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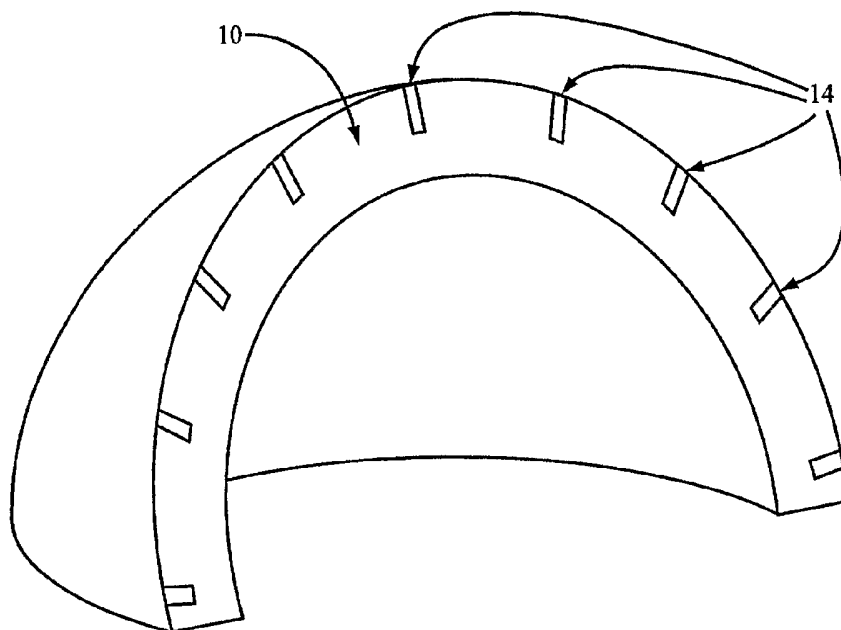
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[Continued on next page]

(54) Title: CUP WITH CONTROLLED RELEASE OF AN OSTEOINDUCTIVE FORMULATION



(57) Abstract: An acetabular cup having one or more osteoinductive formulations, wherein each osteoinductive formulation comprises one or more osteoinductive agent(s). In one embodiment of the invention, the acetabular cup comprises a porous coating into which the osteoinductive formulation is impregnated. In another embodiment of the invention, the acetabular cup comprises microchambers into which the osteoinductive formulation is sealed with a biodegradable or current responsive polymer. The osteoinductive formulations may be available in immediate or sustained release formulations. The invention further relates to preventing and treating osteolytic lesions formed following implantation of an acetabular cup during hip replacement surgery.



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CUP WITH CONTROLLED RELEASE OF AN OSTEOINDUCTIVE FORMULATION

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Field of the Invention

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The invention relates to an acetabular cup having one or more sustained release osteoinductive formulations, wherein the sustained release formulations comprise one or more osteoinductive agents. In one embodiment of the invention, the acetabular cup contains a plurality of microchambers, with each microchamber harboring a reservoir of osteoinductive formulation. In an alternative embodiment of the invention, the acetabular cup comprises a porous coating comprising an osteoinductive formulation impregnated within the porous coating of the acetabular cup. The osteoinductive formulations are available as immediate release or sustained release formulations.

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Background of the Invention

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Thousands of implant surgeries are performed every year in the United States on patients requiring biomedical implants. Of the number of implants performed every year, a large number of implant surgeries are hip implant surgeries. For example, more than 168,000 total hip replacements are performed each year in the United States alone. Shindle, M., *et al.*, BioMechanics, 11(2):22-32 (2004).

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Unfortunately, implants introduced into patients during hip replacement surgeries are known to weaken or fail over time, often requiring revision surgery. The development of osteolytic lesions surrounding the biomedical implants used in hip replacements is known to play a role in the weakening or failure of biomedical devices used in hip replacements. Osteolysis is considered the dissolution of bone, particularly in the context of removal or loss of calcium of bone. In polyethylene implants requiring revision surgery, it is believed that polyethylene wear on adjacent bone tissue contributes to the development of osteolytic lesions.

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One example of osteolysis is periprosthetic osteolysis. Using periprosthetic osteolysis as a model, recent studies have reported a 37% incidence of acetabular

periprosthetic osteolysis and a 32% incidence of femoral osteolysis in patients receiving cemented sockets with an AML prosthesis; a 60% incidence of femoral periprosthetic osteolysis surrounding the HGP femoral component after 10 years, and 62% periprosthetic osteolysis in patients receiving the Omnifit/Dual Geometry combination of total hip replacements after 12 years. W. Harris, *Clin. Orthopaed. Rel. Res.*, 393:66-70 (2001).

The incidence of periprosthetic osteolysis after a duration of 10 years is thought to exceed the incidence of sepsis, dislocation, fatal pulmonary embolization, nerve damage and other complications in patients receiving total hip replacements. W. Harris, p. 66 (2001). As can be seen, osteolysis is a prevalent condition that develops with hip replacements, and is known to play a role in the failure of hip replacements. The progression of osteolysis often results in the need for revision surgery, to replace worn implants and/or to re-seat implant components in endogenous bone.

The description herein of disadvantages and deleterious properties associated with known apparatus, methods, compositions, and devices is not intended to limit the scope of the invention to their exclusion. Indeed, various embodiments of the invention may include one or more known apparatus, methods, compositions, and devices without suffering from the disadvantages and deleterious properties described herein.

Summary of the Invention

Accordingly, there remains a need in the art for biomedical implant devices that function in hip replacements, and which continue to maintain a high level of strength and utility over time. Furthermore, there remains a need in the art for biomedical implant devices that function in hip replacements that remain stable implants over time and in the presence of osteolysis.

Applicants describe herein preferred biomedical devices that fulfill the remaining need in the art for biomedical implant devices, useful in hip replacement surgeries, that continue to function while resisting the effects of osteolysis over time.

In accordance with a feature of an embodiment of the invention, there is provided an acetabular cup including an osteoinductive formulation. In accordance with an

additional feature of an embodiment of the invention, there is provided a kit including an acetabular cup device for implantation and an osteoinductive formulation including an osteoinductive agent.

Another feature of an embodiment of the invention includes a method of of
5 preventing or treating the development of osteolytic lesions in a hip implant patient comprising implanting in the patient an acetabular cup implant device including an osteoinductive formulation.

These and other features of embodiments of the invention will be readily apparent to those skilled in the art upon reading the detailed description that follows.

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Brief Description of the Drawings

Figure 1 provides an acetabular cup having discrete microchambers harboring reservoirs of osteoinductive formulation. In one embodiment of the invention, each osteoinductive formulation in the acetabular cup of Figure 1 is a sustained release
15 composition having a sustained release biodegradable polymer that biodegrades over time, releasing osteoinductive formulation.

Figure 2 provides an acetabular cup having discrete microchambers harboring reservoirs of osteoinductive formulation. Each osteoinductive formulation in the acetabular cup of Figure 2 is a sustained release composition that provides the
20 osteoinductive formulation in bioavailable form over time in response to an electric current.

Figure 3 provides an acetabular cup engineered with at least one electrode secured within the implant coating at the time of manufacture of the acetabular cup that functions to release osteoinductive formulations by applying an electric signal to the
25 electrode

Detailed Description of Preferred Embodiments

For the purposes of promoting an understanding of the present invention, reference will now be made to preferred embodiments and specific language will be used to describe the same. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention. As used throughout this disclosure, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to “an acetabular cup” includes a plurality of such implants, as well as a single implant, and a reference to “an osteoinductive agent” is a reference to one or more agents and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the various implants, osteoinductive agents, and other components that are reported in the publications and that might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosures by virtue of prior invention.

As used herein, “bioavailable” shall mean that the osteoinductive agent(s) are provided *in vivo* in the patient, wherein the osteoinductive agent(s) retain biological activity. By retaining biological activity is meant that the osteoinductive agent(s) retain at least 25% activity, more preferably at least 50% activity, still more preferably at least 75% activity, and most preferably at least 95% or more activity of the osteoinductive agent relative to the activity of the osteoinductive agent prior to implantation.

As used herein, “mature polypeptide” shall mean a post-translationally processed form of a polypeptide. For example, mature polypeptides may lack one or more of a

signal peptide, prepropeptide and propeptide domains following expression in a host expression system. One of skill in the art of proteins is aware of the meanings of signal peptide, prepropeptide and propeptide domains.

As used herein, "electric potential or current" shall mean any electronic stimulus or current provided by a current producing apparatus, and traveling through conductive components to an electrode.

As used herein, "immediate release" shall mean formulations of the invention that provide the osteoinductive formulations in a reasonably immediate period of time.

As used herein, "sustained release" shall mean formulations of the invention that are designed to provide osteoinductive formulations at relatively consistent concentrations in bioavailable form over extended periods of time.

As used herein, "microchamber" shall mean a chamber with dimensions of about 2 mm depth by about 5 mm width, wherein the microchamber is capable of being aseptically sealed and is capable of containing osteoinductive formulations. In a preferred embodiment of the invention, the microchamber is cylindrical in shape.

As used herein, "biodegradable" shall mean a polymer that is degraded during *in vivo* application. In one embodiment of the invention, the degradation of the polymer produces the polymer monomeric subunits.

Acetabular cups for hip implantations are well known in the art, and generally speaking are exemplified by a cup having a cavity for receiving a femoral head, formed of a material having a predetermined tensile strength for implantation into a pelvic bone (*See, e.g., U.S. Patent Nos. 5,549,701; 5,609,648; and 5,879,398*). The cup is typically secured to the patient's pelvic bone *via* bone screws, or alternatively is cemented in place. The outside diameter of the cup may vary depending on the size of the pelvic bone of the patient into which the acetabular cup prosthesis is to be implanted. The femoral head of a femoral implant is designed to reside and rotate within the cup implant, thereby replicating the natural actions of a human hip.

Decreasing the time necessary for the acetabular cup to become secure in the implantation site, or increasing the degree of stability of the acetabular cup implantation over extended periods of time, will increase the overall success of the hip replacement surgery. The present invention describes a novel acetabular cup useful with hip implantations that at least increases the stability of the acetabular cup implant in a hip replacement.

In one embodiment of the invention shown in Figure 1, the acetabular cup allows for the incorporation of discrete microchambers harboring osteoinductive formulations. The acetabular cup preferably includes a plurality of microchambers [14] harboring reservoirs of osteoinductive formulation [16] comprising one or more osteoinductive agents. The acetabular cup [10] optionally comprises one or more biodegradable or current responsive polymer compositions in the form of polymeric plug(s) or polymer coatings [12] that seal the osteoinductive formulation within the microchamber [14] present in the base material of the acetabular cup [10], as displayed in Figure 1. In one embodiment of the invention, the polymeric plugs or polymer coatings include osteoinductive formulations comprising one or more osteoinductive agent(s). The polymeric plugs or polymer coatings preferably are biodegradable or current responsive polymers that degrade, denature or otherwise release the contents of the microchambers following degradation of the polymer plugs or polymer coatings, or alternatively following the application of electric potential or current to the polymer plugs or polymer coatings.

The osteoinductive formulations may be provided in the microchambers present in the acetabular cup and aseptically sealed in the plurality of microchambers with biodegradable or current responsive polymers. The biodegradable polymers may comprise a polymeric formulation resulting in the release of the osteoinductive formulations at about the same time based on biodegradation rates of the polymer. Alternatively, the plurality of microchambers may comprise polymeric formulations having different degradation profiles and resulting in the release of the osteoinductive formulations at differing times or rates of release, again based on differing biodegradation rates of the polymer used to seal the microchambers harboring osteoinductive formulations.

In another embodiment of the invention, the osteoinductive formulation provides osteoinductive agent(s) in bioavailable form as sustained release compositions. The sustained release polymeric formulations comprise a biodegradable polymer that releases osteoinductive formulations comprising osteoinductive agent(s) in a time-wise manner based on the rate of degradation of the biodegradable polymer plug and/or a biodegradable polymer composition into which the osteoinductive formulation was included.

In a further embodiment of the invention, the osteoinductive formulation provides osteoinductive agent(s) in bioavailable form from sustained release formulations due to the application of an electric potential or current to a current responsive polymer that seals the microchamber. As shown in Figure 2, the osteoinductive formulations are sealed in the microchamber by a current responsive polymer [110] that releases osteoinductive formulations comprising osteoinductive agent(s) in response to the induction of an electric current in an electrode [120] embedded within the current responsive polymer [110]. The electrode is positioned in the polymeric plug in a manner that degrades the polymer surrounding the electrode following the induction of the electric current, thus liberating the osteoinductive formulation [130] comprising the osteoinductive agent(s) in bioavailable form from the microchamber [140]. The osteoinductive formulation is released from the microchamber *via* diffusion and endogenous fluid forces applied against the microchamber following application of the electric potential or current to the current responsive polymer. The electrode is conductively coupled to an implantable current-providing device. In one embodiment of the invention, the implantable current-providing device is programmable such that the release of osteoinductive formulations from the plurality of microchambers can be programmed in sequence, in time, or both. A programmable current inducing device (e.g., a voltage supply or current supply) preferably contains one or more of the following components, optionally including all of the listed components: a signal receiver or biosensor and a microprocessor adapted to process signals from the signal receiver or biosensor in order to induce a current in the electrode [120]. Preferably the current inducing device is small and capable of providing sufficient power for extended durations of time, such as for example, by using lithium batteries. In this embodiment of the invention, the acetabular cup orthopaedic device comprises a

plurality of microchambers, each with a current-responsive polymer seal comprising an electrode that is conductively coupled to an implantable current inducing device.

In another embodiment of the invention, an acetabular cup is provided that comprises a porous coating that is impregnated with an osteoinductive formulation. The porous coating may be an integral component of the base material of the acetabular cup, or alternatively may be a secondary coating that is applied over the base material of the acetabular cup. The osteoinductive formulation impregnated into the porous coating may be an immediate release formulation, or alternatively may be a sustained release formulation. The porous coating of the acetabular cup is impregnated with the preferred osteoinductive formulation (immediate release or sustained release) at the time of production of the acetabular cup, or alternatively, prior to implantation.

In a non-limiting hypothesis of the manner in which the acetabular cup will increase the overall success of the hip replacement surgery, the one or more osteoinductive agents present in the osteoinductive formulation promote the in-growth of endogenous bone tissue into the acetabular cup, thereby increasing the degree to which the acetabular cup is secured in the pelvic bone. In another non-limiting hypothesis of the manner in which the acetabular cup will increase the overall success of the hip replacement surgery, the acetabular cup decreases the amount of osteolysis that occurs over time because the endogenous bone ingrowth induced by the osteoinductive agent(s) allows the acetabular cup to become osteointegrated and relatively resistant to the fluids and particulate debris believed to contribute to the development of osteolysis.

In another embodiment of the invention, the acetabular cup of the invention further utilizes bone screws or bone cement as a means of initial fixation of enhanced fixation to the site of implantation, in conjunction with the osteoinductive formulations and microchambers described supra.

Another aspect of the invention relates to osteoinductive formulations useful with the acetabular cup of the invention. Osteoinductive formulations comprise one or more osteoinductive agents, and provide the one or more agents in bioavailable form as immediate release or sustained release formulations. Osteoinductive formulations further optionally comprise one or more of the following components: antibiotics, carriers, bone

marrow aspirate, bone marrow concentrate, demineralized bone matrix, immunosuppressives, agents that enhance isotonicity and chemical stability, and any combination of one or more, including all, of the recited components.

5 The osteoinductive formulations of the invention comprise one or more osteoinductive agent(s) that are provided to induce growth of endogenous bone, or tissues related to the endogenous bone such as connective tissues and vascular tissues. Additionally, the osteoinductive agents are provided to inhibit bone resorption. The osteoinductive formulations comprise osteoinductive agents, such as for example, one or more Bone Morphogenetic Protein (BMP), one or more Connective Tissue Growth Factor (CTGF), one or more Vascular Endothelial Growth Factor (VEGF), Osteoprotegerin (OPG), Periostin and one or more Tissue Growth Factor-*beta* (TGF- β) polynucleotides and polypeptides. In one embodiment of the invention, the osteoinductive agent is provided in bioavailable form from sustained release biodegradable polymers or microchambers sealed with biodegradable polymers due to degradation of biodegradable polymers retaining the osteoinductive formulation. In another embodiment of the invention, osteoinductive agent is provided in bioavailable form from the microchamber in response to application of an electric potential or current.

20 The osteoinductive formulations of the invention are available as immediate release formulations or sustained release formulations. One of skill in the art of implant surgery is able to determine whether a patient would benefit from immediate release formulations or sustained release formulations based on factors such as age and level of physical activity. Therefore, the osteoinductive formulations of the invention are available as immediate or sustained release formulations.

25 Representative immediate release formulations are liquid formulations comprising at least osteoinductive agent(s) that are introduced into the acetabular cup, and remain available in liquid form *in vivo*. The liquid formulations provide osteoinductive agent in bioavailable form at rates that are dictated by the fluid properties of the liquid formulation, such as diffusion rates at the site of implantation, the influence of endogenous fluids, etc. Examples of suitable liquid formulations comprise water, saline, or other acceptable fluid mediums that will not induce host immune responses.

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Immediate release formulations of the invention provide the osteoinductive formulation in a reasonably immediate period of time, although factors such as proximity to bodily fluids, density of application of the formulations, etc, will influence the period of time within which the osteoinductive agent is liberated from the formulation. However, immediate release formulations are not designed to retain the one or more osteoinductive agents for extended periods of time, and typically will lack a biodegradable polymer, except where the biodegradable polymer is used as the component that seals the plurality of microchambers harboring immediate release osteoinductive formulation.

In another embodiment of the invention, osteoinductive formulations are available in sustained release formulations that provide the osteoinductive formulation(s) in bioavailable form over extended periods of time. The duration of release from the sustained release formulations is dictated by the nature of the formulation and other factors discussed *supra*, such as for example proximity to bodily fluids and density of application of the formulations, as well as the degradation rates of biodegradable polymers comprising the osteoinductive formulations. However, sustained release formulations are designed to provide osteoinductive agents in the formulations at relatively consistent concentrations in bioavailable form over extended periods of time. Biodegradable sustained release polymers useful with the osteoinductive formulations are well known in the art and include, but are not limited to, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, poly(L-lactic acid), poly(lactide-co-glycolide), poly(hydroxybutyrate-co-valerate), and copolymers, terpolymers, or combinations or mixtures of the above materials. The release profile of the biodegradable polymer can further be modified by inclusion of biostable polymers that influence the biodegradation rate of the polymer composition. Biostable polymers that could be incorporated into the biodegradable polymers, thereby influencing the rates of biodegradation, include but are not limited to silicones, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers, and cellulotics.

The biodegradable polymers can be solid form polymers or alternatively can be liquid polymers that solidify in a reasonable time after application. Suitable liquid polymers formulations include, but are not limited to those polymer compositions disclosed in, for example, U.S. Patent Nos. 5,744,153, 4,938,763, 5,278,201 and 5,278,202, the contents of each of which are herein incorporated by reference in their entirety. These patents disclose liquid polymer compositions that are useful as controlled drug-release compositions or as implants. The liquid prepolymer has at least one polymerizable ethylenically unsaturated group (e.g., an acrylic-ester-terminated prepolymer). If a curing agent is employed, the curing agent is typically added to the composition just prior to use. The prepolymer remains a liquid for a short period of time after the introduction of the curing agent. During this period of time the liquid delivery composition may be introduced into the acetabular cup, e.g., *via* syringe. The mixture then solidifies to form a solid composition. The liquid polymer compositions may be administered to a patient in liquid form, and will then solidify or cure at the site of introduction to form a solid polymer composition. Biodegradable forms of the polymers are contemplated, and mixtures of biodegradable and biostable polymers that affect the rate of biodegradation of the polymer are further contemplated.

Osteoinductive formulations of the invention further contemplate the use of aqueous and non-aqueous peptide formulations that maintain stability of the osteoinductive agents over extended periods of time. Non-limiting examples of aqueous and non-aqueous formulations useful for the long-term stability of osteoinductive agent(s) include those formulations provided in U.S. Patent Nos. 5,916,582; 5,932,547, and 5,981,489, the disclosures of each of which are herein incorporated by reference.

As noted *supra*, in one embodiment of the invention the osteoinductive formulations are impregnated in a porous coating substrate on the acetabular cup. An amount of the liquid composition is dispensed into the porous substrate, such as by spraying, painting or squirting, and the liquid formulation solidifies following administration to provide a sustained release formulation.

