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(56) Related Art
FEI WANG ET AL, "Apolipoprotein A-IV improves glucose homeostasis by enhancing insulin secretion", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES - PNAS, NATIONAL ACADEMY OF SCIENCES, 2012, vol. 109, no. 24, pages 9641 - 9646
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(57) Abstract: Methods for treating type one diabetes mellitus in a subject in need thereof and pharmaceutical compositions for the treatment of type one diabetes mellitus are disclosed, including combination therapies with insulin. The methods include administering an effective amount of apolipoprotein A-IV to the subject having type I diabetes. The pharmaceutical composition includes apolipoprotein A-IV formulated for administration to a subject for the treatment of type one diabetes mellitus.



**METHOD OF TREATING TYPE I DIABETES USING
APOLIPOPROTEIN AIV**

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/675,659, filed on July 25, 2012, the entire disclosure of which is incorporated herein by reference.

[0002] This invention was made with government support under grant nos. DK 59630, DK 92138, DK 76928, and F32-091173-01 awarded by the National Institutes of Health.

TECHNICAL FIELD

[0003] The present disclosure relates to a method of treating diabetes. More particularly, the present disclosure relates to a method of treating type one diabetes mellitus by administering an effective amount of apolipoprotein A-IV.

BACKGROUND

[0004] The occurrence of diabetes is widespread, with approximately 8% of the population in the United States suffering from diabetes. Diabetes is a chronic disease characterized by high blood sugar due to the body's inability to effectively produce and/or use insulin. Diabetes can lead to a variety of physical complications, including but not limited to renal failure, blindness, nerve damage, heart disease, sleep apnea, and celiac disease. For example, in the United States, diabetes is the leading cause of renal failure, blindness, amputation, stroke, and heart attack. Also in the United States, diabetes is the sixth leading cause of death and has been shown to reduce the life expectancy of middle-aged adults by about five to ten years.

[0005] Over a million people in the U.S. have type I diabetes mellitus (hereinafter T1DM). T1DM results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. According to the American Diabetes Association, the disease causes thousands of deaths every year and costs more than \$20 billion annually. While all patients with T1DM require insulin for treatment, not all patients are effectively treated with insulin alone.

[0006] It has been shown that moderately controlled type 1 diabetic subjects exhibit increased rates of glucose production both at rest and during exercise, which can be accounted for by increased gluconeogenesis (see Petersen, et al., J Clin Endocrinol Metab. 2004 Sep;89(9):4656-64). As such, new therapies for effectively treating T1DM in combination with insulin are needed, including methods of treating T1DM based on inhibition of gluconeogenesis.

SUMMARY

[0007] The present disclosure is based on the surprising discovery that apolipoprotein A-IV (also referred to as “apoA-IV”), inhibits gluconeogenesis in the liver. Accordingly, in one embodiment, methods of treating T1DM in a subject in need thereof are disclosed. The method comprises administering to the subject an effective amount of an apolipoprotein A-IV, or a biologically active analogue thereof having at least 90, 95, 96, 97, 98 or 99% identity to the apolipoprotein A-IV.

[0008] In another embodiment, a pharmaceutical composition comprising apolipoprotein A-IV is disclosed. The pharmaceutical composition comprises an apolipoprotein A-IV or a biologically active analogue thereof having at least 90, 95, 96, 97, 98 or 99% identity to the apolipoprotein A-IV formulated for administration to a subject for the treatment of T1DM.

[0009] In yet another embodiment, a method for inhibiting gluconeogenesis in a subject having type 1 diabetes is disclosed. In one embodiment, the method of treating T1DM includes administering insulin and apoA-IV to a subject in need thereof. The method comprises administering to the subject an effective amount of apolipoprotein A-IV, or a biologically active analogue thereof, having at least 90, 95, 96, 97, 98 or 99% identity to an apolipoprotein A-IV, for example, by systemic administration of the apolipoprotein A-IV or the biologically active analogue thereof.

[0010] In yet still another embodiment, a method for lowering blood glucose level in a subject having T1DM is disclosed. The method comprises administering to the subject an effective amount of apolipoprotein A-IV or a biologically active analogue thereof having at least 90, 95, 96, 97, 98 or 99% identity to the apolipoprotein A-IV to the subject in need, for example, by systemic administration. An “effective amount” is as described below and includes about 0.25 to 2 µg/g of the apoA-IV or the

biologically active analogue thereof. In one embodiment the effective amount is about 0.1 mg/kg to 25 mg/kg. In another embodiment, the effective amount is a fixed dose of about 1 to 1000 mg. In a further embodiment, the effective amount is a fixed dose of about 1 to 10 mg.

[0011] In one embodiment of the invention, apolipoprotein A-IV used in the methods and compositions of the invention is non-glycosylated.

[0012] These and other features and advantages of these and other various embodiments according to the present disclosure will become more apparent in view of the drawings, detailed description, and claims provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The following detailed description of the embodiments of the present disclosure can be better understood when read in conjunction with the following drawings, where like structure is indicated with like reference numerals, and in which:

[0014] FIG. 1 shows the amino acid sequence of full length wild type human apolipoprotein A-IV protein (SEQ ID NO. 1).

[0015] FIG. 2 shows the amino acid sequence of full length wild type mouse apolipoprotein A-IV protein (SEQ ID NO. 2).

[0016] FIG. 3 shows the amino acid sequence of full length wild type human apolipoprotein A-IV protein with the addition of glycine at the *N*-terminus (SEQ ID NO. 3).

[0017] FIG. 4 shows the amino acid sequence of human apolipoprotein A-IV protein containing polymorphic substitutions T347S, Q360H, and/or E165K and the optional addition of glycine, alanine or valine to the *N*-terminus (SEQ ID NO. 4).

[0018] FIG. 5 shows a polynucleotide (SEQ ID NO. 5) encoding full length wild type human apolipoprotein A-IV.

[0019] FIG. 6A is a diagram showing NR1D1 mRNA levels, which were quantified by real time RT-PCR and normalized to β -actin. Primary hepatocytes were treated with or without 20 μ g/ml r-m-apoA-IV (r = recombinant; m = mouse) for the duration as indicated. FIG. 6B includes a diagram and a photograph showing the

results of Western analysis of NR1D1 protein expression in HEK293 cells treated with 50 µg/ml r-h-apoA-IV for 24 h (* $P < 0.05$).

[0020] FIGS. 7A-F are diagrams showing that ApoA-IV suppresses hepatic gluconeogenic genes and lowers glucose production *in vivo* and *in vitro*. In FIGS. 7A and B, 2 h after i.p. r-m-apoA-IV (100 µg/animal) administration in mice, total RNA was isolated from livers of 3 groups of mice (n = 8-9 per group): 1) fasted for 24 h, 2) fasted for 24 h and re-fed for 24 h, and 3) fed *ad libitum*. G6Pase and PEPCK mRNA levels were quantified by real-time RT-PCR and normalized to 18s RNA. In FIG. 7C, plasma glucose was measured in the 3 groups of mice. In FIGS. 7D and E, primary mouse hepatocytes were treated with 20 µg/ml r-m-apoA-IV for 6 h. PEPCK and G6Pase mRNA expression was determined by real time RT-PCR. In FIG. 7F, primary mouse hepatocytes were treated with or without 20 µg/ml r-m-apoA-IV in for 16 h, and then glucose level was measured in the medium (* $P < 0.05$ and ** $P < 0.01$).

[0021] FIG. 8A includes a photograph and a bar graph showing Western analysis and Luc-activity, respectively, in cells transfected with the *G6Pase*-luciferase reporter with or without *Nr1d1* plasmid and treated with or without 50 µg/ml r-h-apoA-IV. FIG. 8B includes three diagrams showing levels of G6Pase, PEPCK, and NR1D1 mRNA in mouse primary hepatocytes transfected with or without siRNA against mouse *Nr1d1* for 48 h, followed by treatment with 20 µg/ml r-m-apoA-IV protein for 6 h. mRNA was quantified by real-time RT-PCR and normalized to β-actin (* $P < 0.05$, ** $P < 0.01$).

[0022] FIG. 9 provides a diagram showing negative regulation of blood glucose in WT fasting mice by apoA-IV in a dose-dependent manner.

[0023] FIG. 10A shows Blood glucose levels during the clamp period. FIG. 10B shows GIR, GU and EGP at 70–100 min during the euglycemic clamp. n = 6-7 per group. * $P < 0.05$ vs. WT mice. FIG 10C shows hepatic gluconeogenic gene expression in WT and apoA-IV-KO mice. Total RNAs were isolated from the livers in 5-h-fasted mice, and then G6Pase and PEPCK mRNA levels were quantitated by real-time RT-PCR and normalized to cyclophilin. n= 6-7 per group. * $P < 0.05$ vs. WT mice.

[0024] Skilled artisans appreciate that elements in the figures are illustrated for simplicity and clarity and are not necessarily drawn to scale. For example, the dimensions of some of the elements in the figures may be exaggerated relative to other

elements, as well as conventional parts removed, to help to improve understanding of the various embodiments of the present disclosure.

DETAILED DESCRIPTION

[0025] The following terms are used in the present application:

[0026] As used herein, the term "effective amount" describes the amount necessary or sufficient to realize a desired biologic effect. The effective amount for any particular application may vary depending on a variety of factors, including but not limited to the particular composition being administered, the size of the subject, and/or the severity of the disease and/or condition being treated. In one embodiment, an "effective amount" is a dose of about 0.25 to 10 $\mu\text{g/g}$ of an apolipoprotein A-IV or biologically active analogue thereof. Alternatively, an "effective amount of an apoA-IV or a biologically active analogue thereof is about 1 to 10 $\mu\text{g/g}$, about 0.25 to 2 $\mu\text{g/g}$, or about 1 $\mu\text{g/g}$, or about 0.1 mg/kg to 25 mg/kg. In another embodiment, the effective amount is a fixed dose of about 1 to 1000 mg. In a further embodiment, the effective amount is a fixed dose of about 1 to 10 mg. An apoA-IV or a biologically active analogue is administered one time daily. Alternatively, an apoA-IV or a biologically active analogue thereof is administered about 2 times per day. In yet another alternative, an apoA-IV or a biologically active analogue thereof is administered more than twice a day, for example, three times per day. In yet another alternative, apoA-IV is administered once every second, third, fourth, fifth or sixth day, or once weekly.

