	Val	Leu	Lys	Phe
	1235					1240								
Val	Met	Asp	Gly	Gly	Tyr	Leu	Asp	Gln	Pro	Asp	Asn	Cys	Pro	Glu
	1250					1255								
Arg	Val	Thr	Asp	Leu	Met	Arg	Met	Cys	Trp	Gln	Phe	Asn	Pro	Lys
	1265					1270								
Met	Arg	Pro	Thr	Phe	Leu	Glu	Ile	Val	Asn	Leu	Leu	Lys	Asp	Asp
	1280					1285								
Leu	His	Pro	Ser	Phe	Pro	Glu	Val	Ser	Phe	Phe	His	Ser	Glu	Glu
	1295					1300								
Asn	Lys	Ala	Pro	Glu	Ser	Glu	Glu	Leu	Glu	Met	Glu	Phe	Glu	Asp
	1310					1315								
Met	Glu	Asn	Val	Pro	Leu	Asp	Arg	Ser	Ser	His	Cys	Gln	Arg	Glu
	1325					1330								
Glu	Ala	Gly	Gly	Arg	Asp	Gly	Gly	Ser	Ser	Leu	Gly	Phe	Lys	Arg
	1340					1345								
Ser	Tyr	Glu	Glu	His	Ile	Pro	Tyr	Thr	His	Met	Asn	Gly	Gly	Lys
	1355					1360								

49321-146.ST25.txt

Lys Asn Gly Arg Ile Leu Thr Leu Pro Arg Ser Asn Pro Ser
 1370 1375 1380

<210> 21
 <211> 79
 <212> PRT
 <213> Homo sapiens

<400> 21

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
 20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
 35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
 50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
 65 70 75

<210> 22
 <211> 79
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (2)..(2)
 <223> Xaa reflects Thr or Ser variants

<400> 22

Gly Xaa His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
 20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
 35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
 50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
 65 70 75

49321-146.ST25.txt

<210> 23
<211> 79
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa reflects Leu or Pro variants

<400> 23

Gly Thr His Ser Xaa Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75

<210> 24
<211> 79
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa reflects Pro or Leu variants

<400> 24

Gly Thr His Ser Leu Xaa Pro Arg Pro Ala Ala Val Pro Val Pro Leu
1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75

49321-146.ST25.txt

<210> 25
<211> 79
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa reflects Leu or Gln variants

<400> 25

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Xaa
1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75

<210> 26
<211> 79
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa reflects Arg or Cys variants

<220>
<221> misc_feature
<222> (18)..(18)
<223> Xaa can be any naturally occurring amino acid

<400> 26

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
1 5 10 15

Arg Xaa Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

49321-146.ST25.txt

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75

<210> 27
<211> 79
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> Xaa reflects Met or Leu variants

<220>
<221> misc_feature
<222> (21)..(21)
<223> Xaa can be any naturally occurring amino acid

<400> 27

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
1 5 10 15

Arg Met Gln Pro Xaa Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
65 70 75

<210> 28
<211> 79
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> Xaa reflects Gly, Asp, Ala or Val variants

<220>
<221> misc_feature
<222> (36)..(36)
<223> Xaa can be any naturally occurring amino acid

<400> 28

49321-146.ST25.txt

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
 20 25 30

Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
 35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
 50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
 65 70 75

<210> 29
 <211> 79
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (31)..(31)
 <223> Xaa reflects Arg or Ile variants

<220>
 <221> misc_feature
 <222> (54)..(54)
 <223> Xaa can be any naturally occurring amino acid

<400> 29

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
 20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
 35 40 45

Ser Pro Thr Ser Val Xaa Ile Ser Pro Val Ser Val Gly Arg Gly Pro
 50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
 65 70 75

<210> 30
 <211> 79
 <212> PRT
 <213> Homo sapiens

49321-146.ST25.txt

<220>

<221> MISC_FEATURE

<222> (36)..(36)

<223> Xaa reflects Leu or Ile variants

<220>

<221> misc_feature

<222> (64)..(64)

<223> Xaa can be any naturally occurring amino acid

<400> 30

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
 20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
 35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Xaa
 50 55 60

Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg Tyr Glu Gly
 65 70 75

<210> 31

<211> 79

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (54)..(54)

<223> Xaa reflects Pro or Arg variants

<220>

<221> misc_feature

<222> (73)..(73)

<223> Xaa can be any naturally occurring amino acid

<400> 31

Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val Pro Val Pro Leu
 1 5 10 15

Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser Phe Leu Arg Pro
 20 25 30

Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro Leu Ala Pro Leu
 35 40 45

Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val Gly Arg Gly Pro
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50

55

60

Asp Pro Asp Ala His Val Ala Val Xaa Leu Ser Arg Tyr Glu Gly
 65 70 75

<210> 32
 <211> 419
 <212> PRT
 <213> Homo sapiens

<400> 32

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

49321-146.ST25.txt

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 33
 <211> 419
 <212> PRT
 <213> Homo sapiens