In another embodiment of the invention, the liquid compositions which are useful for the delivery of osteoinductive formulations *in vivo* include conjugates of the

osteoinductive agent with a water-insoluble biocompatible polymer, with the dissolution of the resultant polymer-active agent conjugate in a biocompatible solvent to form a liquid polymer system. In addition, the liquid polymer system may also include a water-insoluble biocompatible polymer which is not conjugated to the osteoinductive agent. In one embodiment of the invention, these liquid compositions may be introduced into the body of a subject in liquid form. The liquid composition then solidifies or coagulates *in situ* to form a controlled release implant where the osteoinductive agent is conjugated to the solid matrix polymer.

Osteoinductive agents are discussed *infra*. Osteoinductive agents of the invention are administered in the osteoinductive formulations as polypeptides or polynucleotides. Polynucleotide compositions of the isolated osteoinductive agents include, but are not limited to, isolated Bone Morphogenetic Protein (BMP), Vascular Endothelial Growth Factor (VEGF), Connective Tissue Growth Factor (CTGF), Osteoprotegerin, Periostin and Transforming Growth Factor beta (TGF- β) polynucleotides. Polynucleotide compositions of the osteoinductive agents include, but are not limited to, gene therapy vectors harboring polynucleotides encoding the osteoinductive polypeptides of interest. Gene therapy methods require a polynucleotide which codes for the osteoinductive polypeptide operatively linked or associated to a promoter and any other genetic elements necessary for the expression of the osteoinductive polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, *See*, for example, International Publication No. WO90/11092, which is herein incorporated by reference. Suitable gene therapy vectors include, but are not limited to, gene therapy vectors that do not integrate into the host genome. Alternatively, suitable gene therapy vectors include, but are not limited to, gene therapy vectors that integrate into the host genome.

In one embodiment, the polynucleotide of the invention is delivered in plasmid formulations. Plasmid DNA or RNA formulations refer to sequences encoding osteoinductive polypeptides that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. Optionally, gene therapy compositions of the invention can be delivered in liposome formulations and lipofectin formulations, which can be prepared by methods well known to those skilled in the art.

General methods are described, for example, in U.S. Pat. Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

Gene therapy vectors further comprise suitable adenoviral vectors including, but not limited to for example, those described in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.*, 3:499-503 (1993); Rosenfeld *et al.*, *Cell*, 68:143-155 (1992); Engelhardt *et al.*, *Human Genet. Ther.*, 4:759-769 (1993); Yang *et al.*, *Nature Genet.*, 7:362-369 (1994); Wilson *et al.*, *Nature*, 365:691-692 (1993); and U.S. Pat. No. 5,652,224, which are herein incorporated by reference.

Polypeptide compositions of the isolated osteoinductive agents include, but are not limited to, isolated Bone Morphogenetic Protein (BMP), Vascular Endothelial Growth Factor (VEGF), Connective Tissue Growth Factor (CTGF), Osteoprotegerin, Periostin and Transforming Growth Factor beta (TGF- β) polypeptides. Polypeptide compositions of the osteoinductive agents include, but are not limited to, full length proteins, fragments and variants thereof. In a preferred embodiment of the invention, polypeptide fragments of the osteoinductive agents are propeptide forms of the isolated full length polypeptides. In a particularly preferred embodiment of the invention, polypeptide fragments of the osteoinductive agents are mature forms of the isolated full length polypeptides. Also preferred are the polynucleotides encoding the propeptide and mature polypeptides of the osteoinductive agents.

Variants of the osteoinductive agents of the invention include, but are not limited to, protein variants that are designed to increase the duration of activity of the osteoinductive agent *in vivo*. Preferred embodiments of variant osteoinductive agents include, but are not limited to, full length proteins or fragments thereof that are conjugated to polyethylene glycol (PEG) moieties to increase their half-life *in vivo* (also known as pegylation). Methods of pegylating polypeptides are well known in the art (See, e.g., U.S. Patent No. 6,552,170 and European Patent No. 0,401,384 as examples of methods of generating pegylated polypeptides).

In another embodiment of the invention, the osteoinductive agent(s) are provided in the osteoinductive formulation(s) as fusion proteins. In one embodiment, the osteoinductive agent(s) are available as fusion proteins with the F_C portion of human IgG.

In another embodiment of the invention, the osteoinductive agent(s) of the invention are available as hetero- or homodimers or multimers. Examples of preferred fusion proteins include, but are not limited to, ligand fusions between mature osteoinductive polypeptides and the F_C portion of human Immunoglobulin G (IgG). Methods of making fusion proteins and constructs encoding the same are well known in the art.

Osteoinductive agents of the invention that are included with the osteoinductive formulations are sterile. In a non-limiting method, sterility is readily accomplished for example by filtration through sterile filtration membranes (e.g., 0.2 micron membranes or filters).

In one embodiment of the invention, the acetabular cup is packaged without impregnated osteoinductive formulations, such as for example where the acetabular cup comprises a porous substrate into which the osteoinductive formulations of the invention are subsequently impregnated. In such a situation, osteoinductive agents generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. In one embodiment, osteoinductive agents and prepared osteoinductive formulations are stored in separate containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous osteoinductive agent solution, and the resulting mixture is lyophilized. The osteoinductive agent is prepared by reconstituting the lyophilized agent prior to administration in an appropriate solution, admixed with the prepared osteoinductive formulations and administered to the acetabular cup prior to or concurrent with implantation into a patient.

As one of skill in the art will recognize, the concentrations of osteoinductive agent can be variable based on the desired length or degree of osteoinduction. Similarly, one of skill in the art will understand that the duration of sustained release can be modified by the manipulation of the compositions comprising the sustained release formulation, such as for example, modifying the percent of biostable polymers found within a sustained release formulation.

Another method to provide liquid compositions which are useful for the delivery of osteoinductive agents *in vivo* and permit the initial burst of active agent to be controlled more effectively than previously possible is to conjugate the active agent with a water-insoluble biocompatible polymer and dissolve the resultant polymer-active agent conjugate in a biocompatible solvent to form a liquid polymer system similar to that described in U.S. Pat. Nos. 4,938,763, 5,278,201 and 5,278,202. The water-insoluble biocompatible polymers may be those described in the above patents or related copolymers. In addition, the liquid polymer system may also include a water-insoluble biocompatible polymer which is not conjugated to the active agent. In one embodiment of the invention, these liquid compositions may be introduced into the body of a subject in liquid form. The liquid composition then solidifies or coagulates *in situ* to form a controlled release implant where the active agent is conjugated to the solid matrix polymer.

The formulation employed to form the controlled release implant *in situ* may be a liquid delivery composition which includes a biocompatible polymer which is substantially insoluble in aqueous medium, an organic solvent which is miscible or dispersible in aqueous medium, and the controlled release component. The biocompatible polymer is substantially dissolved in the organic solvent. The controlled release component may be either dissolved, dispersed or entrained in the polymer/solvent solution. In a preferred embodiment, the biocompatible polymer is biodegradable and/or bioerodable. The liquid polymer formulation is delivered to the decompression core using instruments well known in the art, for example, canulas capable of delivering liquid formulations.

Osteoinductive formulations of the invention optionally further comprise demineralized bone matrix compositions (hereinafter "DBM" compositions), bone marrow aspirate, bone marrow concentrate, or combinations or permutations of any of the same. Methods for producing DBM are well known in the art, and DBM may be obtained following the teachings of O'Leary *et al* (U.S. Patent No. 5,073,373) or by obtaining commercially available DBM formulations such as, for example, AlloGro® available from suppliers such as AlloSource® (Centennial, CO). Methods of obtaining bone marrow

aspirates as well as devices facilitating extraction of bone marrow aspirate are well known in the art and are described, for example, by Turkel *et al* in U.S. Patent No. 5,257,632.

Osteoinductive formulations of the invention optionally further comprise antibiotics that are administered with the osteoinductive agent. As discussed by Vehmeyer *et al.*, the possibility exists that bacterial contamination can occur for example due to the introduction of contaminated allograft tissue from living donors. Vehmeyer, SB, *et al.*, *Acta Orthop Scand.*, 73(2):165-169 (2002). Antibiotics of the invention are also co-administered with the osteoinductive formulations to prevent infection by obligate or opportunistic pathogens that are introduced to the patient during implant surgery.

Antibiotics useful with the osteoinductive formulations of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin. In addition, one skilled in the art of implant surgery or administrators of locations in which implant surgery occurs may prefer the introduction of one or more the above-recited antibiotics to account for nosocomial infections or other factors specific to the location where the surgery is conducted. Accordingly, the osteoinductive formulations of the invention contemplate that one or more of the antibiotics recited *supra*, and any combination of one or more of the same antibiotics, may be included in the osteoinductive formulations of the invention.

The osteoinductive formulations of the invention optionally further comprise immunosuppressive agents, particularly in circumstances where allograft compositions are administered to the patient. Suitable immunosuppressive agents that may be administered in combination with the osteoinductive formulations of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide, methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the osteoinductive formulations of the invention include, but are not limited to, prednisolone,

methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (bredininTM), brequinar, deoxyspergualin, and azaspirane (SKF 105685), Orthoclone OKTTM 3 (muromonab-CD3), SandimmuneTM, NeoralTM, SangdyaTM (cyclosporine), PrografTM (FK506, tacrolimus), CellceptTM (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), ImuranTM (azathioprine), glucocorticosteroids, adrenocortical steroids such as DeltasoneTM (prednisone) and HydeltrasolTM (prednisolone), FolexTM and MexateTM (methotrexate), Oxsoralen-UltraTM (methoxsalen) and RapamuenTM (sirolimus).

Osteoinductive formulations of the invention may optionally further comprise a carrier vehicle such as water, saline, Ringer's solution, calcium phosphate based carriers, or dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

In one embodiment of the invention, collagen is used as a carrier for the osteoinductive formulations. In another embodiment of the invention, collagen in combination with glycosaminoglycan is utilized as a carrier for the osteoinductive formulations, as described in U.S. Patent No. 5,922,356, which is herein incorporated by reference. The content of glycosaminoglycan in the formulation is preferably less than 40% by weight of the formulation, more preferably 1-10%. Collagen is preferably 20-95% by weight of the formulation, more preferably 40-60 (wt/wt)%.

Any collagen may be used as a carrier for osteoinductive formulations. Examples of suitable collagen to be used as a carrier include, but are not limited to, human collagen type I, human collagen type II, human collagen type III, human collagen type IV, human collagen type V, human collagen type VI, human collagen type VII, human collagen type VIII, human collagen type IX, human collagen type X, human collagen type XI, human collagen type XII, human collagen type XIII, human collagen type XIV, human collagen type XV, human collagen type XVI, human collagen type XVII, human collagen type XVIII, human collagen type XIX, human collagen type XXI, human collagen type XXII, human collagen type XXIII, human collagen type XXIV, human collagen type XXV, human collagen type XXVI, human collagen type XXVII, and human collagen type XXVIII, and combinations thereof. Collagen carriers useful with the invention further

comprise, or alternatively consist of, hetero- and homo-trimers of any of the above-recited collagen types. In a preferred embodiment of the invention, collagen carriers comprise, or alternatively consist of, hetero- or homo-trimers of human collagen type I, human collagen type II, and human collagen type III, or combinations thereof.

5 The collagen utilized as a carrier may be human or non-human, as well as recombinant or non-recombinant. In a preferred embodiment of the invention, the collagen utilized as a carrier is recombinant collagen. Methods of making recombinant collagen are known in the art, for example, by using recombinant methods such as those methods described in U.S. Patent Nos. 5,895,833 (transgenic production), J. Myllyharju, *et*
10 *al.*, *Biotechnology of Extracellular Matrix*, 353-357 (2000) (production of recombinant human types I-III in *Pichia pastoris*), Wong Po Foo, C., *et al.*, *Adv. Drug Del. Rev.*, 54:1131-1143 (2002), or by Toman, P.D., *et al.*, *J. Biol. Chem.*, 275(30):23303-23309 (2001), the disclosures of each of which are herein incorporated by reference. Alternatively, recombinant human collagen types are obtained from commercially
15 available sources, such as for example, as provided by FibroGen (San Francisco, California).

 The osteoinductive formulations of the invention further optionally include substances that enhance isotonicity and chemical stability. Such materials are non-toxic to patients at the dosages and concentrations employed, and include buffers such as
20 phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its
25 derivatives, glucose, mannose, or dextrans; chelating agents such as EDTA; sugaralcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionicsurfactants such as polysorbates, poloxamers, or PEG.

 Osteoinductive formulations of the invention further comprise isolated osteoinductive agents. Isolated osteoinductive agents of the invention promote the in-
30 growth of endogenous bone into the acetabular cup, or aid in preventing resorption of bone

tissue surrounding the acetabular cup implant by osteoclasts. Isolated osteoinductive agents of the invention are available as polypeptides or polynucleotides. Isolated osteoinductive agents of the invention comprise full length proteins and fragments thereof, as well as polypeptide variants or mutants of the isolated osteoinductive agents provided herein.

In another embodiment of the invention, osteoinductive agent polypeptides are available as heterodimers or homodimers, as well as multimers or combinations thereof.

Recombinantly expressed proteins may be in native forms, truncated analogs, muteins, fusion proteins, and other constructed forms capable of inducing bone, cartilage, or other types of tissue formation as demonstrated by in vitro and ex vivo bioassays and in vivo implantation in mammals, including humans.

The invention further contemplates the use of polynucleotides and polypeptides having at least 95% homology, more preferably 97%, and even more preferably 99% homology to the isolated osteoinductive agent polynucleotides and polypeptides provided herein. Typical osteoinductive formulations comprise isolated osteoinductive agent at concentrations of from about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8.

In one embodiment of the invention, isolated osteoinductive agents include one or more polynucleotides or polypeptides of members of the family of Bone Morphogenetic Proteins ("BMPs"). BMPs are a class of proteins thought to have osteoinductive or growth-promoting activities on endogenous bone tissue. Known members of the BMP family include, but are not limited to, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-15, BMP-16, BMP-17, and BMP-18.

BMPs useful as isolated osteoinductive agents include, but are not limited to, the following BMPs:

BMP-1 polynucleotides and polypeptides corresponding to SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4, as well as mature BMP-1 polypeptides and polynucleotides encoding the same;

5 BMP-2 polynucleotides and polypeptides corresponding to SEQ ID NO:5 and SEQ ID NO:6, as well as mature BMP-2 polypeptides and polynucleotides encoding the same;

BMP-3 polynucleotides and polypeptides corresponding to SEQ ID NO:7 and SEQ ID NO:8, as well as mature BMP-3 polypeptides and polynucleotides encoding the same;

BMP-4 polynucleotides and polypeptides corresponding to SEQ ID NO:9 and SEQ ID NO:10, as well as mature BMP-4 polypeptides and polynucleotides encoding the same;

10 BMP-5 polynucleotides and polypeptides corresponding to SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 and SEQ ID NO:14, as well as mature BMP-5 polypeptides and polynucleotides encoding the same;

15 BMP-6 polynucleotides and polypeptides corresponding to SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:18, as well as mature BMP-6 polypeptides and polynucleotides encoding the same;

BMP-7 polynucleotides and polypeptides corresponding to SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21 and SEQ ID NO:22, as well as mature BMP-7 polypeptides and polynucleotides encoding the same;

20 BMP-8 polynucleotides and polypeptides corresponding to SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26, as well as mature BMP-8 polypeptides and polynucleotides encoding the same;

BMP-9 polynucleotides and polypeptides corresponding to SEQ ID NO:27 and SEQ ID NO:28, as well as mature BMP-9 polypeptides and polynucleotides encoding the same;

25 BMP-10 polynucleotides and polypeptides corresponding to SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31 and SEQ ID NO:32, as well as mature BMP-10 polypeptides and polynucleotides encoding the same;

BMP-11 polynucleotides and polypeptides corresponding to SEQ ID NO:33 and SEQ ID NO:34, as well as mature BMP-11 polypeptides and polynucleotides encoding the same;

5 BMP-12 polynucleotides and polypeptides corresponding to SEQ ID NO:35 and SEQ ID NO:36, as well as mature BMP-12 polypeptides and polynucleotides encoding the same;

BMP-13 polynucleotides and polypeptides corresponding to SEQ ID NO:37 and SEQ ID NO:38, as well as mature BMP-13 polypeptides and polynucleotides encoding the same;

10 BMP-15 polynucleotides and polypeptides corresponding to SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41 and SEQ ID NO:42, as well as mature BMP-15 polypeptides and polynucleotides encoding the same;

15 BMP-16 polynucleotides and polypeptides corresponding to SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45 and SEQ ID NO:46, as well as mature BMP-16 polypeptides and polynucleotides encoding the same;

BMP-17 polynucleotides and polypeptides corresponding to SEQ ID NO:47 and SEQ ID NO:48, as well as mature BMP-17 polypeptides and polynucleotides encoding the same; and

20 BMP-18 polynucleotides and polypeptides corresponding to SEQ ID NO:49 and SEQ ID NO:50, as well as mature BMP-18 polypeptides and polynucleotides encoding the same.

25 BMPs utilized as osteoinductive agents of the invention comprise, or alternatively consist of, one or more of BMP-1; BMP-2; BMP-3; BMP-4; BMP-5; BMP-6; BMP-7; BMP-8; BMP-9; BMP-10; BMP-11; BMP-12; BMP-13; BMP-15; BMP-16; BMP-17; and BMP-18; as well as any combination of one or more of these BMPs, including full length BMPs or fragments thereof, or combinations thereof, either as polypeptides or polynucleotides encoding said polypeptide fragments of all of the recited BMPs. The

isolated BMP osteoinductive agents may be administered as polynucleotides, polypeptides, or combinations of both.

In a particularly preferred embodiment of the invention, isolated osteoinductive agents comprise, or alternatively consist of, BMP-2 polynucleotides or polypeptides or mature fragments of the same.

In another embodiment of the invention, isolated osteoinductive agents include osteoclastogenesis inhibitors to inhibit bone resorption of the bone tissue surrounding the site of implantation of the acetabular cup by osteoclasts.

Osteoclast and Osteoclastogenesis inhibitors include, but are not limited to, Osteoprotegerin polynucleotides and polypeptides corresponding to SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53 and SEQ ID NO:54, as well as mature Osteoprotegerin polypeptides and polynucleotides encoding the same. Osteoprotegerin is a member of the TNF-receptor superfamily and is an osteoblast-secreted decoy receptor that functions as a negative regulator of bone resorption. This protein specifically binds to its ligand, osteoprotegerin ligand (TNFSF11/OPGL), both of which are key extracellular regulators of osteoclast development.

Osteoclastogenesis inhibitors further include, but are not limited to, chemical compounds such as bisphosphonate, 5-lipoxygenase inhibitors such as those described in U.S. Patent Nos. 5,534,524 and 6,455,541 (the contents of which are herein incorporated by reference), heterocyclic compounds such as those described in U.S. Patent No. 5,658,935 (herein incorporated by reference), 2,4-dioxoimidazolidine and imidazolidine derivative compounds such as those described in U.S. Patent Nos. 5,397,796 and 5,554,594 (the contents of which are herein incorporated by reference), sulfonamide derivatives such as those described in U.S. Patent No. 6,313,119 (herein incorporated by reference), and acylguanidine compounds such as those described in U.S. Patent No. 6,492,356 (herein incorporated by reference).

In another embodiment of the invention, isolated osteoinductive agents include one or more polynucleotides or polypeptides of members of the family of Connective Tissue Growth Factors ("CTGFs"). CTGFs are a class of proteins thought to have growth-

promoting activities on connective tissues. Known members of the CTGF family include, but are not limited to, CTGF-1, CTGF-2, and CTGF-4.

CTGFs useful as isolated osteoinductive agents include, but are not limited to, the following CTGFs:

5 CTGF-1 polynucleotides and polypeptides corresponding to SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57 and SEQ ID NO:58, as well as mature CTGF-1 polypeptides and polynucleotides encoding the same.

10 CTGF-2 polynucleotides and polypeptides corresponding to SEQ ID NO:59 and SEQ ID NO:60, as well as mature CTGF-2 polypeptides and polynucleotides encoding the same.

 CTGF-4 polynucleotides and polypeptides corresponding to SEQ ID NO:61 and SEQ ID NO:62, as well as mature CTGF-4 polypeptides and polynucleotides encoding the same.

15 In another embodiment of the invention, isolated osteoinductive agents include one or more polynucleotides or polypeptides of members of the family of Vascular Endothelial Growth Factors ("VEGFs"). VEGFs are a class of proteins thought to have growth-promoting activities on vascular tissues. Known members of the VEGF family include, but are not limited to, VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E.