[0027] As used herein, the term "desired biologic effect" describes reducing the effects of, counteracting, and/or eliminating a disease or condition. For example, in the context of T1DM, desired biologic effects include, but are not limited to, inhibiting gluconeogenesis. In a further embodiment, in the context of T1DM, desired biologic effects include, but are not limited to, lowering blood glucose, improving glucose tolerance, or substantially restoring glucose tolerance to a normal level.

[0028] As used herein, the term "normal level" describes a level that is substantially the same as the level in a subject who is not in need of treatment. For example, in the context of treating T1DM, a normal level of blood glucose is from about 70 mg/dL to about 130 mg/dL before meals and less than about 180 mg/dL

about one to two hours after meals, or from about 70 mg/dL to about 100 mg/dL before meals and less than about 140 mg/dL about one to two hours after meals. In another example in the context of treating T1DM, a normal level of glucose tolerance describes the ability of the subject to metabolize carbohydrates such that the level of blood glucose is from about 70 mg/dL to about 130 mg/dL before meals and less than about 180 mg/dL about one to two hours after meals, or from about 70 mg/dL to about 100 mg/dL before meals and less than about 140 mg/dL about one to two hours after meals.

[0029] In the context of blood glucose level, the term "restore" describes changing the blood glucose level of a subject to a normal level. Similarly, in the context of glucose tolerance, the term "restore" describes changing the glucose tolerance of a subject to a normal level.

[0030] In the context of apolipoprotein A-IV, the term "biologically active fragment" describes a fragment of apolipoprotein A-IV which is capable of realizing a desired biologic effect in a subject with T1DM. The term "biologically active analogue " describes an analogue of an apolipoprotein A-IV which is capable of realizing a desired biologic effect in a subject with T1DM. In one example, a desired biological effect is the ability to inhibit gluconeogenesis. In one example, a desired biological effect is to restore glucose tolerance in apoA-IV knockout mice. Another example of a desired biological effect is to cause a statistically significant lowering of abnormal glucose levels in an animal model of T1DM.

[0031] Embodiments of the present disclosure relate to methods for treating T1DM in a subject in need thereof and pharmaceutical compositions for the treatment of T1DM. In one embodiment, a method of treating diabetes is disclosed. In one particular embodiment, a method of treating T1DM in a subject in need thereof is disclosed, wherein the method comprises administering an effective amount of an apolipoprotein A-IV (hereinafter "apoA-IV") or a biologically active analogue thereof to the subject.

[0032] In one embodiment, the method of treating T1DM is effective to lower blood glucose level of a subject. In one embodiment, the method of treating T1DM is effective for inhibiting gluconeogenesis. In one particular embodiment, the method is effective to lower blood glucose level of a subject by about 20 to 50%. In a further

embodiment, the method is effective to lower the blood glucose level of a subject by about 40%. In a further embodiment, the method is effective to lower the blood glucose level of a subject by about 70%. In still a further embodiment, the method is effective to substantially restore blood glucose level to a normal level.

[0033] In one embodiment, the method of treating a T1DM results in a lower blood glucose level of a subject. In one particular embodiment, the method is effective to lower the blood glucose level of a subject having T1DM by about 1 mg/dl, 2 mg/dl, 3 mg/dl, 4 mg/dl, 5 mg/dl, 6 mg/dl, 7 mg/dl, 8 mg/dl, 9 mg/dl, 10 mg/dl, 11 mg/dl, 12 mg/dl, 13 mg/dl, 14 mg/dl, 15 mg/dl, 16 mg/dl, 17 mg/dl, 18 mg/dl, 19 mg/dl, 20 mg/dl, 40 mg/dl, 60 mg/dl, 80 mg/dl, 100 mg/dl, 120 mg/dl, 140 mg/dl, 160 mg/dl, 180 mg/dl, 200 mg/dl, 220 mg/dl, or 240 mg/dl, from a baseline level over the course of the dosing interval.

[0034] In another embodiment, the method of treating T1DM is effective for substantially restore glucose tolerance of a subject to a normal level. In one particular embodiment, the method is effective to substantially restore glucose tolerance of a subject to a normal level within about two hours after administration of a dose of an apoA-IV or a biologically active analogue thereof. In another embodiment, the method is effective to substantially restore glucose levels to a normal level within about three hours or within about four hours after administration of a dose of apoA-IV, or a biologically active analogue thereof. In another embodiment, the glucose tolerance of a subject is substantially restored to a normal level for about eight to twelve hours.

[0035] In one embodiment, an apoA-IV or a biologically active analogue thereof is administered systemically. Systemic administration of the apoA-IV or the analogue thereof is selected from the group consisting of oral, subcutaneous, intravenous, intramuscular, and intraperitoneal administration.

[0036] In another embodiment, a pharmaceutical composition is disclosed. In one particular embodiment, the pharmaceutical composition comprises an apoA-IV or a biologically active analogue thereof. In another embodiment, the apoA-IV or analogue thereof is formulated for administration to a subject for the treatment of T1DM. In this particular embodiment, a method for treating T1DM in a subject in

need thereof is also provided, wherein the method comprises administering an effective amount of the pharmaceutical composition to the subject.

[0037] An “apolipoprotein A-IV” (also referred to herein as “apoA-IV”) refers to mammalian apoA-IV and includes full-length apoA-IV and biologically active fragments of apoA-IV. The full-length human apoA-IV is a 376 amino acid protein (SEQ ID NO: 1), the amino acid sequence of which is shown in FIG. 1; the amino acid sequence of full length mouse apoA-IV (SEQ ID NO. 2) is shown in FIG. 2. Also encompassed by the term “apolipoprotein A-IV” is the known analogue in which a glycine is added to *N*-terminus of the apolipoprotein A-IV of the full length human sequence (SEQ ID NO. 3, as shown in FIG. 3), and analogues thereof having conservative substitutions for the *N*-terminal glycine (such as alanine and valine). An “apolipoprotein A-IV” also includes polymorphic forms thereof, including the T347S, Q360H, or E165K substitutions to the human sequence represented by SEQ ID NO. 1 or the corresponding positions of SEQ ID NO. 3. As such, “apolipoprotein A-IV” includes the protein of SEQ ID NO. 4, shown in FIG. 4. In addition, human “apolipoprotein A-IV” includes variants (SEQ ID NOs: 20-64) each with a missense mutation: P393H, Q385K, Q381K, Q380H, Q377P, T367S, S353A, N352Y, V336M, D335H, G311R, V307L, R305C, R304Q, E291G, V274M, V274A, R264Q, A260T, E250K, N235S, Q231K, R220C, Q214H, E207K, T202M, R200C, D191N, D184N, P181L, A172T, R169W, A161S, R154W, T148M, S147N, A139E, N127K, S95L, R90C, T85A, Q77H, G74S, V13M, or V6M.

A biologically active analogue of apolipoprotein A-IV has at least 90, 95, 96, 97, 98 or 99% identity to an apolipoprotein A-IV. As described in the previous paragraph, an apolipoprotein A-IV includes full length mammalian apolipoprotein A-IV (e.g., human or mammalian), polymorphic forms thereof, the protein of SEQ ID NOS. 3 and 4 and biologically active fragments of any of the foregoing. Amino acid variations in the biologically active analogues preferably have conservative substitutions relative to the wild type sequences. A “conservative substitution” is the replacement of an amino acid with another amino acid that has the same net electronic charge and approximately the same size and shape. Amino acid residues with aliphatic or substituted aliphatic amino acid side chains have approximately the same size when the total number of carbon and heteroatoms in their side chains differs by no more than about four. They have approximately the same shape when the number of

branches in their side chains differs by no more than one. Amino acid residues with phenyl or substituted phenyl groups in their side chains are considered to have about the same size and shape. Listed below are five groups of amino acids. Replacing an amino acid residue with another amino acid residue from the same group results in a conservative substitution:

Group I: glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, and non-naturally occurring amino acids with C1-C4 aliphatic or C1-C4 hydroxyl substituted aliphatic side chains (straight chained or mono-branched).

Group II: glutamic acid, aspartic acid and non-naturally occurring amino acids with carboxylic acid substituted C1-C4 aliphatic side chains (un-branched or one branch point).

Group III: lysine, ornithine, arginine and non-naturally occurring amino acids with amine or guanidine substituted C1-C4 aliphatic side chains (un-branched or one branch point).

Group IV: glutamine, asparagine and non-naturally occurring amino acids with amide substituted C1-C4 aliphatic side chains (un-branched or one branch point).

Group V: phenylalanine, phenylglycine, tyrosine and tryptophan.

[0038] An apolipoprotein A-IV or a biologically active analogue thereof can be glycosylated or unglycosylated. The polynucleotide sequence of full length wild type human apolipoprotein (SEQ ID NO. 1) is shown as SEQ ID NO: 5 in Fig. 5. The apoA-IV may be prepared according to a method known in the molecular biology field. For example, apoA-IV may be prepared via traditional molecular cloning techniques.

[0039] In one embodiment, a bacterial host may be used to produce unglycosylated apoA-IV. Examples of bacterial hosts include, but are not limited to, *E. coli* BL-21, BL-21 (DE3), BL21-AI™, BL21(DE3)pLysS, BL21(DE3)pLysE, BL21 Star™(DE3), and BL21 Star™ (DE3)pLysS, (Invitrogen). *Corynebacterium* may also be used as a

host cell for expressing apoA-IV. Prior to transformation into the bacterial host, the DNA segment encoding ApoA-IV or its analogue may be incorporated in any of suitable expression vectors for transformation into the bacterial host. Suitable expression vectors include plasmid vectors, cosmid vectors, and phage vectors variously known to those of skill in the art, for example, as described in Sambrook, et al., *Molecular Cloning Manual*, 2d Edition, 1989. Examples of the expression vector include pET Vectors (Invitrogen), pDEST vectors (Invitrogen), pRSET vectors (Invitrogen), and pJexpress Vector (DNA2.0 Inc.). In one embodiment, *E. Coli* BL-21 (DE3) is transformed with pET30 expression vector which contains the gene encoding the ApoA-IV.

[0040] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for apoA-IV-encoding vectors.

Saccharomyces cerevisiae, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*; *Kluyveromyces* hosts such as, e.g., *K. lactis*, *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa*; *Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger*.

[0041] Suitable host cells for the expression of apoA-IV are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

[0042] Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco can also be utilized as hosts.