49321-146.ST25.txt

<220>

<221> MISC_FEATURE

<222> (342)..(342)

<223> Xaa reflects Thr or Ser variants

<400> 33

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
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```

225                230                235                240
Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
                245                250                255
His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
                260                265                270
Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
                275                280                285
Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
                290                295                300
Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305                310                315                320
Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
                325                330                335
Pro Cys Ala Arg Gly Xaa His Ser Leu Pro Pro Arg Pro Ala Ala Val
                340                345                350
Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
                355                360                365
Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
                370                375                380
Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
385                390                395                400
Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
                405                410                415

```

Tyr Glu Gly

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<210> 34
<211> 419
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> MISC_FEATURE
<222> (345)..(345)
<223> Xaa reflects Leu or Pro variants

```

```

<400> 34

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49321-146.ST25.txt

```

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
1           5           10           15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
          20           25           30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
          35           40           45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
          50           55           60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65           70           75           80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
          85           90           95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
          100          105          110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
          115          120          125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145           150           155           160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
          165          170          175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
          180          185          190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
          195          200          205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
          210          215          220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225           230           235           240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
          245          250          255

```

49321-146.ST25.txt

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Xaa Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 35
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (346)..(346)
 <223> Xaa reflects Pro or Leu variants

<400> 35

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

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Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

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Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Xaa Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 36
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (356)..(356)
 <223> Xaa reflects Leu or Gln variants

<400> 36

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

49321-146.ST25.txt

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
305 310 315 320

49321-146.ST25.txt

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Xaa Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 37
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (357)..(357)
 <223> Xaa reflects Arg or Cys variants

<220>
 <221> misc_feature
 <222> (358)..(358)
 <223> Xaa can be any naturally occurring amino acid

<400> 37

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

49321-146.ST25.txt

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

49321-146.ST25.txt

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Xaa Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 38
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (358)..(358)
 <223> Xaa reflects Met or Leu variants

<220>
 <221> misc_feature
 <222> (361)..(361)
 <223> Xaa can be any naturally occurring amino acid

<400> 38

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

49321-146.ST25.txt

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

49321-146.ST25.txt

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Xaa Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 39
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (361)..(361)
 <223> Xaa reflects Gly, Asp, Ala or Val variants

<220>
 <221> misc_feature
 <222> (376)..(376)
 <223> Xaa can be any naturally occurring amino acid

<400> 39

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

49321-146.ST25.txt

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

49321-146.ST25.txt

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Xaa Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 40
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (371)..(371)
 <223> Xaa reflects Arg or Ile variants

<220>
 <221> misc_feature
 <222> (394)..(394)
 <223> Xaa can be any naturally occurring amino acid

<400> 40

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

49321-146.ST25.txt

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

49321-146.ST25.txt

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Xaa Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 41
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (376)..(376)
 <223> Xaa reflects Leu or Ile variants

<220>
 <221> misc_feature
 <222> (404)..(404)
 <223> Xaa can be any naturally occurring amino acid

<400> 41

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

49321-146.ST25.txt

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

49321-146.ST25.txt

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
 370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
 385 390 395 400

Gly Arg Gly Xaa Asp Pro Asp Ala His Val Ala Val Asp Leu Ser Arg
 405 410 415

Tyr Glu Gly

<210> 42
 <211> 419
 <212> PRT
 <213> Homo sapiens

<220>
 <221> MISC_FEATURE
 <222> (394)..(394)
 <223> Xaa reflects Pro or Arg variants

<220>
 <221> misc_feature
 <222> (413)..(413)
 <223> Xaa can be any naturally occurring amino acid

<400> 42

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu
 1 5 10 15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys
 20 25 30

Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His
 35 40 45

Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr
 50 55 60

Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val
 65 70 75 80

Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu
 85 90 95

Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr
 100 105 110

49321-146.ST25.txt

Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro
 115 120 125

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

Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln
 145 150 155 160

Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn
 165 170 175

Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys
 180 185 190

His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser
 195 200 205

Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys
 210 215 220

Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys
 225 230 235 240

Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu
 245 250 255

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val
 260 265 270

Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg
 275 280 285

Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu
 290 295 300

Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln
 305 310 315 320

Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys
 325 330 335

Pro Cys Ala Arg Gly Thr His Ser Leu Pro Pro Arg Pro Ala Ala Val
 340 345 350

Pro Val Pro Leu Arg Met Gln Pro Gly Pro Ala His Pro Val Leu Ser
 355 360 365

49321-146.ST25.txt

Phe Leu Arg Pro Ser Trp Asp Leu Val Ser Ala Phe Tyr Ser Leu Pro
370 375 380

Leu Ala Pro Leu Ser Pro Thr Ser Val Pro Ile Ser Pro Val Ser Val
385 390 395 400

Gly Arg Gly Pro Asp Pro Asp Ala His Val Ala Val Xaa Leu Ser Arg
405 410 415

Tyr Glu Gly