20 VEGFs useful as isolated osteoinductive agents include, but are not limited to, the following VEGFs:

 VEGF-A polynucleotides and polypeptides corresponding to SEQ ID NO:63 and SEQ ID NO:64, as well as mature VEGF-A polypeptides and polynucleotides encoding the same.

25 VEGF-B polynucleotides and polypeptides corresponding to SEQ ID NO:65 and SEQ ID NO:66, as well as mature VEGF-B polypeptides and polynucleotides encoding the same.

VEGF-C polynucleotides and polypeptides corresponding to SEQ ID NO:67 and SEQ ID NO:68, as well as mature VEGF-C polypeptides and polynucleotides encoding the same.

5 VEGF-D polynucleotides and polypeptides corresponding to SEQ ID NO:69 and SEQ ID NO:70, as well as mature VEGF-D polypeptides and polynucleotides encoding the same.

VEGF-E polynucleotides and polypeptides corresponding to SEQ ID NO:71 and SEQ ID NO:72, as well as mature VEGF-E polypeptides and polynucleotides encoding the same.

10 In another embodiment of the invention, isolated osteoinductive agents include one or more polynucleotides or polypeptides of Transforming Growth Factor-beta genes ("TGF- β s"). TGF- β s are a class of proteins thought to have growth-promoting activities on a range of tissues, including connective tissues. Known members of the TGF- β family include, but are not limited to, TGF- β -1, TGF- β -2, and TGF- β -3.

15 TGF- β s useful as isolated osteoinductive agents include, but are not limited to, the following TGF- β s:

TGF- β -1 polynucleotides and polypeptides corresponding to SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75 and SEQ ID NO:76, as well as mature TGF- β -1 polypeptides and polynucleotides encoding the same.

20 TGF- β -2 polynucleotides and polypeptides corresponding to SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79 and SEQ ID NO:80, as well as mature TGF- β -2 polypeptides and polynucleotides encoding the same.

25 TGF- β -3 polynucleotides and polypeptides corresponding to SEQ ID NO:81 and SEQ ID NO:82, as well as mature TGF- β -3 polypeptides and polynucleotides encoding the same.

In another embodiment of the invention, isolated osteoinductive agents include polynucleotides and polypeptides promoting bone adhesion, such as Periostin

polynucleotides and polypeptides that are thought to function as adhesion molecules in bone formation.

Bone adhesion promoters include, but are not limited to, Periostin polynucleotides and polypeptides corresponding to SEQ ID NO:83 and SEQ ID NO:84, as well as mature Periostin polypeptides and polynucleotides encoding the same.

In another embodiment of the invention, isolated osteoinductive agents include one or more members of any one of Bone Morphogenetic Proteins (BMPs), Connective Tissue Growth Factors (CTGFs), Vascular Endothelial Growth Factors (VEGFs), Osteoprotegerin or any of the other osteoclastogenesis inhibitors, Periostin, and Transforming Growth Factor-betas (TGF- β s).

Methods for producing acetabular cups are well known in the art, and production methods will depend on the desired compositions of the acetabular cup. Exemplary methods of production that may be utilized to generate a porous substrate surface are known in the art and include, but are not limited to, procedures such as machining the substrate material from wrought bar stock or machining components from castings. In an alternative embodiment of the invention, the substrate surface is generated using acetabular cup implant coatings of materials or production methods that generate a porous substrate surface. Acetabular cup coatings include, but are not limited to, ranges of design from a beaded surface with various bead diameters and pore size, to a fiber metal mesh design. Implant coatings are typically applied through a high heat sintering or plasma spray process.

In one embodiment of the invention, the osteoinductive formulations of the invention comprising osteoinductive agents are admixed with sustained release polymers recited *supra* and applied to the porous surface of the acetabular cup. As noted *supra*, the duration of sustained release may be manipulated by increasing the resistance to biodegradation of the polymer by, for example, introducing or increasing the percentage of biostable polymers contained within the biodegradable polymer compositions.

In another embodiment of the invention, the acetabular cup comprises, or alternatively consists of, a porous substrate surface comprising osteoinductive

formulations. In one embodiment of the invention, the porous substrate surface comprising the osteoinductive formulations is further coated with a biodegradable or bioabsorbable polymer coating. Exemplary biodegradable or bioabsorbable coatings are discussed *supra*. In another embodiment of the invention, the biodegradable or bioabsorbable polymer coating is provided in the form of a sheath or wrap that is placed over the outer surface of the acetabular cup prior to implantation in the patient.

In another embodiment of the invention, the acetabular cup [10] comprises, or alternatively consists of, a plurality of microchambers [14] present in the base material of the acetabular cup, as displayed in Figure 1. The plurality of microchambers present in the base material comprise osteoinductive formulations, and are aseptically sealed with biodegradable or current responsive polymers. The osteoinductive formulations comprise one or more osteoinductive agent(s).

Current-responsive polymers include, but are not limited to, those polymers described in U.S. Patent Application Serial No. US20030007991 as well as those described by Kwon *et al. infra*, the disclosures of each of which are herein incorporated by reference.

In another embodiment of the invention, the microchambers harboring osteoinductive formulations are sealed with thin films of conductive material patterned in the shape of anodes surrounded by cathodes. Any conductive material that can oxidize and dissolve in solution upon application of an electric potential or current can be used for the fabrication of the anodes and cathodes. Examples of such materials include metals such as copper, gold, silver, and zinc, and some polymers, such as those described for example by I. C. Kwon *et al.*, "Electrically erodible polymer gel for controlled release of drugs", *Nature*, 1991, 354, 291-93; and Y. H. Bae *et al.*, "Pulsatile drug release by electric stimulus", *ACS Symposium Series*, 1994, 545, 98-110. The anode is defined as the electrode where oxidation occurs. The portion of the anode directly above the microchamber oxidizes and dissolves into solution upon the application of a potential or current between the cathode and anode. This exposes the microchambers to the surrounding fluids and results in the release of the molecules.

Following production of the acetabular cup, a plurality of microchambers may be drilled in the acetabular cup to allow for introduction of the osteoinductive formulations. The number and width of the plurality of microchambers is variable and based on the needs of the patient. For example, the acetabular cup preferably comprises between about 10 to about 100 microchambers in the acetabular cup base. More preferably, the acetabular cup comprises between about 25 to about 75, and still more preferably between about 40 to about 60 microchambers in the acetabular cup base. As one of skill in the art would realize, however, the number and position of microchambers in the acetabular cup base may vary so long as the structural integrity of the acetabular cup is not compromised.

The microchambers provided within the acetabular cup base may be drilled through the full depth of the acetabular cup base. Alternatively, the microchambers may be drilled to a depth of about 1 to about 2 millimeters. Similarly, the width of the microchambers in the acetabular cup may be about 4 to about 6 millimeters in width. On average, the microchamber is about 5 millimeters in width. However, one of skill in the art would realize that the microchamber width may be variable and is based, in part, on the concentration of osteoinductive agent present in the osteoinductive formulation contained within the microchamber. For example, highly concentrated osteoinductive agent(s) will not require a microchamber as wide as osteoinductive formulations comprising weakly concentrated osteoinductive agent(s) in order to achieve delivery of the same concentration of osteoinductive agent(s). Following introduction of the osteoinductive formulations into the microchambers, the microchambers are aseptically sealed with biodegradable or current responsive polymer coatings or plugs that seal the osteoinductive formulations in the microchamber wells, or alternatively with thin films of conductive materials.

In another embodiment of the invention, the acetabular cup is manufactured with electric conductive capacity provided in the acetabular cup compositions. In one embodiment of the invention displayed in Figure 3, the acetabular cup [20] is engineered with at least one electrode secured within the implant coating at the time of manufacture of the acetabular cup. Release of the osteoinductive formulation may be accomplished by either an internal or an external, non-invasive power source applying an electric signal to

the electrode contained within the implant coating. In one embodiment of the invention, a plurality of electrode leads [22] embedded in current responsive polymers seals [24] are conductively attached by a plurality of conductive wires [26], or comparable conducting materials such as conducting fibers or particles, to a current-providing device [28].

5 Current-providing devices are well known in the art, such as for example, current providing devices associated with pace-makers and other implantable biomedical devices

10 In another embodiment of the invention, current providing devices provide at least one volt of current. One volt of current is considered adequate to melt a thin film coating of gold or other material that seals a microchamber harboring osteoinductive formulations, as discussed *supra*. However, the invention further contemplates current providing devices that provide greater than one volt of current to a polymer coating or thin film sealant comprising gold or other compounds discussed *supra*. Current providing devices are further capable of receiving electric signals from interior or exterior sources. Alternatively, electric current is provided to the micro-electrode leads by conducting
15 materials incorporated into the polymers seals. Such conducting materials include, but are not limited to, particles, fibers, patches wires, strands or any other conducting materials that can be incorporated into the polymer plugs and adequately conduct electric current.

20 In an alternative embodiment of the invention, the acetabular cup is designed to contain microchip drug delivery systems such as those described in U.S. Patent No. 5,797,898 (which is herein incorporated by reference in its entirety). The chip is designed with several "wells" coated with a current-responsive thin film comprising gold and/or other compound as discussed *supra*. When current is supplied to the chip, the gold melts, releasing the material. In this embodiment of the invention, the acetabular cup is produced in substantially the same fashion as described for the microchamber-containing acetabular
25 cups. However, instead of providing polymer-sealed microchambers harboring osteoinductive formulations, the acetabular cup relies on microchip drug delivery systems that are incorporated into the acetabular cup. A plurality of reservoirs in the microchip drug delivery system comprise osteoinductive formulations, which are released from the microchip drug delivery systems upon appropriate or pre-programmed stimulus. A
30 plurality of microchips may be implanted into the acetabular cup.

The present invention also relates to vectors containing the osteoinductive polynucleotides of the present invention, host cells, and the production of osteoinductive polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or
5 replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a
10 virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells. Useful vectors include, but are not limited to, plasmids, bacteriophage, insect and animal cell vectors, retroviruses, cosmids, and other single and double-stranded viruses.

The polynucleotide insert should be operatively linked to an appropriate
15 promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, origin of replication sequence, and, in the transcribed region, a ribosome binding site for translation.
20 The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

The expression construct may further contain sequences such as enhancer sequences, efficient RNA processing signals such as splicing and polyadenylation signals,
25 sequences that enhance translation efficiency, and sequences that enhance protein secretion.

Expression systems and methods of producing osteoinductive agents, such as recombinant proteins or protein fragments, are well known in the art. For example, methods of producing recombinant proteins or fragments thereof using bacterial, insect or
30 mammalian expression systems are well known in the art. (See, e.g., Molecular

Biotechnology: Principles and Applications of Recombinant DNA, B. R. Glick and J. Pasternak, and M.M. Bendig, Genetic Engineering, 7, pp. 91-127 (1988), for a general discussion of recombinant protein production).

The expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate host cells for expression include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as *Pichia* and other yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 and Sf21 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Examples of vectors for use in prokaryotes include pQE30Xa and other pQE vectors available as components in pQE expression systems available from QIAGEN, Inc. (Valencia, CA); pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc. (La Jolla, CA); and ChampionTM, T7, and pBAD vectors available from Invitrogen (Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis *et al.*, Basic Methods In Molecular Biology (1986).

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

In another embodiment of the invention, osteoinductive agents can be produced using bacterial lysates in cell-free expression systems that are well known in the art. Commercially available examples of cell-free protein synthesis systems include the EasyXpress System from Qiagen, Inc. (Valencia, CA).

5 Polypeptides of the present invention can also be recovered from the following: products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells.

10 Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells.

15 While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

20 The osteoinductive agents of the invention may also be isolated from natural sources of polypeptide. Osteoinductive agents may be purified from tissue sources, preferably mammalian tissue sources, using conventional physical, immunological and chemical separation techniques known to those of skill in the art. Appropriate tissue sources for the desired osteoinductive agents are known or are available to those of skill in the art.

25 The acetabular cups of the invention are useful in hip replacement surgeries, as components of total hip replacements. The acetabular cups of the invention are particularly useful in providing formulations that enable ingrowth of the patient's endogenous pelvic bone into the acetabular cup, thereby enhancing the structure and strength of the implant.

Another advantage provided by the acetabular cup of the invention is that the acetabular cup provides a reservoir of osteoinductive formulations that continue to promote bone ingrowth into the acetabular cup implant over extended periods of time, thereby helping to strengthen and secure the acetabular cup implant over extended periods of time and use.

The acetabular cup of the invention also mitigates the damage caused by wear debris and osteolysis by releasing osteoinductive formulations over extended periods of time, thereby continuously promoting osteoinduction, treatment of osteolytic lesions, and securing the acetabular cup to the pelvic bone. Polyethylene wear debris in total joint implantations can lead to osteolysis at the site of implantation. The development of osteolysis over time can lead to implant loosening and require implant revision. Traditional treatment of osteolytic lesion(s) requires surgery to remove the primary components, followed by treatment of the lesion(s) with allograft materials and re-implant revision components. The acetabular cup of the invention addresses these concerns through the osteoinductive capacity of the acetabular cup.

Surgeons skilled in the art of hip replacement are best able to determine whether a given patient is in need of enhanced ingrowth of pelvic bone into the acetabular cup of the invention. As a result, the acetabular cup of the invention is available with variable concentrations of osteoinductive compositions comprising osteoinductive agent(s).

The acetabular cup of the invention further provides for the sustained release of osteoinductive agent(s) over extended periods of time. In one embodiment of the invention, the osteoinductive agent(s) is provided for a period of time of about 10 months to about 48 months. The sustained release of the osteoinductive formulations over a period of time can be achieved in a number of ways. For example, by providing biodegradable polymer seals having differing rates of biodegradation, the acetabular cup provides osteoinductive formulations which release osteoinductive agent(s) in bioavailable form at rates directly proportional to the rates of polymer degradation *in vivo*. Similarly, where the osteoinductive formulations are liberated from the microchambers by application of electric potential or current, the potential or current providing device can be programmed or engineered to provide current to different microchambers at differing

times throughout the life of the acetabular cup implant, thereby liberating osteoinductive agent(s) in bioavailable form at pre-programmed times. Likewise, where the osteoinductive formulations are liberated from microchip drug delivery systems, the microchip device can be programmed or engineered to release osteoinductive formulations at differing times throughout the life of the acetabular cup, thereby liberating osteoinductive agent(s) in bioavailable form at pre-programmed times.

In an additional aspect of the invention, the acetabular cup compositions of the invention are packaged in kits under sterile conditions based on the desired duration of release of osteoinductive formulation. More particularly, it is believed that an implant surgeon skilled in the art of acetabular cup implantation and hip replacement is best able to ascertain and judge the degree and duration of osteoinductive activity desired in any given patient. Accordingly, the acetabular cups of the invention provide osteoinductive formulations in immediate release formulations as well as sustained release formulations. The sustained release formulations optionally provide osteoinductive formulations for short periods of time or extended periods of time. By extended periods of time is meant a sustained release formulation that provides bioavailable osteoinductive formulations not earlier than about 10-12 months following implantation, and preferably provides bioavailable osteoinductive formulations up to about 4 years in time.

Similarly, the kits of the invention provide osteoinductive formulations of differing concentration based on the desired degree of osteoinductive activity. Typical osteoinductive formulations comprise osteoinductive agent at concentrations of from about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8.

The kits of the invention further optionally comprises instructions for the preparation and administration of the osteoinductive formulations and the orthopaedic device.

The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

5 *Examples*

I. Implantation of an Acetabular Cup with a Porous Substrate

10 A patient in need of hip replacement receives hip replacement surgery wherein an acetabular cup of the invention is implanted. The acetabular cup comprises a porous coating into which a sustained release osteoinductive formulation is impregnated. The osteoinductive formulation further comprises mature BMP-2 polypeptides and mature osteoprotegerin polypeptides in concentrations of about 1 mg/ml to 10 mg/ml. The osteoinductive formulation further comprises one or more antibiotics. The sustained release formulation comprises a biodegradable polymer that releases osteoinductive formulation at a rate consistent with biodegradation of the polymer.

15 The acetabular cup is monitored by X-ray examination over the following five years for signs of osteolysis or weakening of the acetabular cup implant. Evidence of endogenous bone in-growth without evidence of osteolysis indicates that the osteoinductive formulation stimulates bone in-growth into the acetabular cup, thereby securing the acetabular cup and increasing the success of the implant.

20

II. Implantation of an Acetabular Cup with Microchambers

25 A patient in need of hip replacement receives hip replacement surgery wherein an acetabular cup of the invention is implanted. The acetabular cup comprises a plurality of microchambers into which sustained release osteoinductive formulations are administered. The osteoinductive formulation further comprises mature BMP-2 polypeptides and mature osteoprotegerin polypeptides in concentrations of about 1 mg/ml to 10 mg/ml. The osteoinductive formulation further comprises one or more antibiotics. The microchambers are sealed with a biodegradable polymer that releases osteoinductive

formulation from the plurality of microchambers at a rate consistent with biodegradation of the polymer.

The acetabular cup is monitored by X-ray examination over the following five years for signs of osteolysis or weakening of the acetabular cup implant. Evidence of endogenous bone in-growth without evidence of osteolysis indicates that the osteoinductive formulation stimulates bone in-growth into the acetabular cup, thereby securing the acetabular cup and increasing the success of the implant.

What is claimed is:

1. An acetabular cup comprising an osteoinductive formulation.
2. The acetabular cup of claim 1, further comprising a porous substrate surface.
- 5 3. The acetabular cup of claim 2, wherein the porous substrate is impregnated with an osteoinductive formulation.
4. The acetabular cup of claim 1, wherein the acetabular cup further comprises one or more microchip drug delivery devices.
- 10 5. The acetabular cup of claim 1, wherein the acetabular cup further comprises a plurality of microchambers.
6. The acetabular cup of claim 5, wherein said plurality of microchambers are distributed in substantially equivalent positions across the surface of the acetabular cup.
7. The acetabular cup of claim 5, wherein the plurality of microchambers comprise one or more osteoinductive formulations.
- 15 8. The acetabular cup of claim 7, wherein said plurality of microchambers are aseptically sealed with a biodegradable polymer.
9. The acetabular cup of claim 7, wherein said plurality of microchambers are aseptically sealed with a current responsive polymer.
- 20 10. The acetabular cup of claim 9, wherein said plurality of microchambers further comprise an electrode capable of distributing a current to the current responsive polymer.
11. The acetabular cup of claim 10, wherein said electrode is connected to an implantable current providing device.
12. The acetabular cup of claim 11, wherein said electrode is connected to an implantable current providing device by a plurality of wires present in the acetabular cup.

13. The acetabular cup of claim 11, wherein the electrode is connected to an implantable current providing device by particles or fibers present in the acetabular cup.

14. The acetabular cup of claim 1, wherein the osteoinductive formulation further comprises one or more osteoinductive agents.

5 15. The acetabular cup implant device of claim 14, wherein the one or more osteoinductive agents comprise BMP-2.

16. The acetabular cup of claim 14, wherein the one or more osteoinductive agents are selected from the group consisting of BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-15, BMP-16,
10 BMP-17, BMP-18, and any combination thereof.

17. The acetabular cup of claim 14, wherein the one or more osteoinductive agents are selected from the group consisting of CTGF-1, CTGF-2, CGTF-3, CTGF-4, and any combination thereof.

18. The acetabular cup of claim 14, wherein the one or more osteoinductive agents are selected from the group consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E,
15 and any combination thereof.

19. The acetabular cup of claim 14, wherein the one or more osteoinductive agents is osteoprotegerin.

20. The acetabular cup of claim 14, wherein the one or more osteoinductive agents are selected from the group consisting of TGF- α -1, TGF- α -2, TGF- α -3, and any
20 combination thereof.

21. The acetabular cup of claim 14, wherein the one or more osteoinductive agents is selected from the group consisting of one or more BMPs, one or more VEGFs, one or more CTGFs, osteoprotegerin, one or more TGF- α s, and any combination thereof.

25 22. The acetabular cup of claim 14, wherein the one or more osteoinductive agents are provided as therapeutic polynucleotides.

23. The acetabular cup of claim 14, wherein the one or more osteoinductive agents are provided as therapeutic polypeptides.

24. The acetabular cup of claim 23, wherein the therapeutic polypeptides are administered as mature polypeptides.

5 25. The acetabular cup of claim 1, wherein the osteoinductive formulation comprises a sustained-release formulation.

26. The acetabular cup of claim 14, wherein the osteoinductive formulation further comprises one or more antibiotics.

10 27. The acetabular cup of claim 14, wherein the osteoinductive formulation further comprises demineralized bone matrix.