[0043] Another suitable host cell for production of apoA-IV protein is a vertebrate cell. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (e.g., 293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol. 36:59 (1977)); baby hamster kidney cells (BHK, e.g., ATCC CCL 10); Chinese hamster ovary cells/-DHFR(CHO, Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)), including, but not limited to CHO K1, CHO pro3.sup.-, CHO DG44, CHO DUXB11, Lec13, B-Ly1, and CHO DP12 cells, preferably a CHO DUX (DHFR-) or subclone thereof (herein called "CHO DUX"); C127 cells, mouse L cells; Ltk.sup.- cells; mouse sertoli cells (TM4, Mather, Biol. Reprod. 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HeLa, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); mouse myeloma cells; NS0; hybridoma cells such as mouse hybridoma cells; COS cells; mouse mammary tumor (MMT 060562, ATCC CCL51); TR1 cells (Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

[0044] Host cells are transformed with expression or cloning vectors for production of the apoA-IV protein, and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

[0045] Apolipoprotein A-IV knockout mice used in the examples were generated according to procedures disclosed in Weinstock, et al, J Lipid Res. 1997;38(9):1782-94, the entire teachings of which are incorporated herein by reference.

[0046] In one particular embodiment, the pharmaceutical composition may further comprise a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers include a wide range of known diluents (i.e., solvents), fillers, extending agents, binders, suspending agents, disintegrates, surfactants, lubricants, excipients,

wetting agents and the like commonly used in this field. The pharmaceutical composition is preferably aqueous, i.e., is a liquid formulation, and preferably comprises pyrogen free water. These carriers may be used singly or in combination according to the form of the pharmaceutical preparation. The resulting preparation may incorporate, if necessary, one or more solubilizing agent, buffers, preservatives, colorants, perfumes, flavorings and the like that are widely used in the field of pharmaceutical preparation.

[0047] The apolipoprotein A-IV or biologically active analogue thereof may be formulated into a dosage form selected from the group consisting of tablets, capsules, granules, pills, injections, solutions, emulsions, suspensions, and syrups. The form and administration route for the pharmaceutical composition are not limited and can be suitably selected. For example, tablets, capsules, granules, pills, syrups, solutions, emulsions, and suspensions may be administered orally. Additionally, injections (e.g. subcutaneous, intravenous, intramuscular, and intraperitoneal) may be administered intravenously either singly or in combination with a conventional replenisher containing glucose, amino acid and/or the like, or may be singly administered intramuscularly, intracutaneously, subcutaneously and/or intraperitoneally.

[0048] The pharmaceutical composition of the invention for treating T1DM may be prepared according to a method known in the pharmaceutical field of this kind using a pharmaceutically acceptable carrier. For example, oral forms such as tablets, capsules, granules, pills and the like are prepared according to known methods using excipients such as saccharose, lactose, glucose, starch, mannitol and the like; binders such as syrup, gum arabic, sorbitol, tragacanth, methylcellulose, polyvinylpyrrolidone and the like; disintegrates such as starch, carboxymethylcellulose or the calcium salt thereof, microcrystalline cellulose, polyethylene glycol and the like; lubricants such as talc, magnesium stearate, calcium stearate, silica and the like; and wetting agents such as sodium laurate, glycerol and the like.

[0049] Injections, solutions, emulsions, suspensions, syrups and the like may be prepared according to a known method suitably using solvents for dissolving the active ingredient, such as ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol, polyethylene glycol, sesame oil and the like; surfactants such as sorbitan fatty acid ester, polyoxyethylenesorbitan fatty acid ester, polyoxyethylene

fatty acid ester, polyoxyethylene of hydrogenated castor oil, lecithin and the like; suspending agents such as cellulose derivatives including carboxymethylcellulose sodium, methylcellulose and the like, natural gums including tragacanth, gum arabic and the like; and preservatives such as parahydroxybenzoic acid esters, benzalkonium chloride, sorbic acid salts and the like.

[0050] The proportion of the active ingredient to be contained in the pharmaceutical composition of the invention for treating diabetes can be suitably selected from a wide range.

[0051] Also included in the methods of the invention are combination therapies for treating T1DM. In one embodiment, apoA-IV is administered in a combination therapy with insulin. In one embodiment, apoA-IV is administered in a combination therapy with incretin mimetics. An additional therapeutic agent, such as, but not limited to, insulin, may be administered prior to, concurrently with, or subsequent to administration of apoA-IV to the subject in need thereof.

[0052] The effective amount of apoA-IV administered to a subject for the treatment of a disorder associated with hyperglycemia may, for example, be a weight-based dose (e.g., mg/kg) or, in another example, be a fixed dose (non-weight dependent). In one embodiment, about 1 to 10 mg/kg, about 0.25 to 2 mg/kg, about 1 mg/kg, or 0.1 mg/kg to 25 mg/kg of apoA-IV is administered to a subject in need thereof. In another embodiment, the effective amount of apoA-IV administered to a subject in need thereof is a fixed dose of about 1 to 1000 mg. In a further embodiment, the effective amount is a fixed dose of apoA-IV administered to a subject in need thereof, is about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 120 mg, 140 mg, 160 mg, 180 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, or 1000 mg.

[0053] In one particular embodiment, the subject in need of treatment of T1DM is a mammal. The mammal may be selected from the group consisting of humans, non-human primates, canines, felines, murines, bovines, equines, porcines, and lagomorphs. In one specific embodiment, the mammal is human. In another

embodiment, apoA-IV or a biologically active analogue thereof may be administered to a subject for the treatment of T1DM wherein the subject is obese. Alternatively, apoA-IV may be administered to a subject for the treatment of T1DM wherein the subject is not obese.

[0054] The following non-limiting examples illustrate the methods of the present disclosure.

EXAMPLES

Introduction

[0055] During meals, pancreatic beta cells secrete insulin to prevent blood glucose from increasing excessively, and this process is dysregulated in diabetes (Marcheva et al. *Nature*. 2010;466(7306):627-631). The intestine also secretes glucoregulatory factors during meals, which include the incretin hormones cholecystokinin (CCK) (Ahren et al. *Journal of Clinical Endocrinology & Metabolism*. 2000;85(3):1043-1048), gastric inhibitory polypeptide (GIP) (Fieseler et al. *American Journal of Physiology-Endocrinology and Metabolism*. 1995;31(5):E949-E955) and glucagon-like peptide I (GLP-I); and Kjems et al. *Diabetes*. 2003;52(2):380-386.), each of which enhances insulin secretion during meals (Lavine and, Attie. *Year in Diabetes and Obesity*. 2010;1212(41-58). Apolipoprotein A-IV (apoA-IV), which is also produced by the gut in response to a meal, is known to acutely decrease food intake (Tso et al. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2004;286(6):G885-G890.). Prior to the examples described below, it was not known if or how apoA-IV is involved in glucose homeostasis. The following Examples show that apoA-IV inhibits hepatic gluconeogenesis and that this action is mediated through the nuclear receptor NR1D1.

[0056] Using in vitro and in vivo mouse models, Examples 1 to 6 below show that apoA-IV acts on hepatocytes to suppress the expression of the gluconeogenic enzymes PEPCK and G6Pase, decreasing hepatic glucose production and reducing plasma glucose in fasted and fed conditions. Using a bacterial two-hybrid system the below examples describe the identification of NR1D1, a nuclear receptor, as a downstream mediator of apoA-IV. The results provided below show that ApoA-IV stimulates NR1D1 gene expression in the liver, and in cells lacking Nr1d1, apoA-IV

failed to inhibit PEPCK and G6Pase gene expression. These findings demonstrate for the first time that: 1) apoA-IV, a gut protein involved in lipid metabolism, also regulates gluconeogenesis and 2) apoA-IV suppresses gluconeogenesis through the nuclear receptor NR1D1.

Materials and Methods

[0057] Bacterial Two-Hybrid library screening. Bacterial Two-Hybrid library screening was carried out using BacterioMatch II Two-Hybrid System XR Plasmid cDNA Library as instructed in the manual. Rat apoA-IV plasmids were used to screen rat liver BacterioMatch II cDNA library.

[0058] Immunofluorescence and confocal microscopy. For apoA-IV uptake and immunofluorescence, HepG2 cells were transfected with human *Nr1d1* plasmid DNA by electroporation. Cells were seeded on 8 well chamber slides, and then incubated with rh-apoAIV-GFP. After 2 h, cells were fixed and permeabilized, then incubated with anti-human NR1D1 and mouse anti-GFP primary antibodies, and then with Alex Flour-594 conjugated goat anti-rabbit and FITC conjugated goat anti-mouse secondary antibodies and then viewed with a confocal fluorescence microscope.

[0059] In Situ Proximity Ligation Assay (PLA). PLA was performed according to the procedure provided by Olink Bioscience (Uppsala, Sweden). Briefly, HepG2 cells were transfected with human *Nr1d1* plasmids and then incubated with r-h-apoA-IV-GFP. This was then followed by fixation, permeabilization, PLA probe incubation, and ultimately a ligation and polymerization step, which generates a concatameric oligonucleotide product linked to the fluorescent antibody complex. The interaction between apoA-IV and NR1D1 as signified by the red PLA signals were visualized by fluorescence microscopy (Zeiss Axiovert 200).

[0060] Animals. C57BL/6J mice were given r-m-apoA-IV or saline by i.p injection 2 h before sacrifice. Intra-cardiac blood and livers were harvested for glucose measurements and gene expression was measured by real time RT-PCR.

[0061] In vitro glucose production in primary hepatocytes. For glucose output measurements *in vitro*, primary hepatocytes were isolated, cultured, and treated as described previously (Yin et al. (2007) *Science* 318(5857): 1786). Cells were

stimulated with dexamethasone and 8-CPT-cAMP with or without r-m-apoA-IV for 16 h and culture medium was collected for glucose assay.

[0062] Luciferase activity. HEK-293T cells were transfected with *G6Pase* luciferase reporter (Yin et al.) with or without pCDNA-*Nr1d1* expression vector, and also with *Renilla* luciferase as a control reporter vector. Relative luciferase activities were determined using a Dual-luciferase Reporter Assay System Kit.

[0063] RNA interference. To deliver siRNA into cells, an AMAXA-based electroporation method (AMAXA) was used as instructed in the manual.

[0064] Statistics. Data represent mean $\pm$ SE from 3-4 wells in each experiment of at least 3 independent cell culture experiments. Significance was determined by unpaired 2-tailed t test. $P < 0.05$ was considered significant.

Example 1: Identification of ApoA-IV Interacting Proteins

[0065] To identify candidate apoA-IV interacting proteins, the bacterial two-hybrid screening approach was used. Rat apoA-IV plasmid was used as the bait to screen a rat liver cDNA library. From the positive bacterial clones, a positive was identified as the C-terminal fragment (amino acids 313-508) of rat nuclear receptor subfamily 1, group D, member 1, NR1D1, also known as REV-ERB α , which is involved in lipid and lipoprotein metabolism, and inflammation (Duez and Staels (2008) *Diabetes and Vascular Dis Res* 5(2):82).

[0066] To verify the interaction between apoA-IV and NR1D1 in mammalian cells, immunofluorescent microscopy and in situ Proximity Ligation Assay (PLA) was performed. Using immunofluorescent microscopy, it was observed that HepG2 cells over-expressing human NR1D1 take up human apoA-IV and that human apoA-IV and NR1D1 are both co-localized in the cytoplasm as well as in the nucleus. To further validate the interaction between apoA-IV and NR1D1, the sensitive in situ PLA assay was used, which enables the detection of protein-protein interactions. In support of the immunofluorescence data, it was observed that apoA-IV and NR1D1 interact with one another, and the signals reflecting this interaction were localized both in the cytoplasm and the nucleus. These data suggest that apoAIV can be taken up by HepG2 cells and then interacts intracellularly with NR1D1.

Example 2: Regulation of Gene Expression of NR1D1 and NcoR by ApoA-IV

[0067] NR1D1 gene expression in liver is known to be stimulated by glucocorticoids and heme and to vary with the circadian rhythm, implying that NR1D1 expression is regulated coordinately by the cellular clock, glucose homeostasis, and energy metabolism (Yin et al; Torra et al. (2000) *Endocrinology* 141(10):3799). To determine if the *Nr1d1* gene is regulated *in vivo* by apoA-IV, primary mouse hepatocytes were treated with recombinant mouse apoA-IV (r-mapoA-IV) and NR1D1 mRNA was measured. The expression of *Nr1d1* was enhanced by treatment with r-mapoA-IV, with a rapid induction of *Nr1d1*, occurring as early as one hour following exposure to r-mapoA-IV. The rapid stimulation was biphasic, with NR1D1 mRNA levels returning to the basal level at 2 h, followed by a second peak expression after 6 h (Figure 6A). The expression of *Nr1d1* is self-regulated transcriptionally (Adelmant et al. (1996) *PNAS USA* 93(8):3553)). Therefore, the decrease in mRNA expression at 2 h in mouse hepatocytes may actually represent negative feedback regulation by NR1D1 itself.

[0068] The function of NR1D1 was dependent upon its interaction and formation of a complex with its nuclear receptor co-repressor (NcoR) and histone deacetylase 3 (HDAC3) (Yin et al.). It was determined that in addition to the induction of NR1D1 mRNA expression, the mRNA expression of NcoR was also increased following stimulation by r-mapoA-IV. Although this change was highly reproducible, the change did not reach statistical significance. This NcoR data might suggest that the recruitment of NcoR by apoA-IV-liganded NR1D1 and the activation of NR1D1 action on the expression of downstream target genes are stimulated by apoA-IV. In an effort to explore the physiological effect of apoA-IV on NR1D1 in human cell lines, HEK-293 (Figure 6B) and HepG2 cells with or without the addition of exogenous recombinant human apoA-IV (r-h-apoA-IV). NR1D1 protein expression was increased by r-h-apoA-IV treatment in both HEK-293 and HepG2 cells.

Example 3: ApoA-IV-Induced Reduction in Expression of G6Pase and PEPCK and the Level of Blood Glucose *in vivo*

[0069] G6Pase and PEPCK mRNA levels were measured in the mouse liver 2 h after the mice received intraperitoneal (i.p) r-mapoA-IV or saline control (Figure 7). Both G6Pase and PEPCK mRNA expression were significantly decreased by r-mapoA-IV (Figure 7A and 7B). The decreases in PEPCK expression were evident under

several dietary states, including ad libitum-fed, and fasted followed by refed conditions, with decreases of greater than 50% relative to the saline controls). The mRNA level of G6Pase was even more responsive to the administration of r-m-apoA-IV with suppressions of 97.09% (refed), 96.62% (ad libitum) and 95.68% (fasting) compared to the saline controls.

[0070] As expected from the action of apoA-IV on gluconeogenesis, it was determined that plasma glucose was significantly decreased in the ad libitum (111.2 ± 16.5 versus 172.7 ± 49.2 mg/dl; respectively, a 35.6% decrease) and refed groups (130.5 ± 35.7 versus 179.2 ± 13.5 mg/dl; respectively, a 27.2% decrease) treated with r-m-apoA-IV (Figure 7C). In the fasted group, there was a trend toward decreased glucose levels in the apoA-IV treated mice (136.8 ± 32.7 versus 166.4 ± 20.7 ; 17.79% lower than in the saline control mice). These data indicate that apoA-IV decreases circulating glucose levels concomitant with an inhibition of hepatic gluconeogenesis.

Example 4: ApoA-IV-induced Reduction in the Expression of G6Pase and PEPCK and Glucose Output *in vitro*

[0071] To determine whether the above effects of apoA-IV on gluconeogenesis were direct, primary mouse hepatocytes were isolated and treated with r-m-apoA-IV. Consistent with the effects observed in whole mouse liver, it was determined that in hepatocytes treated with r-m-apoA-IV, PEPCK and G6Pase mRNA levels and glucose output into the media was decreased by 71.4%, 57.4% and 13.4%, respectively relative to the vehicle control (Figure 7D, 7E and 7F). These data suggest that apoA-IV acts directly to suppress gluconeogenic gene expression in hepatocytes, resulting in decreased glucose production.

Example 5: ApoA-IV-induced Repression in the G6Pase Promoter via the Nuclear Receptor NR1D1

[0072] The basal repression of gluconeogenic genes is mediated transcriptionally by NR1D1 (Yin et al.). The following study was performed in order to determine whether the apoA-IV mediated repression of gluconeogenic genes was also mediated transcriptionally, luciferase activity driven by the human G6pase promoter was analyzed in cells treated with r-h-apoA-IV. ApoA-IV was able to inhibit luciferase activity; it also enhanced the effect of NR1D1 on G6Pase transcription by

further decreasing luciferase activity by 14.5% (Figure 8A). These data indicate that apoA-IV may be working through NR1D1 to inhibit G6Pase transcription.

[0073] To further confirm that the effect of apoA-IV on PEPCK and G6Pase was NR1D1 dependent, NR1D1 in primary mouse hepatocytes was knocked down with siRNA, followed by treatment with r-m-apoA-IV. The expression of PEPCK and G6Pase were significantly decreased with r-m-apoA-IV treatment. In contrast, r-m-apoA-IV did not repress the expression of these two genes when NR1D1 expression was reduced (Figure 8B). These data support an NR1D1-dependent repression of gluconeogenic genes by apoA-IV. This is a novel metabolic pathway for the regulation of gluconeogenesis by an intestinal protein, linking fat absorption with gluconeogenesis.

[0074] In summary, the findings of Examples 1 to 5 present two important observations. First, apoA-IV regulates glucose homeostasis by reducing hepatic gluconeogenesis through an NR1D1-dependent mechanism, causing a reduction in both PEPCK and G6Pase gene expression. Second, these findings demonstrate for the first time direct inter-organ communication between a gut protein (apoA-IV) stimulated by fat absorption and hepatic gluconeogenesis.

Example 6: Inhibition of Glucose Output by ApoA-IV in a Dose-dependent Manner

[0075] The following example examined whether gluconeogenesis could be inhibited in an animal model by apoA-IV in a dose dependent manner. To show inhibition of glucose output by apoA-IV from the liver, C57BL mice were fasted for 5 h and treated with apoA-IV according to one of four different dose amounts (0.5 µg/g, 1 µg/g, 2 µg/g, or 4 µg/g – as well as a saline control). Blood glucose was measured using a Glucometer. The results show that apoA-IV reduced blood glucose in a dose-dependent manner (see Figure 9).

Example 7: Euglycemic-hyperinsulinemic clamps and hepatic gluconeogenic gene expression in apoA-IV-KO mice

[0076] ApoA-IV-KO mice have impaired glucose tolerance relative to the WT controls (Wang, et al., Proc Natl Acad Sci U S A 2012;109:9641-9646). To determine whether apoA-IV-KO mice have impaired gluconeogenesis, euglycemic-

hyperinsulinemic clamp studies were performed, during which blood glucose (Fig. 10A) and insulin levels were similar in apoA-IV-KO and WT. The experiment was performed as described previously (Bajzer, et al., *Diabetologia* 2011;54:3121-3131; Banerjee et al., *Science* 2004;303:1195-1198; and Lo et al., *Diabetes* 2011;60:2000-2007) in 3-month-old apoA-IV-KO and wild-type (WT) mice (Wang, et al., *Proc Natl Acad Sci U S A* 2012;109:9641-9646). Briefly, chow-fed male mice (WT and apoA-IV-KO) underwent surgical placement of a chronic indwelling catheter into the right jugular vein and were allowed to recover for about 4 days. Following a 5-h fast, the following infusions were initiated: a) tracer glucose was administered as a primed-continuous infusion of [3-³H]-D-glucose (bolus of 2 μ Ci followed by 0.1 μ Ci/min; Perkin Elmer, Waltham, MA); b) a primed-continuous infusion of insulin (bolus of 62 mU/kg followed by 3.5 mU $\cdot$ min⁻¹·kg⁻¹; Novolin Regular, Novo Nordisk, Clayton, NC). Euglycemia (130-150 mg/dl) was maintained by an infusion of 20% glucose at a variable rate. Blood samples were taken from the cut tail at 0, 20, 40, 60, 70, 80, 90, and 100 minutes. The glucose infusion rate (GIR) and glucose utilization (GU) were calculated as the means of the values obtained at 10 min intervals during 70-100 min of the clamp. Endogenous glucose production (EGP) was calculated as the difference of between GU and GIR. Under euglycemic conditions, the glucose infusion (GIR) required to maintain euglycemia was significantly lower in apoA-IV-KO mice compared with their WT control (Fig. 10B), indicating that apoA-IV-KO mice are insulin resistant. Although the rate of glucose utilization (GU) did not change significantly, the endogenous glucose production (EGP) was significantly higher in apoA-IV-KO compared to WT mice, indicating that insulin dependent suppression of hepatic glucose production is impaired in apoA-IV deficient mice. In support of this increased endogenous glucose production (EGP), the mRNA levels of hepatic gluconeogenic gene G6Pase and PEPCK were significantly higher in apoA-IV-KO mice compared to the WT animals (Fig. 10C). These results further support above observations that apoA-IV suppresses hepatic gluconeogenesis.