28. The acetabular cup of claim 14, wherein the osteoinductive formulation further comprises bone marrow aspirate.

29. The acetabular cup of claim 14, wherein the osteoinductive formulation further comprises bone marrow concentrate.

15 30. The acetabular cup of claim 14, wherein the osteoinductive formulation further comprises one or more immunosuppressives.

31. The acetabular cup of claim 14, wherein the osteoinductive formulation further comprises a carrier.

32. The acetabular cup of claim 31, wherein the carrier is collagen.

20 33. The acetabular cup of claim 32, wherein the collagen is recombinantly produced collagen.

34. A kit comprising an acetabular cup device for implantation and an osteoinductive formulation comprising an osteoinductive agent.

25 35. The kit of claim 34, wherein the acetabular cup comprises the osteoinductive formulation.

Fig. 1A

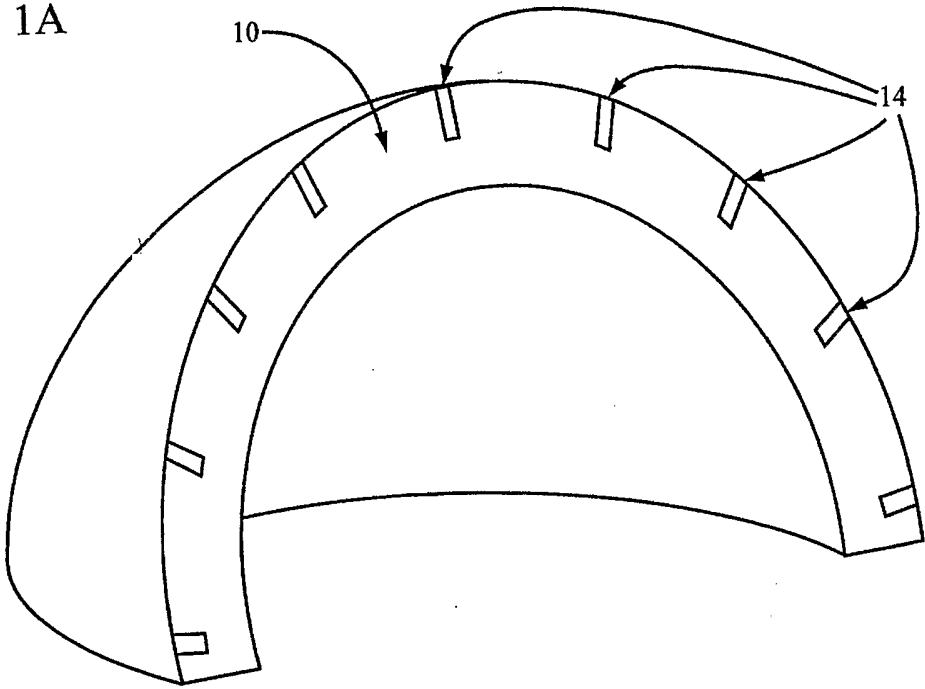


Fig. 1B

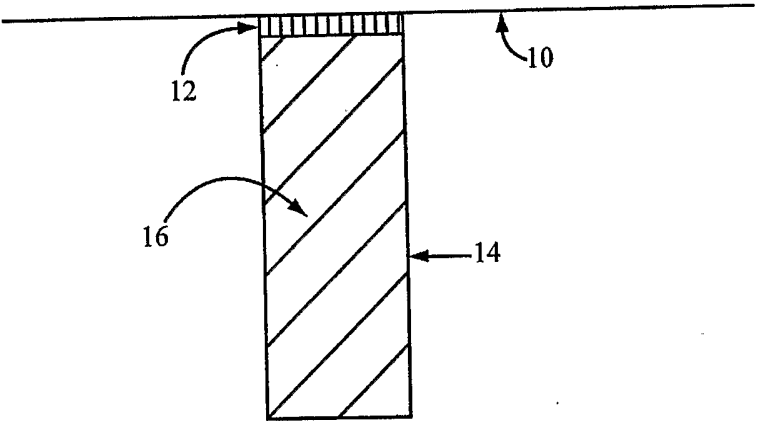


Fig. 2

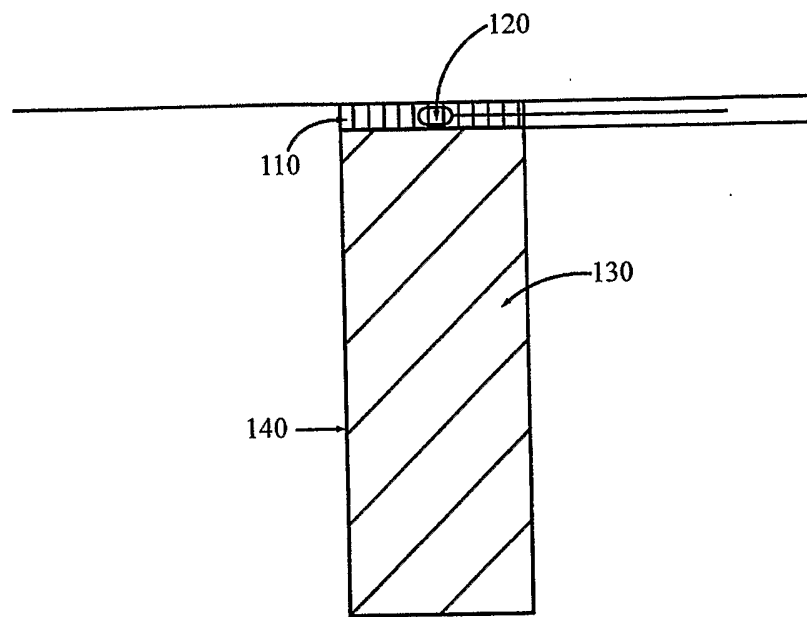
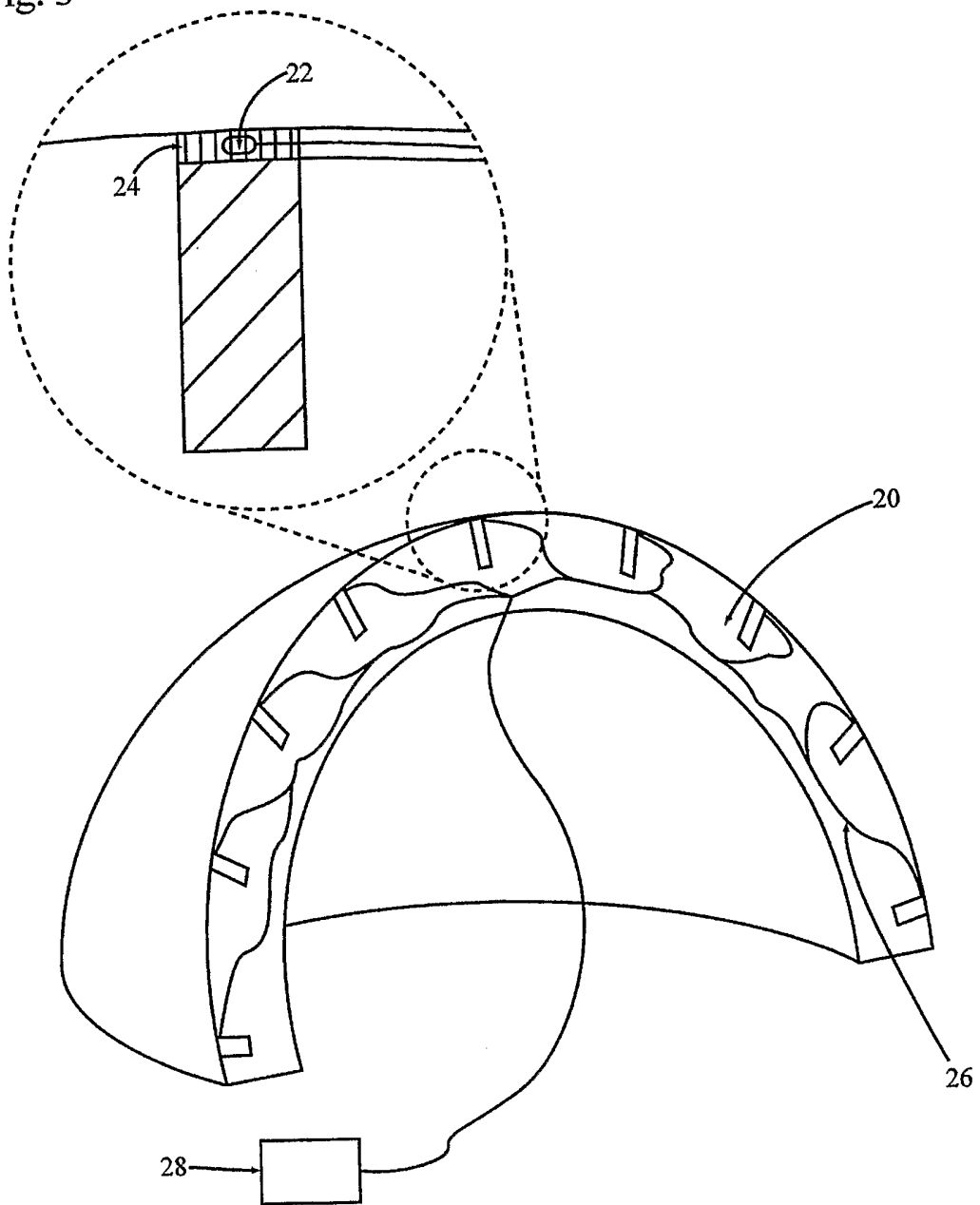


Fig. 3



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<212> PRT

<213> Homo sapiens

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20

25

30

Gln Ala Met Arg His Trp Glu Lys His Thr Cys Val Thr Phe Leu Glu

35

40

45

30

Arg Thr Asp Glu Asp Ser Tyr Ile Val Phe Thr Tyr Arg Pro Cys Gly

50 55 60

5 Cys Cys Ser Tyr Val Gly Arg Arg Gly Gly Gly Pro Gln Ala Ile Ser
65 70 75 80

10 Ile Gly Lys Asn Cys Asp Lys Phe Gly Ile Val Val His Glu Leu Gly
85 90 95

15 His Val Val Gly Phe Trp His Glu His Thr Arg Pro Asp Arg Asp Arg
100 105 110

20 His Val Ser Ile Val Arg Glu Asn Ile Gln Pro Gly Gln Glu Tyr Asn
115 120 125

25 Phe Leu Lys Met Glu Pro Gln Glu Val Glu Ser Leu Gly Glu Thr Tyr
130 135 140

30 Asp Phe Asp Ser Ile Met His Tyr Ala Arg Asn Thr Phe Ser Arg Gly
145 150 155 160

35 Ile Phe Leu Asp Thr Ile Val Pro Lys Tyr Glu Val Asn Gly Val Lys
165 170 175

40 Pro Pro Ile Gly Gln Arg Thr Arg Leu Ser Lys Gly Asp Ile Ala Gln

	180	185	190
	Ala Arg Lys Leu Tyr Lys Cys Pro Ala Cys Gly Glu Thr Leu Gln Asp		
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	Ser Thr Gly Asn Phe Ser Ser Pro Glu Tyr Pro Asn Gly Tyr Ser Ala		
	210	215	220
10			
	His Met His Cys Val Trp Arg Ile Ser Val Thr Pro Gly Glu Lys Ile		
	225	230	235 240
15			
	Ile Leu Asn Phe Thr Ser Leu Asp Leu Tyr Arg Ser Arg Leu Cys Trp		
	245	250	255
20			
	Tyr Asp Tyr Val Glu Val Arg Asp Gly Phe Trp Arg Lys Ala Pro Leu		
	260	265	270
	Arg Gly Arg Phe Cys Gly Ser Lys Leu Pro Glu Pro Ile Val Ser Thr		
25	275	280	285
	Asp Ser Arg Leu Trp Val Glu Phe Arg Ser Ser Ser Asn Trp Val Gly		
	290	295	300
30			
	Lys Gly Phe Phe Ala Val Tyr Glu Ala Ile Cys Gly Gly Asp Val Lys		

305 310 315 320

Lys Asp Tyr Gly His Ile Gln Ser Pro Asn Tyr Pro Asp Asp Tyr Arg

5 325 330 335

Pro Ser Lys Val Cys Ile Trp Arg Ile Gln Val Ser Glu Gly Phe His

340 345 350

10

Val Gly Leu Thr Phe Gln Ser Phe Glu Ile Glu Arg His Asp Ser Cys

355 360 365

15

Ala Tyr Asp Tyr Leu Glu Val Arg Asp Gly His Ser Glu Ser Ser Thr

370 375 380

20

Leu Ile Gly Arg Tyr Cys Gly Tyr Glu Lys Pro Asp Asp Ile Lys Ser

385 390 395 400

Thr Ser Ser Arg Leu Trp Leu Lys Phe Val Ser Asp Gly Ser Ile Asn

405 410 415

25

Lys Ala Gly Phe Ala Val Asn Phe Phe Lys Glu Val Asp Glu Cys Ser

420 425 430

30

Arg Pro Asn Arg Gly Gly Cys Glu Gln Arg Cys Leu Asn Thr Leu Gly

435 440 445

5 Ser Tyr Lys Cys Ser Cys Asp Pro Gly Tyr Glu Leu Ala Pro Asp Lys
450 455 460

10 Arg Arg Cys Glu Ala Ala Cys Gly Gly Phe Leu Thr Lys Leu Asn Gly
465 470 475 480

15 Ser Ile Thr Ser Pro Gly Trp Pro Lys Glu Tyr Pro Pro Asn Lys Asn
485 490 495

Cys Ile Trp Gln Leu Val Ala Pro Thr Gln Tyr Arg Ile Ser Leu Gln
500 505 510

20 Phe Asp Phe Phe Glu Thr Glu Gly Asn Asp Val Cys Lys Tyr Asp Phe
515 520 525

25 Val Glu Val Arg Ser Gly Leu Thr Ala Asp Ser Lys Leu His Gly Lys
530 535 540

30 Phe Cys Gly Ser Glu Lys Pro Glu Val Ile Thr Ser Gln Tyr Asn Asn
545 550 555 560

Met Arg Val Glu Phe Lys Ser Asp Asn Thr Val Ser Lys Lys Gly Phe

565 570 575

Lys Ala His Phe Phe Ser Glu Lys Arg Pro Ala Leu Gln Pro Pro Arg

5 580 585 590

Gly Arg Pro His Gln Leu Lys Phe Arg Val Gln Lys Arg Asn Arg Thr

10 595 600 605

Pro Gln

610

15

<210> 5

<211> 1547

<212> DNA

<213> Homo sapiens

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accatgaaga atctttggaa gaactaccag aaacgagtgg gaaaacaacc cggagattct 720

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25 atgaacacag ctggtcacag ataaggccat tgctagtaac ttttgccat gatggaaaag 1140

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<211> 396

<212> PRT

<213> Homo sapiens

<400> 6

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Leu Leu Gly Gly Ala Ala Gly Leu Val Pro Glu Leu Gly Arg Arg Lys

20 25 30

Phe Ala Ala Ala Ser Ser Gly Arg Pro Ser Ser Gln Pro Ser Asp Glu

35 40 45

Val Leu Ser Glu Phe Glu Leu Arg Leu Leu Ser Met Phe Gly Leu Lys

50 55 60

Gln Arg Pro Thr Pro Ser Arg Asp Ala Val Val Pro Pro Tyr Met Leu
65 70 75 80

5

Asp Leu Tyr Arg Arg His Ser Gly Gln Pro Gly Ser Pro Ala Pro Asp
 85 90 95

10

His Arg Leu Glu Arg Ala Ala Ser Arg Ala Asn Thr Val Arg Ser Phe
 100 105 110

15

His His Glu Glu Ser Leu Glu Glu Leu Pro Glu Thr Ser Gly Lys Thr
 115 120 125

20

Thr Arg Arg Phe Phe Phe Asn Leu Ser Ser Ile Pro Thr Glu Glu Phe
 130 135 140

25

Ile Thr Ser Ala Glu Leu Gln Val Phe Arg Glu Gln Met Gln Asp Ala
145 150 155 160

30

Leu Gly Asn Asn Ser Ser Phe His His Arg Ile Asn Ile Tyr Glu Ile
 165 170 175

Ile Lys Pro Ala Thr Ala Asn Ser Lys Phe Pro Val Thr Arg Leu Leu
 180 185 190

Asp Thr Arg Leu Val Asn Gln Asn Ala Ser Arg Trp Glu Ser Phe Asp
195 200 205

5

Val Thr Pro Ala Val Met Arg Trp Thr Ala Gln Gly His Ala Asn His
210 215 220

10

Gly Phe Val Val Glu Val Ala His Leu Glu Glu Lys Gln Gly Val Ser
225 230 235 240

15

Lys Arg His Val Arg Ile Ser Arg Ser Leu His Gln Asp Glu His Ser
245 250 255

20

Trp Ser Gln Ile Arg Pro Leu Leu Val Thr Phe Gly His Asp Gly Lys
260 265 270

25

Gly His Pro Leu His Lys Arg Glu Lys Arg Gln Ala Lys His Lys Gln
275 280 285

Arg Lys Arg Leu Lys Ser Ser Cys Lys Arg His Pro Leu Tyr Val Asp
290 295 300

30

Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr
305 310 315 320

His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro Leu Ala Asp His
325 330 335

5

Leu Asn Ser Thr Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val
340 345 350

10

Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala
355 360 365

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Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val Val Leu Lys Asn
370 375 380

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Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg
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<210> 7

<211> 1794

<212> DNA

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<213> Homo sapiens

<400> 7

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5 cgcgcgcgg gtacctagcc atggctgggg cgagcaggct gctgtttctg tggtgggct 360

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15 gcaacacgggt tcgcagcttt cgggcggcag cagcagaaac tcttgaaaga aaaggactgt 660

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20 tctgtattgg agagctagga aacatcagcc tgagttgtcc agtgtctgga ggatgctccc 780

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25 ttatgtctg gctgtctaaa gatacactc aattcttgag gaaggccaaa gaaaaagaag 960

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30 ctttccaga gccttatatc ttggtatatg ccaatgatgc cgccattct gagccagaaa 1080

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5 tgtgcctct gcagaacaac gagcttcctg gggcagaata ccagtataaa aaggatgagg 1260

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15 caaatcatgc taccatccag agtatagtga gagctgtggg ggtcgttctt gggattcttg 1620

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20 agaattgagt gcttaaagta taccctaaca tgacagtaga gtcttgcgct tgcagataac 1740

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Val Ser Leu Ala Gln Gly Glu Arg Pro Lys Pro Pro Phe Pro Glu Leu

5 20 25 30

Arg Lys Ala Val Pro Gly Asp Arg Thr Ala Gly Ala Gly Pro Asp Ser

35 40 45

10

Glu Leu Glu Pro Gln Asp Lys Val Ser Glu His Met Leu Arg Leu Tyr

50 55 60

15

Asp Arg Tyr Ser Thr Val Gln Ala Ala Arg Thr Pro Gly Ser Leu Glu

65 70 75 80

20

Gly Gly Ser Glu Pro Trp Arg Pro Arg Leu Leu Arg Glu Gly Asn Thr

85 90 95

Val Arg Ser Phe Arg Ala Ala Ala Ala Glu Thr Leu Glu Arg Lys Gly

25 100 105 110

Leu Tyr Ile Phe Asn Leu Thr Ser Leu Thr Lys Ser Glu Asn Ile Leu

115 120 125

30

Ser Ala Thr Leu Tyr Phe Cys Ile Gly Glu Leu Gly Asn Ile Ser Leu

	130	135	140	
	Ser Cys Pro Val Ser Gly Gly Cys Ser His His Ala Gln Arg Lys His			
5	145	150	155	160
	Ile Gln Ile Asp Leu Ser Ala Trp Thr Leu Lys Phe Ser Arg Asn Gln			
	165	170	175	
10				
	Ser Gln Leu Leu Gly His Leu Ser Val Asp Met Ala Lys Ser His Arg			
	180	185	190	
15				
	Asp Ile Met Ser Trp Leu Ser Lys Asp Ile Thr Gln Phe Leu Arg Lys			
	195	200	205	
20	Ala Lys Glu Lys Glu Glu Phe Leu Ile Gly Phe Asn Ile Thr Ser Lys			
	210	215	220	
	Gly Arg Gln Leu Pro Lys Arg Arg Leu Pro Phe Pro Glu Pro Tyr Ile			
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	Leu Val Tyr Ala Asn Asp Ala Ala Ile Ser Glu Pro Glu Ser Val Val			
	245	250	255	
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	Ser Ser Leu Gln Gly His Arg Asn Phe Pro Thr Gly Thr Val Pro Lys			