Conclusion

[0077] Examples 1 to 7 provide at least two important and novel observations regarding apoA-IV and glucose metabolism. First, the above Examples show that apoA-IV interacts with NR1D1 as well as stimulates the expression of NR1D1, and second, through this interaction, NR1D1 is the downstream mediator of apoA-IV in

the control of hepatic gluconeogenesis. Using both in vitro and in vivo models, the above Examples show that apoA-IV, acting through NR1D1, suppresses expression of the key gluconeogenic genes PEPCK and G6Pase in liver. These results establish apoA-IV as a link between intestinal lipid absorption and hepatic gluconeogenesis.

Incorporation by Reference

[0078] The contents of all references and patents cited herein are hereby incorporated by reference in their entirety.

Equivalents

[0079] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

[0080] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0081] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for treating type I diabetes mellitus in a subject in need thereof, the method comprising administering to the subject an effective amount of apolipoprotein A-IV, or a biologically active analogue thereof, having at least 90% identity to the apolipoprotein A-IV.
2. The method of Claim 1, wherein gluconeogenesis in the subject is decreased.
3. The method of Claim 1 or 2, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered in combination with insulin.
4. The method of claim 3, wherein the insulin is administered prior to, concurrently with, or subsequent to the administration of apolipoprotein A-IV, or the biologically active analogue thereof.
5. The method of any one of Claims 1-4, wherein the biologically active analogue thereof has at least 95% identity to the apolipoprotein A-IV.
6. The method of any one of Claims 1-4, wherein the biologically active analogue thereof has at least 99% identity to the apolipoprotein A-IV.
7. The method of any one of Claims 1-6, wherein the subject is a human.
8. The method of any one of Claims 1-7, wherein the amino acid sequence of the apolipoprotein A-IV is

X₁EVSADQVATVMWDYFSQLSNNAKEAVEHLQKSELTQQLNALFQDKLGEV
NTYAGDLQKKLVPFATELHERLAKDSEKLKEEIGKELEELRARLLPHANEVSQ
KIGDNLRELQQRLEPYADQLRTQVNTQAEQLRRQLTPYAQRMERVLRENADS
LQASLRPHADX₂LKAKIDQNVEELKGRLTPYADEFKVKIDQTVEELRRSLAPY
AQDTQEKLNHQLEGLTFQMKKNAEELKARISASAEELRQRLAPLAEDVRGNL
RGNTEGLQKSLAELGGHLDQQVEEFRRRVEPYGENFNKALVQQMEQLRQKL

GPHAGDVEGHLSFLEKDLRDKVNSFFSTFKEKESQDKX₃LSLPELEQQQE₄Q
EQQQEQVQMLAPLES (SEQ ID NO. 4)

wherein, X₁ is G, A, V or absent;

X₂ is E or K;

X₃ is T or S; and

X₄ is Q or H.

9. The method of any one of Claims 1-7, wherein the apolipoprotein A-IV is a full length human apolipoprotein A-IV.

10. The method of Claim 9, wherein the amino acid of the apolipoprotein A-IV is
EVSADQVATVMWDYFSQLSNNAKEAVEHLQKSELTTQQLNALFQDKLGEVNT
YAGDLQKKLVPFATELHERLAKDSEKLKEEIGKELEELRARLLPHANEVSQKI
GDNRELQQRLEPYADQLRTQVNTQAEQLRRQLTPYAQRMERVLRENADSL
QASLRPHADELKAKIDQNVEELKGRLTPYADEFKVKIDQTVEELRRSLAPYAQ
DTQEKLNHQLEGLTFQMKKNAEELKARISASAEELRQRLAPLAEDVRGNLRG
NTEGLQKSLAELGGHLDQQVEEFRRRVEPYGENFNKALVQQMEQLRQKLGP
HAGDVEGHLSFLEKDLRDKVNSFFSTFKEKESQDKTSLPELEQQQEQQQEQQ
QEQVQMLAPLES (SEQ ID NO. 1).

11. The method of any one of Claims 1-7, wherein the amino acid sequence of the apolipoprotein A-IV is:

GEVSADQVATVMWDYFSQLSNNAKEAVEHLQKSELTTQQLNALFQDK
LGEVNTYAGDLQKKLVPFATELHERLAKDSEKLKEEIGKELEELRARLLPHAN
EVSQKIGDNRELQQRLEPYADQLRTQVNTQAEQLRRQLTPYAQRMERVLRE
NADSLQASLRPHADELKAKIDQNVEELKGRLTPYADEFKVKIDQTVEELRRSL
APYAQDTQEKLNHQLEGLTFQMKKNAEELKARISASAEELRQRLAPLAEDVR
GNLRGNTEGLQKSLAELGGHLDQQVEEFRRRVEPYGENFNKALVQQMEQLR
QKLGP
HAGDVEGHLSFLEKDLRDKVNSFFSTFKEKESQDKTSLPELEQQQEQQ
QEQVQMLAPLES (SEQ ID NO. 3).

12. The method according to any one of Claims 1-11, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is nonglycosylated.

13. The method according to any one of Claims 1-12, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered systemically.
14. The method according to Claim 13, wherein the systemic administration of apolipoprotein A-IV, or biologically active analogue thereof, is selected from the group consisting of oral, subcutaneous, intravenous, intramuscular, and intraperitoneal administration.
15. The method according to any one of Claims 1-14, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered in a dose of about 1 to about 10 $\mu\text{g/g}$.
16. The method according to any one of Claims 1-14, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered in a dose of about 0.25 to about 2 $\mu\text{g/g}$.
17. The method according to any one of Claims 1-14, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered in a dose of about 1 $\mu\text{g/g}$.
18. The method according to any one of Claims 1-14, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered as a fixed dose of about 1 to 1000 mg.
19. The method according to any one of Claims 1-18, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered once daily.
20. The method according to any one of Claim 1-18, wherein the apolipoprotein A-IV, or the biologically active analogue thereof, is administered about 2 times per day.
21. A method for treating type I diabetes mellitus in a subject in need thereof, the method comprising administering an effective amount of a pharmaceutical composition comprising apolipoprotein A-IV, or biologically active analogue thereof, as defined in any one of Claims 1-20.

22. The method of Claim 21, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or diluent.
23. The method of Claim 21 or 22, wherein the pharmaceutical composition is a liquid formulation.
24. The method according to any one of Claims 21-23, wherein the pharmaceutical composition is an aqueous formulation.
25. The method of Claim 24, wherein the aqueous formulation is pyrogen free.
26. The method according to any one of Claims 21-25, further comprising administering insulin.
27. Use of apolipoprotein A-IV, or a biologically active analogue thereof, having at least 90% identity to the apolipoprotein A-IV, in the manufacture of a medicament for treating type I diabetes mellitus in a subject in need thereof.

Figure 1

EVSADQVATVMWDYFSQLSNNAKEAVEHLQKSELTOQLNALFQDKLGEVNTYA
GDLQKKLVPFATELHERLAKDSEKLKEEIGKELEELRARLLPHANEVSQKIGDNLRE
LQQRLEPYADQLRTOQVNTQAEQLRRQLTPYAQRMERVLRENADSLQASLRPHA
DELKAKIDQNVEELKGRLLTPYADEFKVKIDQTVHEELRRSLAPYAQDTQEKLNHQLE
GLTFQMKKNAAEELKARISASAEELRQRLAPLAEDVRGNLRGNTEGLQKSLAELG
GHLDQQVEEFRRRVEPYGENFNKALVQQMEQLRQKLGPHAGDVEGHLSFLEK
DLRDKVNSFFSTFKEKESQDKTSLPELEQQQEQQEQQEQVQMLAPLES

SEQ ID NO. 1

Figure 2

EVTSDQVANVWDYFTQLSNNAKEAVEQFQKTDVQQQLSTLFASTYADGVHNKLVFPFV
VQLSGHLAQETERVKEEIKKELEDLRDRKTQTFGENMQKLQEHLPYAVDLQDQINTQT
QEMKLQLTPYIQRMQTTIKENVVDNLHTSMMPPLATNLKDKFNRNMEEELKGHLTPRANE
LKATIDQNLLEDLRRSLAPLTVGVQEKLNHQMEGLAFQMKKNAEELQTKVSAKIDQLQK
NLAPLVEDVQSKVKGNTGLQKSLEDLNRQLEQQVEEFRRTVEPMGEMFNKALVQQQL
EQFRQQLGPNSGEVESHLSFLEKSLREKVNFSFMSTLEKKGSPDQPQALPLPEQAEQA
QEQAEQVQPKPLES

SEQ ID NO. 2

Figure 3

GEVSADQVATVMWDYFSQLSNNAKEAVEHLQKSELTQQLNALFQDKLGEVNTYA
GDLQKKLVPFATELHERLAKDSEKLEKELEELRARLLPHANEVSQKIGDNLREL
QQRLEPYADQLRTQVNTQAEQLRRQLTPYAQRMERVLRENADSLQASLRPHADEL
KAKIDQNVEELKGRLLTPYADEFKVKIDQTVVEELRRSLAPYAQDTQEKLNHQLEGLTFQ
MKKNAAEELKARISASAEELRQRLAPLAEDVRGNLRGNTGLQKSLAELGGHLDQQV
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SEQ ID NO. 3

Figure 4

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ISASAEELRQRLAPLAEDVRGNLRGNT EQLQKSLAELGGHLDQQVEEFRRRVEPYGENF
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X₁ is G, A, V or absent

X₂ is E or K

X₃ is T or S

X₄ is Q or H

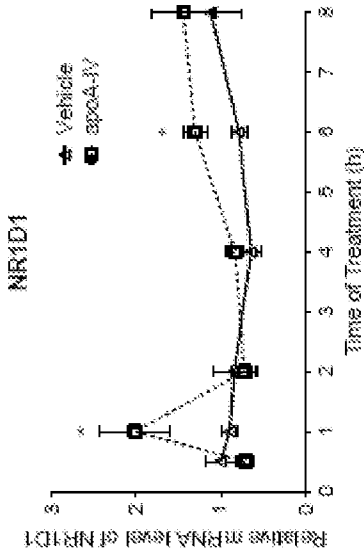
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Figure 5

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GAGTTCCGACGCCGGGTGAGCCCTACGGGGAAACTTCAACAAAGCCCTGGTGCAGCAGATGGAAACAGCTCAGGC
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SEQ ID NO. 5

Figure 6

• A



B

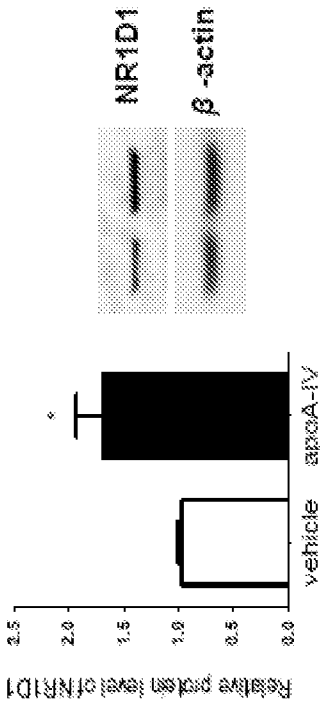


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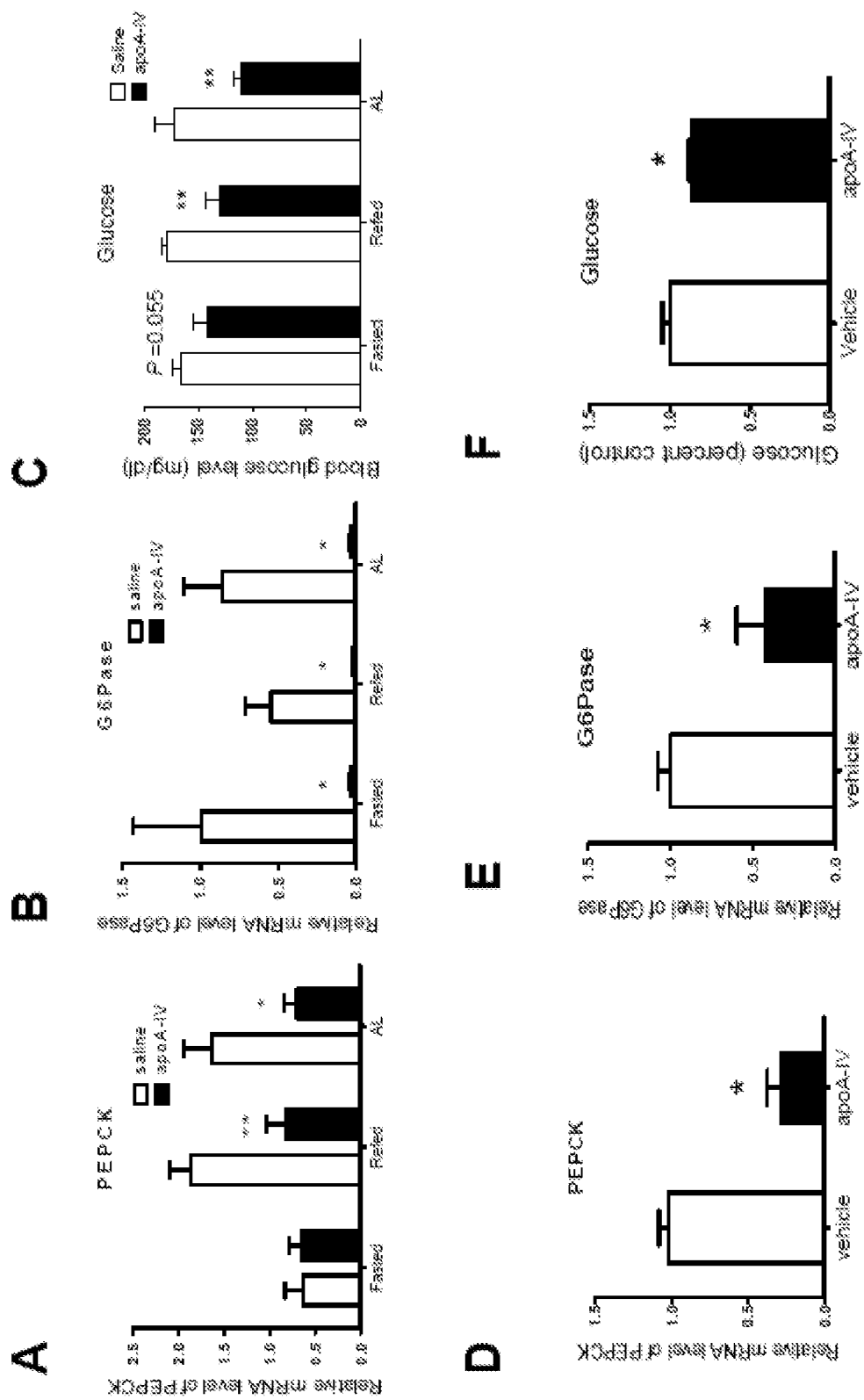


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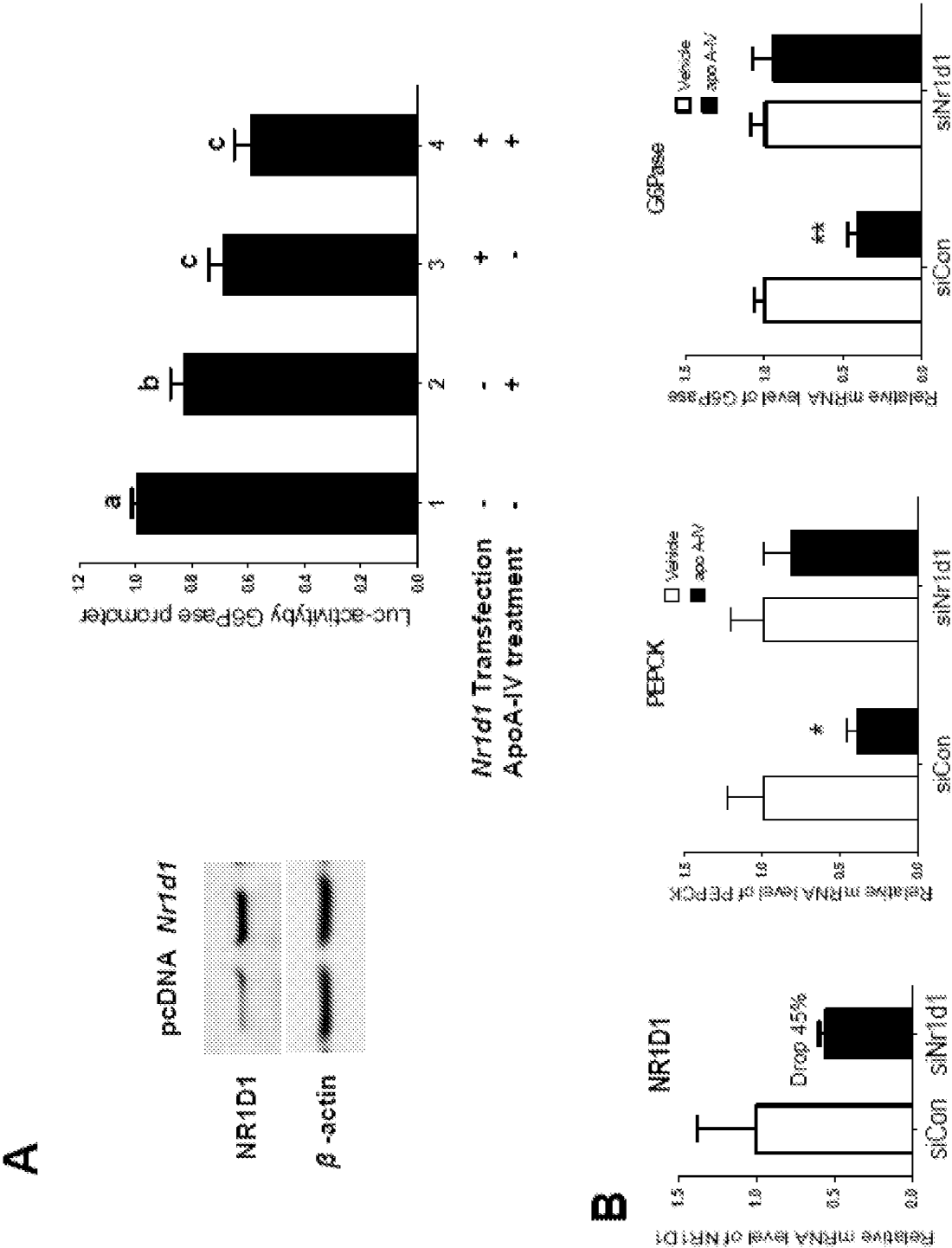