	260	265	270
	Trp	Asp	Ser
	His	Ile	Arg
	Ala	Ala	Leu
	Ser	Ile	Glu
	Arg	Arg	Lys
	Lys		
5	275	280	285
	Arg	Ser	Thr
	Gly	Leu	Leu
	Leu	Pro	Leu
	Gln	Asn	Asn
	Glu	Leu	Pro
	Gly		
10	290	295	300
	Ala	Glu	Tyr
	Gln	Tyr	Lys
	Lys	Asp	Glu
	Val	Trp	Glu
	Glu	Arg	Lys
	Pro		
15	305	310	315
	320		
	Tyr	Lys	Thr
	Leu	Gln	Ala
	Gln	Ala	Pro
	Glu	Lys	Ser
	Lys	Asn	Lys
	Lys		
20	325	330	335
	Lys	Gln	Arg
	Lys	Gly	Pro
	His	Arg	Lys
	Ser	Gln	Arg
	Leu	Gln	Phe
	Asp		
25	340	345	350
	Glu	Gln	Thr
	Leu	Lys	Lys
	Ala	Arg	Arg
	Lys	Gln	Trp
	Ile	Glu	Pro
	Arg		
30	355	360	365
	Asn	Cys	Ala
	Arg	Arg	Tyr
	Leu	Lys	Val
	Asp	Phe	Ala
	Asp	Ile	Gly
	Trp		
35	370	375	380
	Ser	Glu	Trp
	Ile	Ile	Ser
	Pro	Lys	Ser
	Phe	Asp	Ala
	Tyr	Tyr	Cys
	Ser		

385 390 395 400

Gly Ala Cys Gln Phe Pro Met Pro Lys Ser Leu Lys Pro Ser Asn His

5 405 410 415

Ala Thr Ile Gln Ser Ile Val Arg Ala Val Gly Val Val Pro Gly Ile

10 420 425 430

Pro Glu Pro Cys Cys Val Pro Glu Lys Met Ser Ser Leu Ser Ile Leu

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Phe Phe Asp Glu Asn Lys Asn Val Val Leu Lys Val Tyr Pro Asn Met

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Thr Val Glu Ser Cys Ala Cys Arg

25 465 470

<210> 9

<211> 1999

<212> DNA

<213> Homo sapiens

<400> 9

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25 cacagactgc ttctttag ctggactttt atttaaaaaa aaaaaaaaaa aaatggaaaa 1860

aatccctaaa cattcacctt gacctatftt atgactttac gtgcaaatgt ttgaccata 1920

30 ttgatcatat attttgacaa aatatattta taactacgta ttaaagaaa aaaataaaat 1980

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<211> 408
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<213> Homo sapiens

<400> 10

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15 20 25 30

Lys Lys Val Ala Glu Ile Gln Gly His Ala Gly Gly Arg Arg Ser Gly
35 40 45
20

Gln Ser His Glu Leu Leu Arg Asp Phe Glu Ala Thr Leu Leu Gln Met
50 55 60

25
Phe Gly Leu Arg Arg Arg Pro Gln Pro Ser Lys Ser Ala Val Ile Pro
65 70 75 80

30 Asp Tyr Met Arg Asp Leu Tyr Arg Leu Gln Ser Gly Glu Glu Glu Glu
85 90 95

Glu Gln Ile His Ser Thr Gly Leu Glu Tyr Pro Glu Arg Pro Ala Ser
100 105 110

5

Arg Ala Asn Thr Val Arg Ser Phe His His Glu Glu His Leu Glu Asn
115 120 125

10

Ile Pro Gly Thr Ser Glu Asn Ser Ala Phe Arg Phe Leu Phe Asn Leu
130 135 140

Ser Ser Ile Pro Glu Asn Glu Ala Ile Ser Ser Ala Glu Leu Arg Leu
15 145 150 155 160

Phe Arg Glu Gln Val Asp Gln Gly Pro Asp Trp Glu Arg Gly Phe His
165 170 175

20

Arg Ile Asn Ile Tyr Glu Val Met Lys Pro Pro Ala Glu Val Val Pro
180 185 190

25

Gly His Leu Ile Thr Arg Leu Leu Asp Thr Arg Leu Val His His Asn
195 200 205

30

Val Thr Arg Trp Glu Thr Phe Asp Val Ser Pro Ala Val Leu Arg Trp
210 215 220

Thr Arg Glu Lys Gln Pro Asn Tyr Gly Leu Ala Ile Glu Val Thr His
225 230 235 240

5

Leu His Gln Thr Arg Thr His Gln Gly Gln His Val Arg Ile Ser Arg
 245 250 255

10

Ser Leu Pro Gln Gly Ser Gly Asn Trp Ala Gln Leu Arg Pro Leu Leu
 260 265 270

15

Val Thr Phe Gly His Asp Gly Arg Gly His Ala Leu Thr Arg Arg Arg
 275 280 285

20

Arg Ala Lys Arg Ser Pro Lys His His Ser Gln Arg Ala Arg Lys Lys
 290 295 300

25

Asn Lys Asn Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val
305 310 315 320

30

Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr
 325 330 335

35

Cys His Gly Asp Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr
 340 345 350

Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val Asn Ser Ser Ile

355 360 365

5

Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu

370 375 380

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Tyr Leu Asp Glu Tyr Asp Lys Val Val Leu Lys Asn Tyr Gln Glu Met

385 390 395 400

Val Val Glu Gly Cys Gly Cys Arg

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405

<210> 11

<211> 2207

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<212> DNA

<213> Homo sapiens

<400> 11

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aagtgaagat tactttggga actacagttt atcagaagat caacttttgc taattcaa 360

5 accaaaggcc tgattatcat aaattcatat aggaatgcat aggtcatctg atcaaataat 420

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10 taggacagga aaatcgggga ggatgtgtg ctgagaaatg tcactgtcat gaaaaatagg 600

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25 attaatgcc atctctgttc tgaacttga tgacagctcc aatgtcattt tgaaaaata 2040

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<210> 12
<211> 454
5 <212> PRT
<213> Homo sapiens

<400> 12

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Ser Cys Trp Val Leu Val Gly Tyr Ala Lys Gly Gly Leu Gly Asp Asn
15 20 25 30

His Val His Ser Ser Phe Ile Tyr Arg Arg Leu Arg Asn His Glu Arg
35 40 45
20

Arg Glu Ile Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg
50 55 60

25 Pro Arg Pro Phe Ser Pro Gly Lys Gln Ala Ser Ser Ala Pro Leu Phe
65 70 75 80

30 Met Leu Asp Leu Tyr Asn Ala Met Thr Asn Glu Glu Asn Pro Glu Glu
85 90 95

Ser Glu Tyr Ser Val Arg Ala Ser Leu Ala Glu Glu Thr Arg Gly Ala
100 105 110

5 Arg Lys Gly Tyr Pro Ala Ser Pro Asn Gly Tyr Pro Arg Arg Ile Gln
115 120 125

10 Leu Ser Arg Thr Thr Pro Leu Thr Thr Gln Ser Pro Pro Leu Ala Ser
130 135 140

Leu His Asp Thr Asn Phe Leu Asn Asp Ala Asp Met Val Met Ser Phe
15 145 150 155 160

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

20 Tyr Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro His Gly Glu Ala
180 185 190

25 Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp Arg Ser Asn Asn Arg
195 200 205

30 Phe Glu Asn Glu Thr Ile Lys Ile Ser Ile Tyr Gln Ile Ile Lys Glu
210 215 220

Tyr Thr Asn Arg Asp Ala Asp Leu Phe Leu Leu Asp Thr Arg Lys Ala
225 230 235 240

5

Gln Ala Leu Asp Val Gly Trp Leu Val Phe Asp Ile Thr Val Thr Ser
245 250 255

10

Asn His Trp Val Ile Asn Pro Gln Asn Asn Leu Gly Leu Gln Leu Cys
260 265 270

15

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

20

Val Gly Arg Gln Gly Pro Gln Ser Lys Gln Pro Phe Met Val Ala Phe
290 295 300

25

Phe Lys Ala Ser Glu Val Leu Leu Arg Ser Val Arg Ala Ala Asn Lys
305 310 315 320

30

Arg Lys Asn Gln Asn Arg Asn Lys Ser Ser Ser His Gln Asp Ser Ser
325 330 335

Arg Met Ser Ser Val Gly Asp Tyr Asn Thr Ser Glu Gln Lys Gln Ala
340 345 350

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln
355 360 365

5

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly
370 375 380

10

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala
385 390 395 400

15

Ile Val Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys
405 410 415

20

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe
420 425 430

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Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val
435 440 445

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Arg Ser Cys Gly Cys His
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<210> 13
<211> 396
<212> DNA

<213> Homo sapiens

<400> 13

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cgggatctgg gatggcagga ctggattata gcaccagaag gatacgtgc attttattgt 180

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<210> 14

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<211> 132

<212> PRT

<213> Homo sapiens

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Asn Gln Asn Arg Asn Lys Ser Ser Ser His Gln Asp Ser Ser Arg Met

1 5 10 15

30

Ser Ser Val Gly Asp Tyr Asn Thr Ser Glu Gln Lys Gln Ala Cys Lys

20 25 30

Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp
35 40 45

5

Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly Glu Cys
50 55 60

10

Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala Ile Val
65 70 75 80

Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys Pro Cys
15 85 90 95

Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp
100 105 110

20

Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ser
115 120 125

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Cys Gly Cys His
130

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<212> DNA

<213> Homo sapiens

<400> 15

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25 ggtagaacc aacgaagaaa ataaaatgag ggtgccccagc ttataagaat ggtgttaggg 2640

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cgg

2943

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<211> 513

<212> PRT

<213> Homo sapiens

<400> 16

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Met Pro Gly Leu Gly Arg Arg Ala Gln Trp Leu Cys Trp Trp Trp Gly

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Leu Leu Cys Ser Cys Cys Gly Pro Pro Pro Leu Arg Pro Pro Leu Pro

20 25 30

Ala Ala Ala Ala Ala Ala Ala Gly Gly Gln Leu Leu Gly Asp Gly Gly

25

35 40 45

Ser Pro Gly Arg Thr Glu Gln Pro Pro Pro Ser Pro Gln Ser Ser Ser

50 55 60

30

Gly Phe Leu Tyr Arg Arg Leu Lys Thr Gln Glu Lys Arg Glu Met Gln

65 70 75 80

Lys Glu Ile Leu Ser Val Leu Gly Leu Pro His Arg Pro Arg Pro Leu

5 85 90 95

His Gly Leu Gln Gln Pro Gln Pro Pro Ala Leu Arg Gln Gln Glu Glu

10 100 105 110

Gln Gln Gln Gln Gln Gln Leu Pro Arg Gly Glu Pro Pro Pro Gly Arg

15 115 120 125

Leu Lys Ser Ala Pro Leu Phe Met Leu Asp Leu Tyr Asn Ala Leu Ser

130 135 140

Ala Asp Asn Asp Glu Asp Gly Ala Ser Glu Gly Glu Arg Gln Gln Ser

20 145 150 155 160

Trp Pro His Glu Ala Ala Ser Ser Ser Gln Arg Arg Gln Pro Pro Pro

25 165 170 175

Gly Ala Ala His Pro Leu Asn Arg Lys Ser Leu Leu Ala Pro Gly Ser

30 180 185 190

Gly Ser Gly Gly Ala Ser Pro Leu Thr Ser Ala Gln Asp Ser Ala Phe

	195	200	205
	Leu Asn Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu Tyr		
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	Asp Lys Glu Phe Ser Pro Arg Gln Arg His His Lys Glu Phe Lys Phe		
10	225	230	235 240
	Asn Leu Ser Gln Ile Pro Glu Gly Glu Val Val Thr Ala Ala Glu Phe		
15	245	250	255
	Arg Ile Tyr Lys Asp Cys Val Met Gly Ser Phe Lys Asn Gln Thr Phe		
20	260	265	270
	Leu Ile Ser Ile Tyr Gln Val Leu Gln Glu His Gln His Arg Asp Ser		
25	275	280	285
	Asp Leu Phe Leu Leu Asp Thr Arg Val Val Trp Ala Ser Glu Glu Gly		
30	290	295	300
	Trp Leu Glu Phe Asp Ile Thr Ala Thr Ser Asn Leu Trp Val Val Thr		
	305	310	315 320
	Pro Gln His Asn Met Gly Leu Gln Leu Ser Val Val Thr Arg Asp Gly		

	325	330	335
	Val His Val His Pro Arg Ala Ala Gly Leu Val Gly Arg Asp Gly Pro		
5	340	345	350
	Tyr Asp Lys Gln Pro Phe Met Val Ala Phe Phe Lys Val Ser Glu Val		
10	355	360	365
	His Val Arg Thr Thr Arg Ser Ala Ser Ser Arg Arg Arg Gln Gln Ser		
15	370	375	380
	Arg Asn Arg Ser Thr Gln Ser Gln Asp Val Ala Arg Val Ser Ser Ala		
	385	390	395 400
20	Ser Asp Tyr Asn Ser Ser Glu Leu Lys Thr Ala Cys Arg Lys His Glu		
	405	410	415
	Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala		
25	420	425	430
	Pro Lys Gly Tyr Ala Ala Asn Tyr Cys Asp Gly Glu Cys Ser Phe Pro		
30	435	440	445
	Leu Asn Ala His Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu		

450 455 460

Val His Leu Met Asn Pro Glu Tyr Val Pro Lys Pro Cys Cys Ala Pro

5 465 470 475 480

Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Asn Ser Asn

10 485 490 495

Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys

15 500 505 510

His

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<211> 420
<212> DNA
<213> Homo sapiens

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30 aagcatgagc tgtatgtgag ttccaagac ctgggatggc aggactggat cattgcaccc 180

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aatgcaacca accacgegat tgtgcagacc ttggffcacc ttatgaaccc cgagtatgtc 300

cccaaaccgt gctgtgcgcc aactaagcta aatgcatct cggttcttta ctttgatgac 360

aactccaatg tcattctgaa aaaatacagg aatatggttg taagagcttg tggatgccac 420

<210> 18

<211> 140

<212> PRT

<213> Homo sapiens

<400> 18

Arg Ser Ala Ser Ser Arg Arg Arg Gln Gln Ser Arg Asn Arg Ser Thr

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Gln Ser Gln Asp Val Ala Arg Val Ser Ser Ala Ser Asp Tyr Asn Ser

20 25 30

Ser Glu Leu Lys Thr Ala Cys Arg Lys His Glu Leu Tyr Val Ser Phe

35 40 45

Gln Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Lys Gly Tyr Ala

50 55 60

Ala Asn Tyr Cys Asp Gly Glu Cys Ser Phe Pro Leu Asn Ala His Met

65 70 75 80

Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Leu Met Asn

5 85 90 95

Pro Glu Tyr Val Pro Lys Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala

10 100 105 110

Ile Ser Val Leu Tyr Phe Asp Asp Asn Ser Asn Val Ile Leu Lys Lys

15 115 120 125

Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His

130 135 140

20 <210> 19

<211> 1878

<212> DNA

<213> Homo sapiens

25 <400> 19

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30 cgatgcacgt gcgtcactg cgagctgcgg cgccgcacag ctctgtggcg ctctgggcac 180

ccctgttct getgegetcc gccctggcgg acttcagcct ggacaacgag gtgcactcga 240

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10 gcctgcaaga tagccatttc ctaccgacg cgcacatggt catgagette gtcaacctcg 540

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caataaaacg aatgaatg 1878

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<210> 20

<211> 431

<212> PRT

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<213> Homo sapiens

<400> 20

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala
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Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser
 20 25 30

10

Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser
 35 40 45

15

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu
 50 55 60

20

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro
65 70 75 80

25

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly
 85 90 95

30

Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser
 100 105 110

30

Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr
 115 120 125

Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys
130 135 140

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Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu
145 150 155 160

10

Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile
165 170 175

15

Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile
180 185 190

20

Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu
195 200 205

25

Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu
210 215 220

30

Val Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg
225 230 235 240

His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser
245 250 255

Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn
260 265 270

5

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe
275 280 285

10

Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser
290 295 300

15

Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu
305 310 315 320

20

Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr
325 330 335

25

Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu
340 345 350

30

Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn
355 360 365

30

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His
370 375 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln
385 390 395 400

5

Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile
405 410 415

10

Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
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<210> 21

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<211> 417

<212> DNA

<213> Homo sapiens

<400> 21

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aagccctget gtgcgccac gcagctcaat gccatctccg tcctctactt cgatgacagc 360

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<210> 22

<211> 139

5 <212> PRT

<213> Homo sapiens

<400> 22

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Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu Asn Ser Ser Ser

15 20 25 30

Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg

35 40 45

20

Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala

50 55 60

25

Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met Asn

65 70 75 80

30 Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe Ile Asn Pro

85 90 95

Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala Ile

100 105 110

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Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr

115 120 125

10

Arg Asn Met Val Val Arg Ala Cys Gly Cys His

130 135

<210> 23

15

<211> 3536

<212> DNA

<213> Homo sapiens

<400> 23

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tgagcgcgcc cggcctgcca tgaccgcgt ccccgcccg cttggctcc tggcctggc 180

25

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10 caggaggtct gacttgttct ttttgatct tcagacgtc cgagctggag acgagggtcg 720

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gggactccgc ctctatgtgg agactgagga cgggcacagc gtggatcctg gcctggccgg 840

15 cctgtgggt caacgggccc cacgtccca acagccttc gtggtaactt tcttcagggc 900

cagtcgagt cccatccga cccctcgggc agtgaggcca ctgaggagga ggcagccgaa 960

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<210> 24

<211> 402

<212> PRT

<213> Homo sapiens

<400> 24

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Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro Gly Cys Pro

20 25 30

Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln Arg Glu Ile

35 40 45

Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Pro Pro

50 55 60

Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu
65 70 75 80

5

Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala Pro Ala Glu
 85 90 95

10

Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val
 100 105 110

15

Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp Lys Glu Phe
 115 120 125

20

Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala
 130 135 140

25

Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu Asn Arg Thr
 145 150 155 160

30

Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser Asn Arg Glu
 165 170 175

30

Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala Gly Asp Glu
 180 185 190

Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys Trp Leu Leu
195 200 205

5

Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Glu Asp
210 215 220

10

Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly Gln Arg Ala
225 230 235 240

15

Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg Ala Ser Pro
245 250 255

20

Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg Arg Arg Gln
260 265 270

25

Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu Pro Gly Ile
275 280 285

30

Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His
290 295 300

35

Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp Val Ile
305 310 315 320

Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe
325 330 335

5

Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser
340 345 350

10

Leu Val His Leu Met Met Pro Asp Ala Val Pro Lys Ala Cys Cys Ala
355 360 365

15

Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn
370 375 380

20

Asn Val Ile Leu Arg Lys His Arg Asn Met Val Val Lys Ala Cys Gly
385 390 395 400

Cys His

25

<210> 25

<211> 417

<212> DNA

<213> Homo sapiens

30

<400> 25

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cacgagctct acgtcagett ccaggacctc ggettggtgg actgggtcat cgtccccaa 180

5 ggctactcgg cctattactg tgagggggag tgctccttc cactggacte ctgcatgaat 240

gccaccaacc acgccatct gcagtcctg gtgcacctga tgatccaga cgcagtccec 300

10 aaggcgtget gtgcaccac caagetgagc gccaccttg tgcttacta tgacagcagc 360

aacaatgtca tcttgcgcaa gcaccgcaac atggtgggtca aggctgcgg ctgccac 417

15 <210> 26

<211> 139

<212> PRT

<213> Homo sapiens

20 <400> 26

Ala Val Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu

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25 Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser

20 25 30

30 His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln

35 40 45

Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala
50 55 60

5

Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn
65 70 75 80

10

Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Met Pro
85 90 95

15

Asp Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr
100 105 110

20

Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His
115 120 125

25

Arg Asn Met Val Val Lys Ala Cys Gly Cys His
130 135

30

<210> 27

<211> 1942

<212> DNA

<213> Homo sapiens

<400> 27

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ggccgcctgc agtctctct ctgggtgatt gcggggcct aagatgtgtc ctggggcact 180