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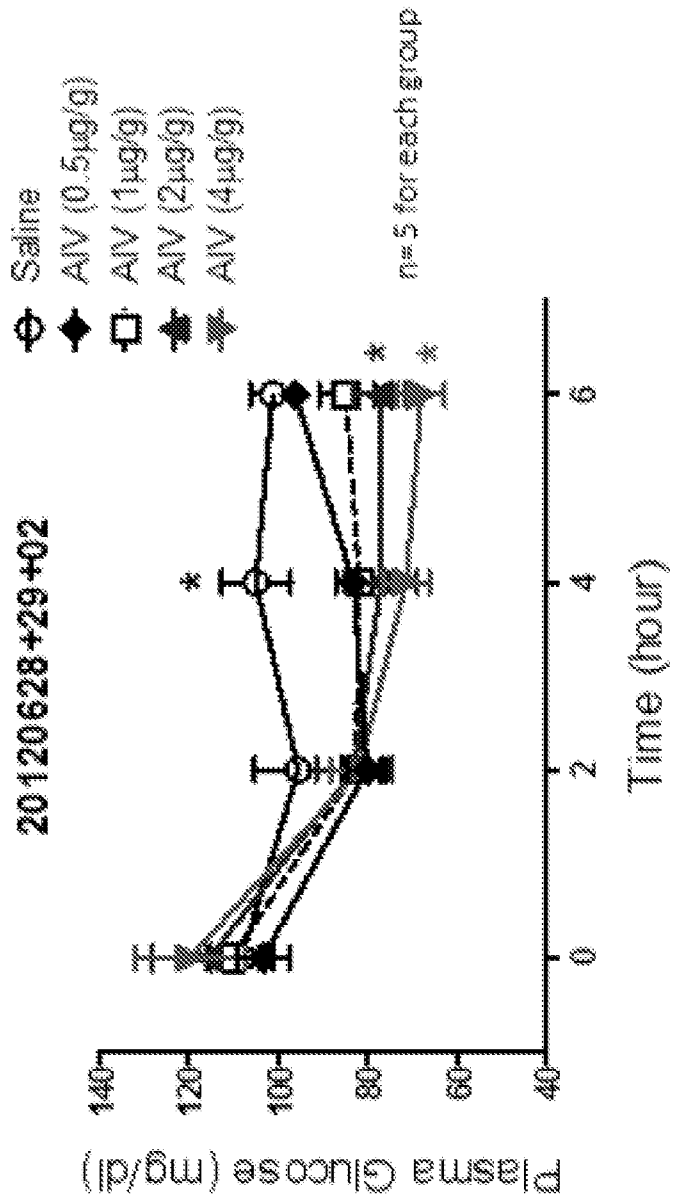
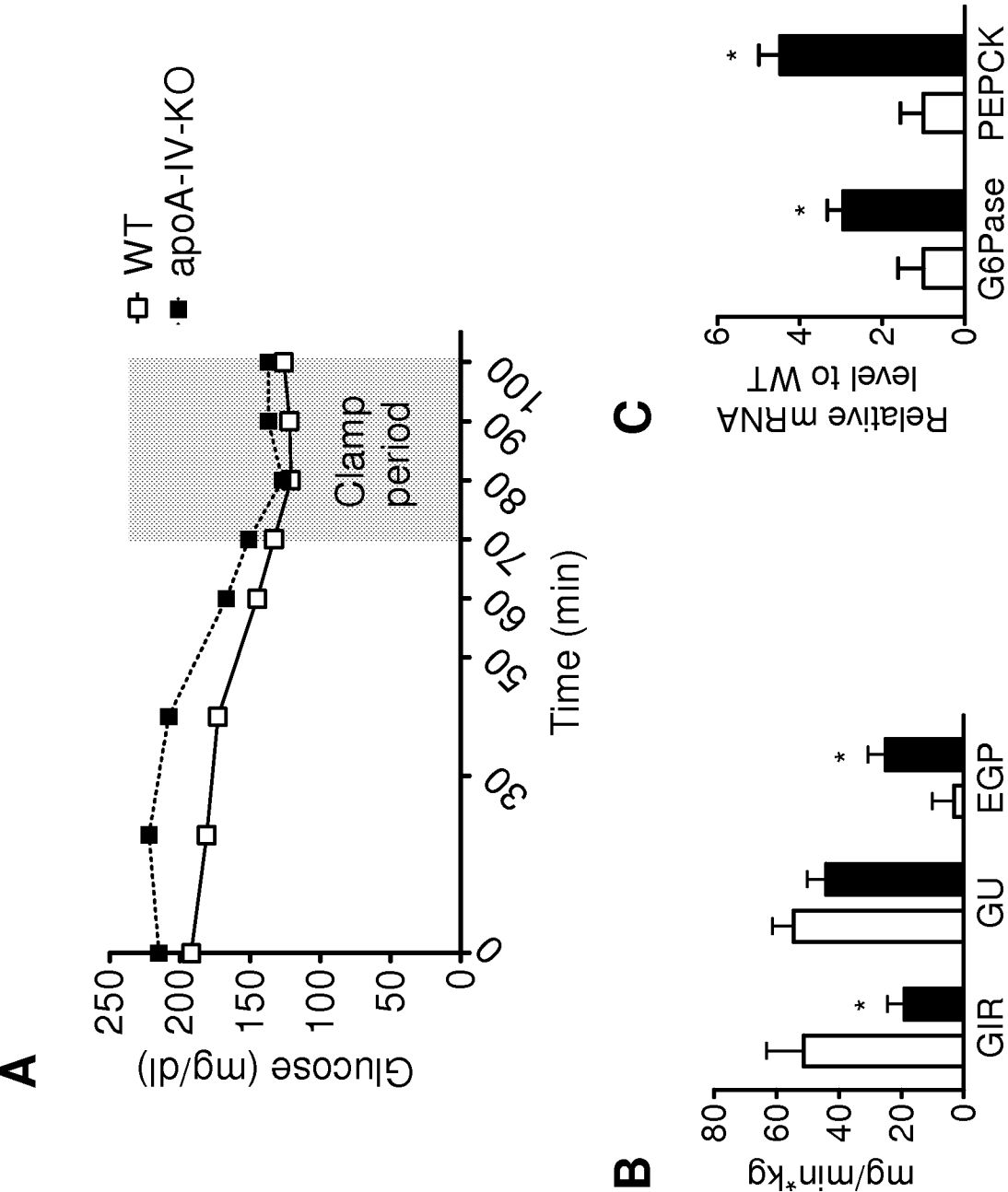


Figure 10



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SEQUENCE LISTING

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TSO, Patrick
DAVIDSON, Sean
WOODS, Stephen
Wang , Fei

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<130> 120946-00220

<150> US61/675,659
<151> 2012-07-25

<160> 50

<170> PatentIn version 3.5

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35 40 45

Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu Val Pro Phe Ala
50 55 60

Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu Lys Leu Lys Glu
65 70 75 80

Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg Leu Leu Pro His
85 90 95

Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu Arg Glu Leu Gln
100 105 110

Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr Gln Val Asn Thr
115 120 125

Gln Ala Glu Gln Leu Arg Arg Gln Leu Thr Pro Tyr Ala Gln Arg Met
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Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln Ala Ser Leu Arg
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120946-00220_SequenceListing.txt

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210 215 220

Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile Ser Ala Ser Ala
225 230 235 240

Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu Asp Val Arg Gly
245 250 255

Asn Leu Arg Gly Asn Thr Glu Gly Leu Gln Lys Ser Leu Ala Glu Leu
260 265 270

Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg Arg Arg Val Glu
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Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln Gln Met Glu Gln
290 295 300

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 65 70 75 80
 Asp Leu Arg Asp Arg Lys Thr Gln Thr Phe Gly Glu Asn Met Gln Lys
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 Leu Gln Glu His Leu Lys Pro Tyr Ala Val Asp Leu Gln Asp Gln Ile
 100 105 110
 Asn Thr Gln Thr Gln Glu Met Lys Leu Gln Leu Thr Pro Tyr Ile Gln
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 Arg Met Gln Thr Thr Ile Lys Glu Asn Val Asp Asn Leu His Thr Ser
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 Met Met Pro Leu Ala Thr Asn Leu Lys Asp Lys Phe Asn Arg Asn Met
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 165 170 175
 Thr Ile Asp Gln Asn Leu Glu Asp Leu Arg Arg Ser Leu Ala Pro Leu
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 Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Gln Thr Lys Val Ser Ala
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 245 250 255
 Asp Leu Asn Arg Gln Leu Glu Gln Gln Val Glu Glu Phe Arg Arg Thr
 260 265 270
 Val Glu Pro Met Gly Glu Met Phe Asn Lys Ala Leu Val Gln Gln Leu
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120946-00220_SequenceListing.txt

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Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu Val Pro Phe
50 55 60

Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu Lys Leu Lys
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Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg Leu Leu Pro
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His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu Arg Glu Leu
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Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr Gln Val Asn
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Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Thr Pro Tyr Ala Gln Arg
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 195 200 205

Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly Leu Thr Phe
 210 215 220

Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile Ser Ala Ser
 225 230 235 240

Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu Asp Val Arg
 245 250 255

Gly Asn Leu Arg Gly Asn Thr Glu Gly Leu Gln Lys Ser Leu Ala Glu
 260 265 270

Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg Arg Arg Val
 275 280 285

Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln Gln Met Glu
 290 295 300

Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val Glu Gly His
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Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn Ser Phe Phe
 325 330 335

Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu Ser Leu Pro
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Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu Val Pro Phe
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Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg Leu Leu Pro
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Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr Gln Val Asn
 115 120 125

Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Thr Pro Tyr Ala Gln Arg
 130 135 140

Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln Ala Ser Leu
 145 150 155 160

Arg Pro His Ala Asp Xaa Leu Lys Ala Lys Ile Asp Gln Asn Val Glu
 165 170 175

Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe Lys Val Lys
 180 185 190

Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala Pro Tyr Ala
 195 200 205

Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly Leu Thr Phe
 Page 6

210

215

220

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Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu Asp Val Arg
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Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg Arg Arg Val
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Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln Gln Met Glu
 290 295 300

Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val Glu Gly His
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 ttccaggaca aacttggaga agtgaacact tacgcaggtg acctgcagaa gaagctggtg 180
 ccctttgcca ccgagctgca tgaacgcctg gccaaggact cggagaaact gaaggaggag 240
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120946-00220_SequenceListing.txt

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gagagccagg acaagactct ctccctccct gagctcgagc aacagcagga acagcagcag     1080
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Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln

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175

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Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
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Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
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Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
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Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

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Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
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Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
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Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
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Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
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Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
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Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
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Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
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Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
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Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
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Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

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120946-00220_SequenceListing.txt

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Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
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Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

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Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

120946-00220_SequenceListing.txt

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln His Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 10
<211> 396
<212> PRT
<213> Homo sapiens

<400> 10

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu

355

360

365

Ser Leu Pro Glu Leu Glu Gln Gln Pro Glu Gln Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 11
 <211> 396
 <212> PRT
 <213> Homo sapiens

<400> 11

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

120946-00220_SequenceListing.txt

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Ser Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380
 Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395
 <210> 12
 <211> 396
 <212> PRT
 <213> Homo sapiens
 <400> 12
 Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15
 Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30
 Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

120946-00220_SequenceListing.txt

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60
 Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80
 Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95
 Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

120946-00220_SequenceListing.txt

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ala Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 13
<211> 396
<212> PRT
<213> Homo sapiens

<400> 13

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

120946-00220_SequenceListing.txt

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Tyr
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 14
<211> 396
<212> PRT
<213> Homo sapiens

<400> 14

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala

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1           5           10           15
Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
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Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
      35      40      45
Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
      50      55      60
Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
      65      70      75      80
Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
      85      90      95
Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
      100      105      110
Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
      115      120      125
Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
      130      135      140
Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
      145      150      155      160
Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
      165      170      175
Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
      180      185      190
Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
      195      200      205
Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
      210      215      220
Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
      225      230      235      240
Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
      245      250      255
Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
      260      265      270
Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser

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275

280

285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Met
 325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 15

<211> 396

<212> PRT

<213> Homo sapiens

<400> 15

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

120946-00220_SequenceListing.txt

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly His Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

120946-00220_SequenceListing.txt

<210> 16
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 <212> PRT
 <213> Homo sapiens

<400> 16

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

120946-00220_SequenceListing.txt

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Arg Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380
 Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395
 <210> 17
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 <212> PRT
 <213> Homo sapiens
 <400> 17
 Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15
 Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30
 Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45
 Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60
 Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

120946-00220_SequenceListing.txt

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95
 Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Leu Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

120946-00220_SequenceListing.txt

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 18
<211> 396
<212> PRT
<213> Homo sapiens

<400> 18

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe

195

200

205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Cys Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 19

<211> 396

<212> PRT

<213> Homo sapiens

<400> 19

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

120946-00220_SequenceListing.txt

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60
 Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80
 Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95
 Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Gln
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

120946-00220_SequenceListing.txt

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 20
<211> 396
<212> PRT
<213> Homo sapiens

<400> 20

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

120946-00220_SequenceListing.txt

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Gly Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 21
<211> 396
<212> PRT
<213> Homo sapiens
<400> 21

120946-00220_SequenceListing.txt

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Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1      5      10      15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20      25      30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35      40      45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50      55      60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65      70      75      80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85      90      95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100     105     110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115     120     125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130     135     140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145     150     155     160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165     170     175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180     185     190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195     200     205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210     215     220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225     230     235     240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245     250     255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260     265     270

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120946-00220_SequenceListing.txt

Asp Met Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 22
<211> 396
<212> PRT
<213> Homo sapiens

<400> 22

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu

115

120

125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270

Asp Ala Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser

385

390

395

<210> 23
 <211> 396
 <212> PRT
 <213> Homo sapiens

<400> 23

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

120946-00220_SequenceListing.txt

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Gln Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380
 Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395
 <210> 24
 <211> 396
 <212> PRT
 <213> Homo sapiens
 <400> 24
 Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15
 Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30
 Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45
 Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60
 Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

120946-00220_SequenceListing.txt

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Thr Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

120946-00220_SequenceListing.txt

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 25
<211> 396
<212> PRT
<213> Homo sapiens

<400> 25

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

120946-00220_SequenceListing.txt

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Lys Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 26
<211> 396
<212> PRT
<213> Homo sapiens

<400> 26

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His

35

40

45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Ser His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 Page 40

305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

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<210> 27
<211> 396
<212> PRT
<213> Homo sapiens
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<400> 27

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

120946-00220_SequenceListing.txt

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Lys Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 28
<211> 396
<212> PRT
<213> Homo sapiens

<400> 28

120946-00220_SequenceListing.txt

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

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

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

120946-00220_SequenceListing.txt

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 29
<211> 396
<212> PRT
<213> Homo sapiens
<400> 29

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

120946-00220_SequenceListing.txt

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp His Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

120946-00220_SequenceListing.txt

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 30
<211> 396
<212> PRT
<213> Homo sapiens

<400> 30

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Lys Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

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<210> 31
<211> 396
<212> PRT
<213> Homo sapiens
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<400> 31

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

120946-00220_SequenceListing.txt

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Met Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

120946-00220_SequenceListing.txt

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 32
<211> 396
<212> PRT
<213> Homo sapiens

<400> 32

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

120946-00220_SequenceListing.txt

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Asn Val Glu Glu Leu Lys Gly Cys Leu Thr Pro Tyr Ala Asp Glu Phe
    195                200                205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
    210                215                220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
    225                230                235                240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
                245                250                255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
                260                265                270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
    275                280                285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
    290                295                300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
    305                310                315                320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
    325                330                335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
    340                345                350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
    355                360                365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
    370                375                380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
    385                390                395

<210> 33
<211> 396
<212> PRT
<213> Homo sapiens

<400> 33

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
  1      5      10

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
    20                25                30

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120946-00220_SequenceListing.txt

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asn Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

120946-00220_SequenceListing.txt

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 34
<211> 396
<212> PRT
<213> Homo sapiens

<400> 34

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu

145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asn Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380
 Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 35
 <211> 396
 <212> PRT
 <213> Homo sapiens

<400> 35

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Leu His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270

120946-00220_SequenceListing.txt

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 36
<211> 396
<212> PRT
<213> Homo sapiens

<400> 36

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

120946-00220_SequenceListing.txt

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Thr Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

120946-00220_SequenceListing.txt

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 37
<211> 396
<212> PRT
<213> Homo sapiens
<400> 37

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Trp Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

120946-00220_SequenceListing.txt

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 38
<211> 396
<212> PRT
<213> Homo sapiens

<400> 38

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu

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65                               70          75          80
Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
                        85                      90                      95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
                100                105                110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
        115                120                125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
    130                135                140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145                150                155                160

Ser Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
                165                170                175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
                180                185                190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
        195                200                205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
    210                215                220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225                230                235                240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
        245                250                255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
                260                265                270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
        275                280                285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
    290                295                300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305                310                315                320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
                325                330                335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn

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340

345

350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Glu Gln Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 39

<211> 396

<212> PRT

<213> Homo sapiens

<400> 39

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Trp Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

120946-00220_SequenceListing.txt

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 40
<211> 396
<212> PRT
<213> Homo sapiens

<400> 40

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

120946-00220_SequenceListing.txt

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45
 Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60
 Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80
 Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95
 Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Met Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

120946-00220_SequenceListing.txt

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 41
<211> 396
<212> PRT
<213> Homo sapiens

<400> 41

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

120946-00220_SequenceListing.txt

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 42
<211> 396
<212> PRT
<213> Homo sapiens

120946-00220_SequenceListing.txt

<400> 42

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Glu Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
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270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 43
 <211> 396
 <212> PRT
 <213> Homo sapiens

<400> 43

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

120946-00220_SequenceListing.txt

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Lys Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335
 Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350
 Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365
 Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

120946-00220_SequenceListing.txt

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 44
<211> 396
<212> PRT
<213> Homo sapiens

<400> 44

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Leu Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
210 215 220

120946-00220_SequenceListing.txt

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Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225                230                235                240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
                245                250                255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
                260                265                270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
                275                280                285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
    290                295                300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305                310                315                320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
                325                330                335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
                340                345                350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
                355                360                365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
    370                375                380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385                390                395

<210> 45
<211> 396
<212> PRT
<213> Homo sapiens

<400> 45

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1                5                10                15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
                20                25                30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
    35                40                45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
    50                55                60

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120946-00220_SequenceListing.txt

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80
 Val Pro Phe Ala Thr Glu Leu His Glu Cys Leu Ala Lys Asp Ser Glu
 85 90 95
 Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300
 Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320
 Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335

120946-00220_SequenceListing.txt

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 46

<211> 396

<212> PRT

<213> Homo sapiens

<400> 46

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Ala Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln

180

185

190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
 370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
 385 390 395

<210> 47
 <211> 396
 <212> PRT
 <213> Homo sapiens

<400> 47

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

120946-00220_SequenceListing.txt

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45
 Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60
 Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu His Lys Lys Leu
 65 70 75 80
 Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95
 Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110
 Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125
 Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140
 Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160
 Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175
 Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190
 Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205
 Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220
 Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240
 Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255
 Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270
 Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285
 Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

120946-00220_SequenceListing.txt

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 48
<211> 396
<212> PRT
<213> Homo sapiens
<400> 48

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Ser Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
130 135 140

120946-00220_SequenceListing.txt

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Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
145          150          155          160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
          165          170          175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
          180          185          190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
          195          200          205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
          210          215          220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
225          230          235          240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
          245          250          255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
          260          265          270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
          275          280          285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
          290          295          300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305          310          315          320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
          325          330          335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
          340          345          350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
          355          360          365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln
          370          375          380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385          390          395

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<210> 49
 <211> 396
 <212> PRT

<213> Homo sapiens

<400> 49

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Met Ala Val Ala
 1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
 20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
 35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
 50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
 65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
 85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg
 100 105 110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

120946-00220_SequenceListing.txt

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln Gln
370 375 380

Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

<210> 50
<211> 396
<212> PRT
<213> Homo sapiens

<400> 50

Met Phe Leu Lys Ala Val Val Leu Thr Leu Ala Leu Val Ala Val Ala
1 5 10 15

Gly Ala Arg Ala Glu Val Ser Ala Asp Gln Val Ala Thr Val Met Trp
20 25 30

Asp Tyr Phe Ser Gln Leu Ser Asn Asn Ala Lys Glu Ala Val Glu His
35 40 45

Leu Gln Lys Ser Glu Leu Thr Gln Gln Leu Asn Ala Leu Phe Gln Asp
50 55 60

Lys Leu Gly Glu Val Asn Thr Tyr Ala Gly Asp Leu Gln Lys Lys Leu
65 70 75 80

Val Pro Phe Ala Thr Glu Leu His Glu Arg Leu Ala Lys Asp Ser Glu
85 90 95

Lys Leu Lys Glu Glu Ile Gly Lys Glu Leu Glu Glu Leu Arg Ala Arg

100

105

110

Leu Leu Pro His Ala Asn Glu Val Ser Gln Lys Ile Gly Asp Asn Leu
 115 120 125

Arg Glu Leu Gln Gln Arg Leu Glu Pro Tyr Ala Asp Gln Leu Arg Thr
 130 135 140

Gln Val Asn Thr Gln Ala Glu Gln Leu Arg Arg Gln Leu Asp Pro Leu
 145 150 155 160

Ala Gln Arg Met Glu Arg Val Leu Arg Glu Asn Ala Asp Ser Leu Gln
 165 170 175

Ala Ser Leu Arg Pro His Ala Asp Glu Leu Lys Ala Lys Ile Asp Gln
 180 185 190

Asn Val Glu Glu Leu Lys Gly Arg Leu Thr Pro Tyr Ala Asp Glu Phe
 195 200 205

Lys Val Lys Ile Asp Gln Thr Val Glu Glu Leu Arg Arg Ser Leu Ala
 210 215 220

Pro Tyr Ala Gln Asp Thr Gln Glu Lys Leu Asn His Gln Leu Glu Gly
 225 230 235 240

Leu Thr Phe Gln Met Lys Lys Asn Ala Glu Glu Leu Lys Ala Arg Ile
 245 250 255

Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala Glu
 260 265 270

Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys Ser
 275 280 285

Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe Arg
 290 295 300

Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val Gln
 305 310 315 320

Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp Val
 325 330 335

Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val Asn
 340 345 350

Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr Leu
 355 360 365

Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Gln Glu Gln Gln

370

Gln	Glu	Gln	Val	Gln	Met	Leu	Ala	Pro	Leu	Glu	Ser
385					390					395	