5 gtgggtggcc ctgcccctgc tctcctgtct ggctggctcc ctacagggga agccactgca 240

gagctgggga cgagggtctg ctgggggaaa cgccacagc ccactggggg tgcctggagg 300

10 tgggtgcct gacacacct tcaacctgaa gatgtttctg gagaactga aggtggattt 360

cctgcgcagc cttaacctga gtggggctcc ttgcaggac aaaaccaggg tggagccgcc 420

gcagtacatg attgacctgt acaacaggta cacgtccgat aagtcgacta cgccagcgtc 480

15 caacattgtg cggagcttca gcatggaaga tgccatctcc ataactgcca cagaggactt 540

ccccctcag aagcacatct tctcttcaa catctccatt cctaggcatg agcagatcac 600

20 cagagctgag ctccgactct atgtctctg tcaaaatac gtggaccct ctcatgacct 660

gaaaggaagc gtggatcttt atgatgttct ggatggaaca gatgcctggg atagtgtac 720

agagaccaag accttcttgg tctcccagga cattcaggat gagggctggg agaccttgga 780

25 agtgtccagc gccgtgaagc gctgggtccg gtccgactcc accaagagca aaaataagct 840

ggaagtgact gtggagagcc acaggaaggg ctgcgacacg ctggacatca gtgtccccc 900

30 aggttccaga aacctgccct tctttgtgt cttctccaat gaccacagca gtgggaccaa 960

ggagaccagg ctggagctga gggagatgat cagccatgaa caagagagcg tgctcaagaa 1020

gctgtccaag gacggctcca cagaggcagg tgagagcagt cacgaggagg acacggatgg 1080

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tgacccaag gagtatgaag cctacgagt taagggcggc tgcttcttc cttggctga 1260

10 cgatgtgacg ccgacgaaac acgtatcgt gcagacctg gtgcatctca agttccccac 1320

aaagtgggc aaggcctgt gtgtccccac caaactgagc cccatctccg tcctctacaa 1380

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15 tgggtgcagg tagtatctgc ctgcggggct ggggaggcag gccaaagggg ctccacatga 1500

gaggtcctgc atgcccctgg gcacaacaag gactgattca atctgcatgc cagcctggag 1560

20 gaggaaagg agcctgtct cctccccac accccacca aagcatacac cgtgagctc 1620

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tgttgggatg caaggagggt atgaaaagga gacaggggga aaaataatcc atagtcagca 1740

25 gaaaacaaca gcagtgagcc agaggagcac aggcgggcag gtcactgcag agactgatgg 1800

aagttagaga ggtggaggag gccagctgc tccaaaacce ttggggagta gagggaagga 1860

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<210> 28

<211> 429

5 <212> PRT

<213> Homo sapiens

<400> 28

10 Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu
1 5 10 15

Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser
15 20 25 30

Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Gly Leu
35 40 45
20

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val
50 55 60

25 Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys
65 70 75 80

30 Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
85 90 95

Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
100 105 110

5 Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
115 120 125

10 Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
130 135 140

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
15 145 150 155 160

Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
165 170 175

20 Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
180 185 190

25 Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
195 200 205

30 Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
210 215 220

Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
225 230 235 240

5

Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
 245 250 255

10

Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
 260 265 270

15

Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
 275 280 285

20

Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
 290 295 300

25

Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
305 310 315 320

30

Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
 325 330 335

30

Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
 340 345 350

Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
355 360 365

5

Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
370 375 380

10

Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
385 390 395 400

15

Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
405 410 415

20

His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg
420 425

<210> 29

<211> 1584

<212> DNA

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<213> Homo sapiens

<400> 29

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taaaccttcc tggettggcc taggagctcg agcggagtca tgggctctct ggtcctgaca 180

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5 ggtgtcgact ttaacacact gctccagagc atgaaggatg agtttcttaa gacactaaac 360

ctctctgaca tccccagca ggattcagcc aaggaggacc caccagagta catgttgga 420

10 ctctacaaca aatttgcaac agatcggacc tccatgcct ctgccaacat cattaggagt 480

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15 tacacactgg tgcaaaggga tcgtatgata tacgatggag tagaccgga aattaccatt 660

tttgaagtgc tggagagcaa aggggataat gagggagaaa gaaacatgct ggtcttggtg 720

20 tctggggaga tatatggaac caacagtga tgggagactt ttgatgtcac agatgccatc 780

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25 aagcataacc ctttgcctat cgtgtttct gatgacaaa gcagtgaca ggagaggaag 960

gaggaactga atgaaatgat tccccag caactccag agctggaca cttgggcctg 1020

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15 tttgtttag gaaatgcata tttt 1584

<210> 30

20 <211> 424

<212> PRT

<213> Homo sapiens

<400> 30

25 Met Gly Ser Leu Val Leu Thr Leu Cys Ala Leu Phe Cys Leu Ala Ala

1 5 10 15

30 Tyr Leu Val Ser Gly Ser Pro Ile Met Asn Leu Glu Gln Ser Pro Leu

20 25 30

Glu Glu Asp Met Ser Leu Phe Gly Asp Val Phe Ser Glu Gln Asp Gly
35 40 45

5

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

10

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

15

Pro Pro Glu Tyr Met Leu Glu Leu Tyr Asn Lys Phe Ala Thr Asp Arg
85 90 95

20

Thr Ser Met Pro Ser Ala Asn Ile Ile Arg Ser Phe Lys Asn Glu Asp
100 105 110

25

Leu Phe Ser Gln Pro Val Ser Phe Asn Gly Leu Arg Lys Tyr Pro Leu
115 120 125

30

Leu Phe Asn Val Ser Ile Pro His His Glu Glu Val Ile Met Ala Glu
130 135 140

Leu Arg Leu Tyr Thr Leu Val Gln Arg Asp Arg Met Ile Tyr Asp Gly
145 150 155 160

Val Asp Arg Lys Ile Thr Ile Phe Glu Val Leu Glu Ser Lys Gly Asp
165 170 175

5

Asn Glu Gly Glu Arg Asn Met Leu Val Leu Val Ser Gly Glu Ile Tyr
180 185 190

10

Gly Thr Asn Ser Glu Trp Glu Thr Phe Asp Val Thr Asp Ala Ile Arg
195 200 205

15

Arg Trp Gln Lys Ser Gly Ser Ser Thr His Gln Leu Glu Val His Ile
210 215 220

20

Glu Ser Lys His Asp Glu Ala Glu Asp Ala Ser Ser Gly Arg Leu Glu
225 230 235 240

25

Ile Asp Thr Ser Ala Gln Asn Lys His Asn Pro Leu Leu Ile Val Phe
245 250 255

30

Ser Asp Asp Gln Ser Ser Asp Lys Glu Arg Lys Glu Glu Leu Asn Glu
260 265 270

Met Ile Ser His Glu Gln Leu Pro Glu Leu Asp Asn Leu Gly Leu Asp
275 280 285

Ser Phe Ser Ser Gly Pro Gly Glu Glu Ala Leu Leu Gln Met Arg Ser
290 295 300

5

Asn Ile Ile Tyr Asp Ser Thr Ala Arg Ile Arg Arg Asn Ala Lys Gly
305 310 315 320

10

Asn Tyr Cys Lys Arg Thr Pro Leu Tyr Ile Asp Phe Lys Glu Ile Gly
325 330 335

15

Trp Asp Ser Trp Ile Ile Ala Pro Pro Gly Tyr Glu Ala Tyr Glu Cys
340 345 350

20

Arg Gly Val Cys Asn Tyr Pro Leu Ala Glu His Leu Thr Pro Thr Lys
355 360 365

25

His Ala Ile Ile Gln Ala Leu Val His Leu Lys Asn Ser Gln Lys Ala
370 375 380

30

Ser Lys Ala Cys Cys Val Pro Thr Lys Leu Glu Pro Ile Ser Ile Leu
385 390 395 400

Tyr Leu Asp Lys Gly Val Val Thr Tyr Lys Phe Lys Tyr Glu Gly Met
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Ala Val Ser Glu Cys Gly Cys Arg

420

5

<210> 31

<211> 324

<212> DNA

<213> Homo sapiens

10

<400> 31

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cacctcaaga attcccagaa agcttccaaa gcctgctgtg tgcccacaaa gctagagccc 240

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gccgtctccg aatgtggctg taga 324

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<210> 32

<211> 108

<212> PRT

<213> Homo sapiens

30

<400> 32

Asn Ala Lys Gly Asn Tyr Cys Lys Arg Thr Pro Leu Tyr Ile Asp Phe

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5 Lys Glu Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Pro Gly Tyr Glu
 20 25 30

10 Ala Tyr Glu Cys Arg Gly Val Cys Asn Tyr Pro Leu Ala Glu His Leu
 35 40 45

15 Thr Pro Thr Lys His Ala Ile Ile Gln Ala Leu Val His Leu Lys Asn
 50 55 60

20 Ser Gln Lys Ala Ser Lys Ala Cys Cys Val Pro Thr Lys Leu Glu Pro
 65 70 75 80

25 Ile Ser Ile Leu Tyr Leu Asp Lys Gly Val Val Thr Tyr Lys Phe Lys
 85 90 95

30 Tyr Glu Gly Met Ala Val Ser Glu Cys Gly Cys Arg
 100 105

<210> 33

<211> 1443

30 <212> DNA

<213> Homo sapiens

<400> 33

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5

ccgcggcggc ggcggcggcg gcggcggcgg cggcagcggc gggggtcggg ggggagcgct 180

ccagecgccc agccccctc gtggcgcccc agccggacgg ctgccccgtg tgcgtttggc 240

10

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cccgccagc cacagtctac ctgcagatct tgcgactaaa acccctaact ggggaaggga 660

ccgcaggggg agggggcgga ggccggcgtc acatccgtat ccgctcactg aagattgagc 720

25

tgcactcagc ctgaggecat tggeagagca tcgactcaa gcaagtgcta cacagctggt 780

tccgccagcc acagagcaac tggggcatcg agatcaacgc ctttgatccc agtggcacag 840

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<210> 34

<211> 407

<212> PRT

<213> Homo sapiens

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<400> 34

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Glu Leu Arg Pro Arg Gly Glu Ala Ala Glu Gly Pro Ala Ala Ala Ala

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	Ser Arg Pro Ala Pro Ser Val Ala Pro Glu Pro Asp Gly Cys Pro Val		
	50	55	60
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	Cys Val Trp Arg Gln His Ser Arg Glu Leu Arg Leu Glu Ser Ile Lys		
	65	70	75 80
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	Ser Gln Ile Leu Ser Lys Leu Arg Leu Lys Glu Ala Pro Asn Ile Ser		
	85	90	95
20			
	Arg Glu Val Val Lys Gln Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln		
	100	105	110
	Ile Leu Asp Leu His Asp Phe Gln Gly Asp Ala Leu Gln Pro Glu Asp		
25	115	120	125
	Phe Leu Glu Glu Asp Glu Tyr His Ala Thr Thr Glu Thr Val Ile Ser		
	130	135	140
30			
	Met Ala Gln Glu Thr Asp Pro Ala Val Gln Thr Asp Gly Ser Pro Leu		

145 150 155 160

Cys Cys His Phe His Phe Ser Pro Lys Val Met Phe Thr Lys Val Leu

5 165 170 175

Lys Ala Gln Leu Trp Val Tyr Leu Arg Pro Val Pro Arg Pro Ala Thr

180 185 190

10

Val Tyr Leu Gln Ile Leu Arg Leu Lys Pro Leu Thr Gly Glu Gly Thr

195 200 205

15

Ala Gly Gly Gly Gly Gly Gly Arg Arg His Ile Arg Ile Arg Ser Leu

210 215 220

20

Lys Ile Glu Leu His Ser Arg Ser Gly His Trp Gln Ser Ile Asp Phe

225 230 235 240

Lys Gln Val Leu His Ser Trp Phe Arg Gln Pro Gln Ser Asn Trp Gly

25 245 250 255

Ile Glu Ile Asn Ala Phe Asp Pro Ser Gly Thr Asp Leu Ala Val Thr

260 265 270

30

Ser Leu Gly Pro Gly Ala Glu Gly Leu His Pro Phe Met Glu Leu Arg

275 280 285

5 Val Leu Glu Asn Thr Lys Arg Ser Arg Arg Asn Leu Gly Leu Asp Cys
290 295 300

10 Asp Glu His Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
305 310 315 320

15 Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
325 330 335

Lys Ala Asn Tyr Cys Ser Gly Gln Cys Glu Tyr Met Phe Met Gln Lys
340 345 350

20 Tyr Pro His Thr His Leu Val Gln Gln Ala Asn Pro Arg Gly Ser Ala
355 360 365

25 Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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Val Asp Arg Cys Gly Cys Ser

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<213> Homo sapiens

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15 agcggccgc gtgtgcgag cggcgggggc tgggccggtc cggagcccag ggggcggcgg 180

cgccgcgcgc ggcggcgggc gccgcgggc gactcttgc caggctgccc gcgcgcgcgc 240

tgtcccgcc gccgcggtc cccgggccc cgcgcgcgc cgcgcgcgc gctccggtt 300

20 caggaacgc tcggtgtgc cgcaccatt catgatgtc cttaccga gccggccgc 360

gagggctcc gccggggcag ccgctgttc cgcctcggc catggtcgc cggacacat 420

25 caccggttc acagaccag cagccaaga cgaatcgga gccgaaacag gccagagctt 480

cctgttcgac gtgtccagc ttaacgac agacaggtg gtgggtcgc agctgcgcgt 540

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30 gctgtccag tccccgggc cgcgcgcgc gccacgctg ctgtactgc gggcagctga 660

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5 ggcagaggag cgcgcgggtgc tagtcgtctc ctccgcacg cagaggaaag agagcttatt 900

ccgggagatc cgcgccagg cccgcgcgt cggggcgcgt ctggcctcag agccgtgcc 960

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<210> 36

30 <211> 453

<212> PRT

<213> Homo sapiens

<400> 36

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15	Gly Ala Gly Pro Val Arg Ser Pro Gly Gly Gly Gly Gly Gly Gly Gly
	35 40 45
20	Gly Gly Gly Gly Gly Arg Thr Leu Ala Gln Ala Ala Gly Ala Ala Ala
	50 55 60
25	Val Pro Ala Ala Ala Val Pro Arg Ala Arg Ala Ala Arg Arg Ala Ala
	65 70 75 80
30	Gly Ser Gly Phe Arg Asn Gly Ser Val Val Pro His His Phe Met Met
	85 90 95
	Ser Leu Tyr Arg Ser Leu Ala Gly Arg Ala Pro Ala Gly Ala Ala Ala
	100 105 110
	Val Ser Ala Ser Gly His Gly Arg Ala Asp Thr Ile Thr Gly Phe Thr

115 120 125

Asp Gln Ala Thr Gln Asp Glu Ser Ala Ala Glu Thr Gly Gln Ser Phe

5 130 135 140

Leu Phe Asp Val Ser Ser Leu Asn Asp Ala Asp Glu Val Val Gly Ala

10 145 150 155 160

Glu Leu Arg Val Leu Arg Arg Gly Ser Pro Glu Ser Gly Pro Gly Ser

15 165 170 175

Trp Thr Ser Pro Pro Leu Leu Leu Leu Ser Thr Cys Pro Gly Ala Ala

180 185 190

Arg Ala Pro Arg Leu Leu Tyr Ser Arg Ala Ala Glu Pro Leu Val Gly

20 195 200 205

Gln Arg Trp Glu Ala Phe Asp Val Ala Asp Ala Met Arg Arg His Arg

25 210 215 220

Arg Glu Pro Arg Pro Pro Arg Ala Phe Cys Leu Leu Leu Arg Ala Val

30 225 230 235 240

Ala Gly Pro Val Pro Ser Pro Leu Ala Leu Arg Arg Leu Gly Phe Gly

	245	250	255
	Trp Pro Gly Gly Gly Gly Ser Ala Ala Glu Glu Arg Ala Val Leu Val		
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	Val Ser Ser Arg Thr Gln Arg Lys Glu Ser Leu Phe Arg Glu Ile Arg		
10	275	280	285
	Ala Gln Ala Arg Ala Leu Gly Ala Ala Leu Ala Ser Glu Pro Leu Pro		
15	290	295	300
	Asp Pro Gly Thr Gly Thr Ala Ser Pro Arg Ala Val Ile Gly Gly Arg		
	305	310	315 320
20	Arg Arg Arg Arg Thr Ala Leu Ala Gly Thr Arg Thr Ala Gln Gly Ser		
	325	330	335
	Gly Gly Gly Ala Gly Arg Gly His Gly Arg Arg Gly Arg Ser Arg Cys		
25	340	345	350
	Ser Arg Lys Pro Leu His Val Asp Phe Lys Glu Leu Gly Trp Asp Asp		
30	355	360	365
	Trp Ile Ile Ala Pro Leu Asp Tyr Glu Ala Tyr His Cys Glu Gly Leu		

370 375 380

Cys Asp Phe Pro Leu Arg Ser His Leu Glu Pro Thr Asn His Ala Ile
5 385 390 395 400

Ile Gln Thr Leu Leu Asn Ser Met Ala Pro Asp Ala Ala Pro Ala Ser
10 405 410 415

Cys Cys Val Pro Ala Arg Leu Ser Pro Ile Ser Ile Leu Tyr Ile Asp
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Ala Ala Asn Asn Val Val Tyr Lys Gln Tyr Glu Asp Met Val Val Glu
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Ala Cys Gly Cys Arg
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<210> 37
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<210> 38

<211> 830

<212> PRT

<213> Homo sapiens

<400> 38

Met Asp Thr Pro Arg Val Leu Leu Ser Ala Val Phe Leu Ile Ser Phe

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Ser Ser Ala Glu Leu Gly Ser Thr Lys Gly Met Arg Ser Arg Lys Glu

35 40 45

10

Gly Lys Met Gln Arg Ala Pro Arg Asp Ser Asp Ala Gly Arg Glu Gly

50 55 60

15

Gln Glu Pro Gln Pro Arg Pro Gln Asp Glu Pro Arg Ala Gln Gln Pro

65 70 75 80

20

Arg Ala Gln Glu Pro Pro Gly Arg Gly Pro Arg Val Val Pro His Glu

85 90 95

Tyr Met Leu Ser Ile Tyr Arg Thr Tyr Ser Ile Ala Glu Lys Leu Gly

25 100 105 110

Ile Asn Ala Ser Phe Phe Gln Ser Ser Lys Ser Ala Asn Thr Ile Thr

115 120 125

30

Ser Phe Val Asp Arg Gly Leu Ala Ser Pro Pro Pro Ser Pro Pro Leu

130 135 140

Arg Cys Met Pro Pro Ile Leu Glu Ile Glu Gly Leu His Val His
5 145 150 155 160

Pro Val Trp Gly Gly Leu Cys Ser Arg Ala Lys Ala Ser Arg Leu Ala
10 165 170 175

Gly Pro Arg Ser Thr Ser Thr Ala Thr Thr Pro Glu Cys Gly Gly Gly
180 185 190

15 Leu Gly Met Arg Ala Val His Ser Gly Arg Arg Arg Cys Met Thr Thr
195 200 205

20 Arg Thr Ala Ser Ser Lys Ala Leu Ser Pro Pro Arg Leu Arg Val Leu
210 215 220

Arg Lys Cys Glu Glu Arg Gln Phe Val Asp Trp Glu Gly Ala Phe Val
25 225 230 235 240

Glu Asp Leu Val Ala Pro Leu Gly Ser Arg Val Thr Tyr Arg Ser Thr
30 245 250 255

Val Gln Gly Arg Pro Pro Leu Ala Asn Pro Pro Glu Thr Lys Gly Val

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	Ser Cys Pro His Lys Arg Thr Pro Lys Trp Gly Lys Lys Arg Ile Leu		
	290	295	300
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	Arg Pro Leu Arg Ala Ala Leu Pro Ala Arg Glu Ser Phe Gly Leu Ala		
	305	310	315 320
15			
	Gln Gly Leu Ser Leu Ala Leu Thr Pro Ala Glu Glu Glu Thr Cys Lys		
	325	330	335
20	Lys Gly Trp Ile Leu Asp Val Ala Gly Val Glu Val Ile Cys Ser Pro		
	340	345	350
	Gly Thr Val Gly Gly Thr Ala Val Val Thr Gly Pro His Arg Thr Glu		
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	Lys Asn Arg Asp Asp Glu His Leu Ser Ser Thr His Phe Trp Asn Leu		
	370	375	380
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	Val Glu Arg Ser Gly Pro Gln Gly Leu Lys Ser Arg Glu Leu Asp Phe		

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	Lys Gly Ser Gln Glu Lys Asp Ser Cys Gln Glu Thr Lys Ile Ser Pro			
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	Thr Pro Leu Thr Glu Val Ser Arg Gln Gln Ala Lys Cys Leu Gln Gly			
	435	440	445	
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	Asn Ser Ala Trp Cys Cys Ile His Ser Pro Gly Trp Met Pro Pro Leu			
	450	455	460	
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	Ser Tyr Phe Cys Asp Ala Gly Leu Asp Arg Leu Gly His Val Arg Lys			
	465	470	475	480
	Ser Glu Pro Ala Ser Ala Thr Val Ser Pro Glu Tyr Lys Leu Gly Val			
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	Ala Glu Ala Pro Glu Pro Val Pro Pro Gly Tyr Ile Trp Thr Asp Asp			
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	Leu Ser His Thr Pro Leu Arg Arg Gln Lys Tyr Leu Phe Asp Val Ser			

515 520 525

Met Leu Ser Asp Lys Glu Glu Leu Val Gly Ala Glu Leu Arg Leu Phe

5 530 535 540

Arg Gln Ala Pro Ser Ala Pro Trp Gly Pro Pro Ala Gly Pro Leu His

10 545 550 555 560

Val Gln Leu Phe Pro Cys Leu Ser Pro Leu Leu Leu Asp Ala Arg Thr

15 565 570 575

Leu Asp Pro Gln Gly Ala Pro Pro Ala Gly Trp Glu Val Phe Asp Val

20 580 585 590

Trp Gln Gly Leu Arg His Gln Pro Trp Lys Gln Leu Cys Leu Glu Leu

25 595 600 605

Arg Ala Ala Trp Gly Glu Leu Asp Ala Gly Glu Ala Glu Ala Arg Ala

30 610 615 620

Arg Gly Pro Gln Gln Pro Pro Pro Pro Asp Leu Arg Ser Leu Gly Phe

35 625 630 635 640

Gly Arg Arg Val Arg Pro Pro Gln Glu Arg Ala Leu Leu Val Val Phe

645 650 655

Thr Arg Ser Gln Arg Lys Asn Leu Phe Ala Glu Met Arg Glu Gln Leu

5 660 665 670

Gly Ser Ala Glu Ala Ala Gly Pro Gly Ala Gly Ala Glu Gly Ser Trp

675 680 685
10

Pro Pro Pro Ser Gly Ala Pro Asp Ala Arg Pro Trp Leu Pro Ser Pro

690 695 700
15

Gly Arg Arg Arg Arg Arg Thr Ala Phe Ala Ser Arg His Gly Lys Arg

705 710 715 720

His Gly Lys Lys Ser Arg Leu Arg Cys Ser Lys Lys Pro Leu His Val

725 730 735
20

Asn Phe Lys Glu Leu Gly Trp Asp Asp Trp Ile Ile Ala Pro Leu Glu

740 745 750
25

Tyr Glu Ala Tyr His Cys Glu Gly Val Cys Asp Phe Pro Leu Arg Ser

755 760 765
30

His Leu Glu Pro Thr Asn His Ala Ile Ile Gln Thr Leu Met Asn Ser

770 775 780

Met Asp Pro Gly Ser Thr Pro Pro Ser Cys Cys Val Pro Thr Lys Leu

5 785 790 795 800

Thr Pro Ile Ser Ile Leu Tyr Ile Asp Ala Gly Asn Asn Val Val Tyr

805 810 815

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Lys Gln Tyr Glu Asp Met Val Val Glu Ser Cys Gly Cys Arg

820 825 830

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<210> 39

<211> 1179

<212> DNA

<213> Homo sapiens

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<400> 39

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<213> Homo sapiens

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Met Val Leu Leu Ser Ile Leu Arg Ile Leu Phe Leu Cys Glu Leu Val

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10

Leu Phe Met Glu His Arg Ala Gln Met Ala Glu Gly Gly Gln Ser Ser

20 25 30

15

Ile Ala Leu Leu Ala Glu Ala Pro Thr Leu Pro Leu Ile Glu Glu Leu

35 40 45

20

Leu Glu Glu Ser Pro Gly Glu Gln Pro Arg Lys Pro Arg Leu Leu Gly

50 55 60

25

His Ser Leu Arg Tyr Met Leu Glu Leu Tyr Arg Arg Ser Ala Asp Ser

65 70 75 80

30

His Gly His Pro Arg Glu Asn Arg Thr Ile Gly Ala Thr Met Val Arg

85 90 95

Leu Val Lys Pro Leu Thr Ser Val Ala Arg Pro His Arg Gly Thr Trp

100 105 110

His Ile Gln Ile Leu Gly Phe Pro Leu Arg Pro Asn Arg Gly Leu Tyr
115 120 125

5 Gln Leu Val Arg Ala Thr Val Val Tyr Arg His His Leu Gln Leu Thr
130 135 140

10 Arg Phe Asn Leu Ser Cys His Val Glu Pro Trp Val Gln Lys Asn Pro
145 150 155 160

15 Thr Asn His Phe Pro Ser Ser Glu Gly Asp Ser Ser Lys Pro Ser Leu
165 170 175

Met Ser Asn Ala Trp Lys Glu Met Asp Ile Thr Gln Leu Val Gln Gln
180 185 190

20 Arg Phe Trp Asn Asn Lys Gly His Arg Ile Leu Arg Leu Arg Phe Met
195 200 205

25 Cys Gln Gln Gln Lys Asp Ser Gly Gly Leu Glu Leu Trp His Gly Thr
210 215 220

30 Ser Ser Leu Asp Ile Ala Phe Leu Leu Leu Tyr Phe Asn Asp Thr His
225 230 235 240

Lys Ser Ile Arg Lys Ala Lys Phe Leu Pro Arg Gly Met Glu Glu Phe

245 250 255

5

Met Glu Arg Glu Ser Leu Leu Arg Arg Thr Arg Gln Ala Asp Gly Ile

260 265 270

10

Ser Ala Glu Val Thr Ala Ser Ser Ser Lys His Ser Gly Pro Glu Asn

275 280 285

Asn Gln Cys Ser Leu His Pro Phe Gln Ile Ser Phe Arg Gln Leu Gly

15

290 295 300

Trp Asp His Trp Ile Ile Ala Pro Pro Phe Tyr Thr Pro Asn Tyr Cys

305 310 315 320

20

Lys Gly Thr Cys Leu Arg Val Leu Arg Asp Gly Leu Asn Ser Pro Asn

325 330 335

25

His Ala Ile Ile Gln Asn Leu Ile Asn Gln Leu Val Asp Gln Ser Val

340 345 350

30

Pro Arg Pro Ser Cys Val Pro Tyr Lys Tyr Val Pro Ile Ser Val Leu

355 360 365

Met Ile Glu Ala Asn Gly Ser Ile Leu Tyr Lys Glu Tyr Glu Gly Met
370 375 380

5

Ile Ala Glu Ser Cys Thr Cys Arg
385 390

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<210> 41
<211> 375
<212> DNA
<213> Homo sapiens

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<400> 41
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tggatcattg ctccccctt ctacaccca aactactgta aaggaactg tctccgagta 180

ctacgcgatg gtctcaattc cccaatcac gccattatc agaaccttat caatcagttg 240

gtggaccaga gtgtcccccg gccctcctgt gtcccgata agtatgttc aattagtgtc 300

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cttatgattg aggcaaatgg gagtattttg tacaaggagt atgagggtat gattgctgag 360

tcttgtaacat gcaga 375

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<210> 42
<211> 125

<212> PRT

<213> Homo sapiens

<400> 42

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Gln Ala Asp Gly Ile Ser Ala Glu Val Thr Ala Ser Ser Ser Lys His

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Ser Gly Pro Glu Asn Asn Gln Cys Ser Leu His Pro Phe Gln Ile Ser

20 25 30

15

Phe Arg Gln Leu Gly Trp Asp His Trp Ile Ile Ala Pro Pro Phe Tyr

35 40 45

20

Thr Pro Asn Tyr Cys Lys Gly Thr Cys Leu Arg Val Leu Arg Asp Gly

50 55 60

25

Leu Asn Ser Pro Asn His Ala Ile Ile Gln Asn Leu Ile Asn Gln Leu

65 70 75 80

30

Val Asp Gln Ser Val Pro Arg Pro Ser Cys Val Pro Tyr Lys Tyr Val

85 90 95

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120

125

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<210> 43

<211> 1744

<212> DNA

<213> Homo sapiens

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<400> 43

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ctggcgtaaa tgctgagcct ctaccgcgac ccgctgccga gggcagacat catccgcage 180

ctacaggcag aagatgtggc agtggatggg cagaactgga cgtttgcttt tgactctcc 240

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ttctgagcc aacaagagga tctggcatgg gctgagctcc ggtgcagct gtccagcct 300

gtggacctcc cactgaggg ctcacttgc attgagattt tccaccagcc aaagcccgac 360

acagagcagg ctccagacag ctgcttagag cggtttcaga tggacctatt cactgtcact 420

25

ttgtccagg tcacctttc ctgggcagc atggttttgg aggtgaccag gcctctctcc 480

aagtggctga agcgcctgg ggcctggag aagcagatgt ccagggtagc tggagagtgc 540

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tggccgggc cccccacac gcctgcacc aatgtctcc ttatgtcta ctccaacctc 600

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5 tggggctcct ggatcatcta cccaagcag tacaacgcct atcgtgtga gggcgagtgt 840
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gttctctgct aatgagctgt acaacaataa agccattgtc tagttaaaaa aaaaaaaaaa 1680

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5

aaaa

1744

<210> 44

10

<211> 347

<212> PRT

<213> Homo sapiens

<400> 44

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Met His Ala His Cys Leu Pro Phe Leu Leu His Ala Trp Trp Ala Leu

1 5 10 15

20

Leu Gln Ala Gly Ala Ala Thr Val Ala Thr Ala Leu Leu Arg Thr Arg

20 25 30

Gly Gln Pro Ser Ser Pro Ser Pro Leu Ala Tyr Met Leu Ser Leu Tyr

25

35 40 45

Arg Asp Pro Leu Pro Arg Ala Asp Ile Ile Arg Ser Leu Gln Ala Glu

50 55 60

30

Asp Val Ala Val Asp Gly Gln Asn Trp Thr Phe Ala Phe Asp Phe Ser

65 70 75 80

5 Phe Leu Ser Gln Gln Glu Asp Leu Ala Trp Ala Glu Leu Arg Leu Gln
 85 90 95

10 Leu Ser Ser Pro Val Asp Leu Pro Thr Glu Gly Ser Leu Ala Ile Glu
 100 105 110

15 Ile Phe His Gln Pro Lys Pro Asp Thr Glu Gln Ala Ser Asp Ser Cys
 115 120 125

20 Leu Glu Arg Phe Gln Met Asp Leu Phe Thr Val Thr Leu Ser Gln Val
 130 135 140

25 Thr Phe Ser Leu Gly Ser Met Val Leu Glu Val Thr Arg Pro Leu Ser
 145 150 155 160

30 Lys Trp Leu Lys Arg Pro Gly Ala Leu Glu Lys Gln Met Ser Arg Val
 165 170 175

35 Ala Gly Glu Cys Trp Pro Arg Pro Pro Thr Pro Pro Ala Thr Asn Val
 180 185 190

40 Leu Leu Met Leu Tyr Ser Asn Leu Ser Gln Glu Gln Arg Gln Leu Gly

195 200 205

5 Gly Ser Thr Leu Leu Trp Glu Ala Glu Ser Ser Trp Arg Ala Gln Glu
210 215 220

10 Gly Gln Leu Ser Trp Glu Trp Gly Lys Arg His Arg Arg His His Leu
225 230 235 240

15 Pro Asp Arg Ser Gln Leu Cys Arg Lys Val Lys Phe Gln Val Asp Phe
245 250 255

20 Asn Leu Ile Gly Trp Gly Ser Trp Ile Ile Tyr Pro Lys Gln Tyr Asn
260 265 270

25 Ala Tyr Arg Cys Glu Gly Glu Cys Pro Asn Pro Val Gly Glu Glu Phe
275 280 285

30 His Pro Thr Asn His Ala Tyr Ile Gln Ser Leu Leu Lys Arg Tyr Gln
290 295 300

35 Pro His Arg Val Pro Ser Thr Cys Cys Ala Pro Val Lys Thr Lys Pro
305 310 315 320

40 Leu Ser Met Leu Tyr Val Asp Asn Gly Arg Val Leu Leu Asp His His

325 330 335

Lys Asp Met Ile Val Glu Glu Cys Gly Cys Leu

5 340 345

<210> 45

<211> 504

10 <212> DNA

<213> Homo sapiens

<400> 45

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cgggcccagg agggacagct gtcctgggag tggggcaaga ggcaccgtcg acatcacttg 180

20 ccagacagaa gtcaactgtg tcggaaggtc aagtccagg tggacttcaa cctgatcgga 240

tggggctcct ggatcatcta cccaagcag tacaacgcct atcgctgtga gggcgagtgt 300

25 cctaatectg ttggggagga gtttcatccg accaaccatg catacatcca gagtctgtctg 360

aaacgttacc agccccaccg agtcccttcc acttgttgtg cccagtgaa gaccaagccg 420

ctgagcatgc tgtatgtgga taatggcaga gtgtctctag atcaccataa agacatgate 480

30 gtggaagaat gtgggtgcct ctga 504

<210> 46

<211> 167

<212> PRT

<213> Homo sapiens

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<400> 46

Trp Pro Arg Pro Pro Thr Pro Pro Ala Thr Asn Val Leu Leu Met Leu

1 5 10 15

10

Tyr Ser Asn Leu Ser Gln Glu Gln Arg Gln Leu Gly Gly Ser Thr Leu

20 25 30

15

Leu Trp Glu Ala Glu Ser Ser Trp Arg Ala Gln Glu Gly Gln Leu Ser

35 40 45

20

Trp Glu Trp Gly Lys Arg His Arg Arg His His Leu Pro Asp Arg Ser

50 55 60

25

Gln Leu Cys Arg Lys Val Lys Phe Gln Val Asp Phe Asn Leu Ile Gly

65 70 75 80

30

Trp Gly Ser Trp Ile Ile Tyr Pro Lys Gln Tyr Asn Ala Tyr Arg Cys

85 90 95

Glu Gly Glu Cys Pro Asn Pro Val Gly Glu Glu Phe His Pro Thr Asn

100 105 110

His Ala Tyr Ile Gln Ser Leu Leu Lys Arg Tyr Gln Pro His Arg Val

5 115 120 125

Pro Ser Thr Cys Cys Ala Pro Val Lys Thr Lys Pro Leu Ser Met Leu

10 130 135 140

Tyr Val Asp Asn Gly Arg Val Leu Leu Asp His His Lys Asp Met Ile

145 150 155 160
15

Val Glu Glu Cys Gly Cys Leu

165

20 <210> 47

<211> 1101

<212> DNA

<213> Homo sapiens

25 <400> 47

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30 cccaccctgg acagggccga catggaggag ctggtcatcc ccaccacgt gagggcccag 180

tacgtggccc tgctgcagcg cagccaaggg gaccgtccc ggggaaagag gttcagccag 240

agcttccgag aggtggccgg caggttcctg gcggtggagg ccagcacaca cctgctggtg 300

ttcgcatgg agcagcggtt gccgcccaac agcgagctgg tgcaggcgt gtgcggctc 360

5 ttccaggagc cgggtcccaa ggccgcgtg cacaggcacg ggccggctgt cccgcgcagc 420

gcccggggccc gggtgaccgt cgagtggctg cgcgtccgg acgacggctc caaccgcacc 480

10 tccctcatcg actccaggtt ggtgtccgtc cagcagagcg gctggaaggc cttegacgtg 540

accgagggccg tgaacttctg gcagcagctg agccggcccc ggcagccgt gtgtctacag 600

gtgtcgggtc agagggagca tctgggcccc ctggcgctcg gcgccacaa gtgggtccgc 660

15 tttgctcgc agggggcgcc agccgggctt ggggagcccc agctggagct gcacacctg 720

gaccttgggg actatggagc tcaggcgac tgtgacctg aagcaccaat gaccgagggc 780

20 acccgctgt gccgccagga gatgtacatt gacctgcagg ggatgaagt ggccgagaac 840

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ccggagggccc tggccttcaa gtggccgtt ctggggctc gacagtgcac cgcctcggag 960

25 actgcctcgc tgcccatgat cgtcagcacc aaggaggag gcaggaccag gccccaggtg 1020

gtcagcctgc ccaacatgag ggtgcagaag tgcagctgtg cctcggatgg tgcgctcgtg 1080

30 ccaaggagc tccagccata g 1101

<210> 48

<211> 366

<212> PRT

<213> Homo sapiens

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<400> 48

Met Gln Pro Leu Trp Leu Cys Trp Ala Leu Trp Val Leu Pro Leu Ala
1 5 10 15

10

Ser Pro Gly Ala Ala Leu Thr Gly Glu Gln Leu Leu Gly Ser Leu Leu
20 25 30

15

Arg Gln Leu Gln Leu Lys Glu Val Pro Thr Leu Asp Arg Ala Asp Met
35 40 45

20

Glu Glu Leu Val Ile Pro Thr His Val Arg Ala Gln Tyr Val Ala Leu
50 55 60

25

Leu Gln Arg Ser His Gly Asp Arg Ser Arg Gly Lys Arg Phe Ser Gln
65 70 75 80

30

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

His Leu Leu Val Phe Gly Met Glu Gln Arg Leu Pro Pro Asn Ser Glu

	100	105	110
	Leu Val Gln Ala Val Leu Arg Leu Phe Gln Glu Pro Val Pro Lys Ala		
5	115	120	125
	Ala Leu His Arg His Gly Arg Leu Ser Pro Arg Ser Ala Arg Ala Arg		
10	130	135	140
	Val Thr Val Glu Trp Leu Arg Val Arg Asp Asp Gly Ser Asn Arg Thr		
	145	150	155 160
15	Ser Leu Ile Asp Ser Arg Leu Val Ser Val His Glu Ser Gly Trp Lys		
	165	170	175
	Ala Phe Asp Val Thr Glu Ala Val Asn Phe Trp Gln Gln Leu Ser Arg		
20	180	185	190
	Pro Arg Gln Pro Leu Leu Leu Gln Val Ser Val Gln Arg Glu His Leu		
25	195	200	205
	Gly Pro Leu Ala Ser Gly Ala His Lys Leu Val Arg Phe Ala Ser Gln		
	210	215	220
30	Gly Ala Pro Ala Gly Leu Gly Glu Pro Gln Leu Glu Leu His Thr Leu		

225 230 235 240

Asp Leu Gly Asp Tyr Gly Ala Gln Gly Asp Cys Asp Pro Glu Ala Pro

5 245 250 255

Met Thr Glu Gly Thr Arg Cys Cys Arg Gln Glu Met Tyr Ile Asp Leu

260 265 270

10

Gln Gly Met Lys Trp Ala Glu Asn Trp Val Leu Glu Pro Pro Gly Phe

275 280 285

15

Leu Ala Tyr Glu Cys Val Gly Thr Cys Arg Gln Pro Pro Glu Ala Leu

290 295 300

20

Ala Phe Lys Trp Pro Phe Leu Gly Pro Arg Gln Cys Ile Ala Ser Glu

305 310 315 320

Thr Ala Ser Leu Pro Met Ile Val Ser Ile Lys Glu Gly Gly Arg Thr

25 325 330 335

Arg Pro Gln Val Val Ser Leu Pro Asn Met Arg Val Gln Lys Cys Ser

340 345 350

30

Cys Ala Ser Asp Gly Ala Leu Val Pro Arg Arg Leu Gln Pro

355 360 365

<210> 49

5 <211> 1098

<212> DNA

<213> Homo sapiens

<400> 49

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cccgtactgg acagggccga catggagaag ctggctatcc ccgcccacgt gagggcccag 180

15 tatgtagtcc tgctgcggcg cagccacggg gaccgtccc gcggaaagag gtfcagccag 240

agcttcagag aggtggccgg caggttcctg gcgtcggagg ccagcacaca cctgtgtgtg 300

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gcccaggccc gggtgaccgt cgagtggctg cgcgtcccg acgacggctc caaccgcacc 480

25 tccctcatcg actccaggct ggtgtccgtc cagcagagcg gctggaaggc ctfcagctg 540

accgaggccg tgaacttctg gcagcagctg agccggcccc ggcagccgt gctgtacag 600

30 gtgtcgtg agagggagca tctgggccc ctggcgtccg gcgccacaa gctgtccgc 660

tttgctcgc agggggcgcc agccgggctt ggggagcccc agctggagct gcacacctg 720

gacctcaggg actatggagc tcagggcgac tgtgacctg aagcaccaat gaccgagggc 780
accgctgct gccgccagga gatgtacatt gacctgcagg ggatgaagtg ggccaagaac 840
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aggaggetcc agccatag 1098
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<210> 50
<211> 365
<212> PRT
20 <213> Homo sapiens

<400> 50

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25 1 5 10 15

Gly Pro Gly Ala Ala Leu Thr Glu Glu Gln Leu Leu Gly Ser Leu Leu
20 25 30
30

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

35 40 45

5 Glu Lys Leu Val Ile Pro Ala His Val Arg Ala Gln Tyr Val Val Leu
50 55 60

10 Leu Arg Arg Ser His Gly Asp Arg Ser Arg Gly Lys Arg Phe Ser Gln
65 70 75 80

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

15 His Leu Leu Val Phe Gly Met Glu Gln Arg Leu Pro Pro Asn Ser Glu
100 105 110

20 Leu Val Gln Ala Val Leu Arg Leu Phe Gln Glu Pro Val Pro Lys Ala
115 120 125

25 Ala Leu His Arg His Gly Arg Leu Ser Pro Arg Ser Ala Gln Ala Arg
130 135 140

30 Val Thr Val Glu Trp Leu Arg Val Arg Asp Asp Gly Ser Asn Arg Thr
145 150 155 160

Ser Leu Ile Asp Ser Arg Leu Val Ser Val His Glu Ser Gly Trp Lys

	165	170	175
	Ala Phe Asp Val Thr Glu Ala Val Asn Phe Trp Gln Gln Leu Ser Arg		
5	180	185	190
	Pro Arg Gln Pro Leu Leu Leu Gln Val Ser Val Gln Arg Glu His Leu		
10	195	200	205
	Gly Pro Leu Ala Ser Gly Ala His Lys Leu Val Arg Phe Ala Ser Gln		
15	210	215	220
	Gly Ala Pro Ala Gly Leu Gly Glu Pro Gln Leu Glu Leu His Thr Leu		
	225	230	235 240
20	Asp Leu Arg Asp Tyr Gly Ala Gln Gly Asp Cys Asp Pro Glu Ala Pro		
	245	250	255
	Met Thr Glu Gly Thr Arg Cys Cys Arg Gln Glu Met Tyr Ile Asp Leu		
25	260	265	270
	Gln Gly Met Lys Trp Ala Lys Asn Trp Val Leu Glu Pro Pro Gly Phe		
30	275	280	285
	Leu Ala Tyr Glu Cys Val Gly Thr Cys Gln Gln Pro Pro Glu Ala Leu		

290 295 300

Ala Phe Asn Trp Pro Phe Leu Gly Pro Arg Gln Cys Ile Ala Ser Glu
5 305 310 315 320

Thr Ala Ser Leu Pro Met Ile Val Ser Ile Lys Glu Gly Gly Arg Arg
10 325 330 335

Pro Gln Val Val Ser Leu Pro Asn Met Arg Val Gln Lys Cys Ser Cys
15 340 345 350

Ala Ser Asp Gly Ala Leu Val Pro Arg Arg Leu Gln Pro
355 360 365

20 <210> 51
<211> 2291
<212> DNA
<213> Homo sapiens

25 <400> 51
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30 gatcaaagge aggcgatact tctgttgcc gggacgtat atataacgtg atgagcgcac 180
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cggggaccac aatgaacaag ttgctgtgct gcegetegt gttctggac atctccatta 300

agtggaacac ccaggaaacg ttctctcaa agtacctca ttatgacgaa gaaacctctc 360

5 atcagctgtt gtgtgacaaa tgcctctctg gtacctacct aaaacaacac tgtacagcaa 420

agtggaagac cgtgtgccc ccttgccctg accactacta cacagacagc tggcacacca 480

10 gtgacgagtg tctatactgc agccccgtgt gcaaggagct gcagtacgtc aagcaggagt 540

gcaatgcac ccacaaccgc gtgtgcaat gcaaggaagg gcgtacctt gagatagagt 600

tctgcttgaa acataggagc tgccctctg gatttggagt ggtgcaagct ggaaccccag 660

15 agcgaaatac agtttgcaa agatgtccag atgggttctt ctcaaatgag acgtcatcta 720

aagcaccctg tagaaaacac acaattgca gtgtctttgg tctctgcta actcagaag 780

20 gaaatgcaac acacgacaac atatgttccg gaaacagtga atcaactcaa aaatgtggaa 840

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ctaactggct tagtgtcttg gtagacaatt tgctggcac caaagtaa acgcagagagt 960

25 tagagaggat aaaacggcaa cacagctcac aagaacagac ttccagctg ctgaagttat 1020

ggaaacatca aaacaagac caagatatag tcaagaagat catccaagat attgacctct 1080

30 gtgaaaacag cgtgcagcgg cacattggac atgctaacct caccttcgag cagcttcgta 1140

gcttgatgga aagcttaccg ggaaagaaag tgggagcaga agacattgaa aaaacaataa 1200

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5 tteccaaaac tgtcactcag agtctaaaga agaccatcag gttccttcac agcttcacaa 1380

tgtacaaatt gtatcagaag ttatttttag aaatgatagg taaccaggtc caatcagtaa 1440

10 aaataagctg cttataactg gaaatggcca ttgagctgtt tectcacaat tggcgagatc 1500

ccatggatga gtaaactgtt tctcaggcac ttgaggcttt cagtgatatc tttctcatta 1560

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15 atctctcca ataaaccca aatgggtaat ccaactgtca gatctggatc gttatctact 1680

gactatattt tcecttatta ctgcttcag taattcaact ggaaattaaa aaaaaaaaaac 1740

20 tagactccat tgtgccttac taaatatggg aatgtctaac ttaaataagct ttgagatttc 1800

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tctgtaacac tattacagta ttgctattta tattcattca gatataagat ttgtacatat 1920

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tataaattat ctgaatatta gatgctctga gaaattgaat gtaccttatt taaaagattt 2220

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5

aaaaaaaaa a

2291

<210> 52

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<211> 401

<212> PRT

<213> Homo sapiens

<400> 52

15

Met Asn Lys Leu Leu Cys Cys Ala Leu Val Phe Leu Asp Ile Ser Ile

1 5 10 15

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Lys Trp Thr Thr Gln Glu Thr Phe Pro Pro Lys Tyr Leu His Tyr Asp

20 25 30

Glu Glu Thr Ser His Gln Leu Leu Cys Asp Lys Cys Pro Pro Gly Thr

25

35 40 45

Tyr Leu Lys Gln His Cys Thr Ala Lys Trp Lys Thr Val Cys Ala Pro

50 55 60

30

Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His Thr Ser Asp Glu Cys

	195	200	205
	Phe Ala Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val .		
5	210	215	220
	Asp Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg Ile		
10	225	230	235 240
	Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys Leu		
	245	250	255
15	Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile Ile Gln		
	260	265	270
20	Asp Ile Asp Leu Cys Glu Asn Ser Val Gln Arg His Ile Gly His Ala		
	275	280	285
	Asn Leu Thr Phe Glu Gln Leu Arg Ser Leu Met Glu Ser Leu Pro Gly		
25	290	295	300
	Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr Ile Lys Ala Cys Lys		
30	305	310	315 320
	Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser Leu Trp Arg Ile Lys Asn		

325 330 335

Gly Asp Gln Asp Thr Leu Lys Gly Leu Met His Ala Leu Lys His Ser

5 340 345 350

Lys Thr Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys Lys Thr

10 355 360 365

Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys Leu

15 370 375 380

Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val Lys Ile Ser Cys

385 390 395 400

20 Leu

<210> 53

25 <211> 1014

<212> DNA

<213> Homo sapiens

<400> 53

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tgccctcctg gatttggagt ggtgcaagct ggaaccccag agcgaaatac agtttgcaaa 240
5 agatgtccag atgggttctt ctcaaatgag acgtcatcta aagcacctg tagaaaacac 300
acaaattgca gtgtctttgg tctctgcta actcagaaaag gaaatgcaac acacgacaac 360
10 atatgttccg gaaacagtga atcaactcaa aaatgtggaa tagatgttac cctgtgtgag 420
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caagatatag tcaagaagat catccaagat attgacctct gtgaaaacag cgtgcagcgg 660
20 cacattggac atgetaacct caccttcgag cagcttcgta gcttgatgga aagcttaccg 720
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agtctaaaga agaccatcag gttccttcac agcttcacaa tgtacaaatt gtatcagaag 960
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<210> 54

<211> 338

<212> PRT

<213> Homo sapiens

5

<400> 54

Pro Cys Pro Asp His Tyr Tyr Thr Asp Ser Trp His Thr Ser Asp Glu

1 5 10 15

10

Cys Leu Tyr Cys Ser Pro Val Cys Lys Glu Leu Gln Tyr Val Lys Gln

20 25 30

15

Glu Cys Asn Arg Thr His Asn Arg Val Cys Glu Cys Lys Glu Gly Arg

35 40 45

20

Tyr Leu Glu Ile Glu Phe Cys Leu Lys His Arg Ser Cys Pro Pro Gly

50 55 60

Phe Gly Val Val Gln Ala Gly Thr Pro Glu Arg Asn Thr Val Cys Lys

65 70 75 80

25

Arg Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro

85 90 95

30

Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly Leu Leu Leu Thr Gln

100 105 110

5 Lys Gly Asn Ala Thr His Asp Asn Ile Cys Ser Gly Asn Ser Glu Ser
115 120 125

10 Thr Gln Lys Cys Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe
130 135 140

15 Arg Phe Ala Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu
145 150 155 160

Val Asp Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg
165 170 175

20 Ile Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys
180 185 190

25 Leu Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile Ile
195 200 205

30 Gln Asp Ile Asp Leu Cys Glu Asn Ser Val Gln Arg His Ile Gly His
210 215 220

Ala Asn Leu Thr Phe Glu Gln Leu Arg Ser Leu Met Glu Ser Leu Pro

225 230 235 240

5 Gly Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr Ile Lys Ala Cys
 245 250 255

10 Lys Pro Ser Asp Gln Ile Leu Lys Leu Leu Ser Leu Trp Arg Ile Lys
 260 265 270

15 Asn Gly Asp Gln Asp Thr Leu Lys Gly Leu Met His Ala Leu Lys His
 275 280 285

Ser Lys Thr Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys Lys
290 295 300

20 Thr Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys
305 310 315 320

25 Leu Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val Lys Ile Ser
 325 330 335

Cys Leu

30

<210> 55

<211> 2312

<212> DNA

<213> Homo sapiens

5

<400> 55

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ctccgtccg cccgcagtgc caaccatgac cgcgccagt atgggcccgc tccgcgtgc 180

cttcgtggc ctcctgcgc tctgcagcc gccggccgc gcccagaact gcagcgggc 240

gtgccgggtc ccggacgagc cggcgccgc ctgccgggc ggctgagcc tctgtctgga 300

15

cggctgcgc tctgcgcgc tctgcgcaa gcagctgggc gagctgtga ccgagcgcga 360

cccctgcgc ccgcacaagg gcctctctg tgaattcgc tcccggcca accgcaagat 420

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cggagagtc ttccagagca gctgcaagta ccagtgcac tgctggacg gggcgggtgg 540

ctgcatgcc ctgtgcagca tggacgttc tctcccagc cctgaatgcc cttcccag 600

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gagggtcaag ctgcccgga aatgctgca ggagtgggtg tgtgacgag ccaaggacca 660

aaccgtggt ggccctgcc tccggctta ccactggaa gacacgttg gccagacc 720

30

aactatgatt agagccaact gcctgtcca gaccacagag tggagcgc gtccaagac 780

ctgtgggatg ggcatctcca cccgggttac caatgacaac gcctctgca ggctagagaa 840

gcagagccgc ctgtgcatgg tcaggccttg cgaagctgac ctggaagaga acattaagaa 900

gggcaaaaag tgcacccgta ctcccaaaat ctccaagcct atcaagtttg agctttctgg 960

5 ctgcaccage atgaagacat accgagctaa attctgtgga gtatgtaccg acggccgatg 1020

ctgcaccccc cacagaacca ccacctgcc ggtggagttc aagtgcctg acggcgaggt 1080

10 catgaagaag aacatgatgt tcataagac ctgtgcctgc cattacaact gtcccgaga 1140

caatgacatc ttgaaatcgc tgtactacag gaagatgtac ggagacatgg catgaagcca 1200

gagagtgaga gacattaact cattagactg gaactgaac tgattcacat ctcatttttc 1260

15 cgtaaaaatg attcagtag cacaagttat ttaaactgt ttttctaact gggggaaaag 1320

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agatagctct tatacgagta atatgcctgc tatttgaagt gtaattgaga aggaaaattt 1560

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gtgtgtgtgt gtgtatatat atatatatat gtacagttat ctaagttaat ttaaagttgt 1860

ttgtgccttt ttatttttgt tttaaatget ttgatatttc aatgttagcc tcaatttctg 1920

5 aacaccatag gtagaatgta aagcttgtct gatcgttcaa agcatgaaat ggatacttat 1980

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taatgaacaa atggccttta ttaaaaactg agtgactcta tatagetgat cagtttttcc 2160

acctggaagc atttgtttct actttgatat gactgttttt cggacagttt atttgttgag 2220

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aaaaaaaaa aaaaacgaca gcaacggaat tc 2312

20

<210> 56

<211> 349

<212> PRT

<213> Homo sapiens

25

<400> 56

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	20	25	30		
5	Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser	35	40	45	
10	Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu	50	55	60	
15	Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu	65	70	75	80
20	Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr	85	90	95	
25	Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser	100	105	110	
30	Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp	115	120	125	
	Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro	130	135	140	
	Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys				

	145	150	155	160
	Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly			
5	165	170	175	
	Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro			
	180	185	190	
10				
	Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala			
	195	200	205	
15				
	Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp			
	210	215	220	
20				
	Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg			
	225	230	235	240
	Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys			
25	245	250	255	
	Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly			
	260	265	270	
30				
	Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr			

275 280 285

5 Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
290 295 300

10 Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305 310 315 320

15 Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe
325 330 335

Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340 345

20 <210> 57
<211> 1069
<212> DNA
<213> Homo sapiens

25 <400> 57
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30 ctgtgcaccg agcgcgaccc ctgcgacccg cacaagggcc tcttctgtga cttcggtccc 180

ccggccaacc gcaagatcgg cgtgtgcacc gccaaagatg gtgtccctg catcttcggt 240

5
10
15
20
25
30

ggtaagggtgt accgcagcgg agagtccctc cagagcagct gcaagtacca gtgcacgtgc 300

ctggacgggg eggtgggctg catgccctg tgcagcatgg acgttcgtct gccagccct 360

gactgccctt tcccgaggag ggtcaagctg cccgggaaat gctgcgagga gtgggtgtgt 420

gacgagccca aggaccaaac cgtggttggg cctgccctcg cggttaccg actggaagac 480

acgtttggcc cagaccaaac tatgattaga gccaaactgcc tggtcagac cacagagtgg 540

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tctgcagge tagagaagca gagecgctg tgcattgta ggcttgca agctgacctg 660

gaagagaaca ttaagaaggg caaaaagtgc atccgtact ccaaaatct caagcctatc 720

aagtttgage ttctggctg caccagcatg aagacatacc gagctaaatt ctgtggagta 780

tgtaccgacg gccgatgtg cccccccac agaaccacca ccctgccgt ggagttaag 840

tgcctgacg gcgaggtcat gaagaagaac atgatgtca tcaagacctg tgcctgcat 900

tacaactgtc ccggagacaa tgacatctt gaatcgctgt actacaggaa gatgtacgga 960

gacatggcat gaagccagag agtgagagac attaactcat tagactggaa cttgaactga 1020

ttcacatctc attttccgt aaaaatgatt tcagtagcac aagttattt 1069

<210> 58

<211> 323

<212> PRT

<213> Homo sapiens

<400> 58

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Gln Asn Cys Ser Gly Pro Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg

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10

Cys Pro Ala Gly Val Ser Leu Val Leu Asp Gly Cys Gly Cys Cys Arg

20 25 30

15

Val Cys Ala Lys Gln Leu Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys

35 40 45

20

Asp Pro His Lys Gly Leu Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg

50 55 60

Lys Ile Gly Val Cys Thr Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly

65 70 75 80

25

Gly Thr Val Tyr Arg Ser Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr

85 90 95

30

Gln Cys Thr Cys Leu Asp Gly Ala Val Gly Cys Met Pro Leu Cys Ser

100 105 110

Met Asp Val Arg Leu Pro Ser Pro Asp Cys Pro Phe Pro Arg Arg Val
115 120 125

5

Lys Leu Pro Gly Lys Cys Cys Glu Glu Trp Val Cys Asp Glu Pro Lys
130 135 140

10

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

15

Thr Phe Gly Pro Asp Pro Thr Met Ile Arg Ala Asn Cys Leu Val Gln
165 170 175

20

Thr Thr Glu Trp Ser Ala Cys Ser Lys Thr Cys Gly Met Gly Ile Ser
180 185 190

25

Thr Arg Val Thr Asn Asp Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser
195 200 205

30

Arg Leu Cys Met Val Arg Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile
210 215 220

30

Lys Lys Gly Lys Lys Cys Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile
225 230 235 240

Lys Phe Glu Leu Ser Gly Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys
245 250 255

5

Phe Cys Gly Val Cys Thr Asp Gly Arg Cys Cys Thr Pro His Arg Thr
260 265 270

10

Thr Thr Leu Pro Val Glu Phe Lys Cys Pro Asp Gly Glu Val Met Lys
275 280 285

15

Lys Asn Met Met Phe Ile Lys Thr Cys Ala Cys His Tyr Asn Cys Pro
290 295 300

20

Gly Asp Asn Asp Ile Phe Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly
305 310 315 320

Asp Met Ala

25

<210> 59

<211> 1985

<212> DNA

<213> Homo sapiens

30

<400> 59

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cgtcgccgcg ctgccccgg gctactcctg cgcgccacaa tgagctcccg catcgccagg 180
5 ggcctgcct tagtcgtcac cttctccac ttgaccagge tggcgtctc cacctgcccc 240
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10 gacggctgcg gctgctgtaa ggtctgcgc aagcagctca acgaggactg cagcaaaacg 360
cagccctgcg accacaccaa ggggctggaa tgcaacttcg gcgccagctc caccgtctg 420
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15 caaacgggg aaagtcca gcccaactgt aaacatcagt gcacatgtat tgatggcgcc 540
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25 aagcgctcc ctgttttg aatggagcct cgcctctat acaaccctt acaaggccag 840
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30 tccacacgag ttaccaatga caacctgag tgccgcctg tgaagaaac ccggatttgt 960
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aaataccggc ccaagtaactg cggttcctgc gtggacggcc gatgtgcac gcccagctg 1140

5 accaggactg tgaagatgcg gttccgctgc gaagatgggg agacatttc caagaacgtc 1200

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ccagggcaca cctagacaaa caaggagaa gagtgtcaga atcagaatca tggagaaaat 1380

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15 ggagcattaa ggtatttga aactccaag ggtgtgggtg cggtggaca ctaatgcage 1500

cacgattgga gaatacttg ctcatagta ttggagcaca tgttactgt tcattttga 1560

20 gcttgggag ttgatgactt tctgtttct gttgtaaat tatttctaa gcatatttc 1620

tctagcttt tttctttg gggttctaca gtcgtaaaag agataataag attagtggga 1680

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25 ctgaaggggg acactccatg agtgtctgtg agaggcagct atctgcactc taaactgcaa 1800

acagaaatca ggtgttttaa gactgaatgt tttatttacc aaaatgtage tttggggag 1860

30 ggaggggaaa tgaataactg gaataattg taaatgattt taattttata ttcagtga 1920

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aaaaa

1985

5 <210> 60
 <211> 381
 <212> PRT
 <213> Homo sapiens

10 <400> 60

Met Ser Ser Arg Ile Ala Arg Ala Leu Ala Leu Val Val Thr Leu Leu

1 5 10 15

15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His Cys

20 25 30

20 Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp

35 40 45

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys

25 50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe

65 70 75 80

30

Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu

	85	90	95
	Gly	Arg	Pro
	Cys	Glu	Tyr
	Asn	Ser	Arg
	Ile	Tyr	Gln
	Asn	Gly	Glu
	Ser		
5	100	105	110
	Phe	Gln	Pro
	Asn	Cys	Lys
	His	Gln	Cys
	Thr	Cys	Ile
	Asp	Gly	Ala
	Val		
10	115	120	125
	Gly	Cys	Ile
	Pro	Leu	Cys
	Pro	Gln	Glu
	Leu	Ser	Leu
	Pro	Asn	Leu
	Gly		
15	130	135	140
	Cys	Pro	Asn
	Pro	Arg	Leu
	Val	Lys	Val
	Thr	Gly	Gln
	Cys	Cys	Glu
	Glu		
20	145	150	155
	160		
	Trp	Val	Cys
	Asp	Glu	Asp
	Ser	Ile	Lys
	Asp	Pro	Met
	Glu	Asp	Gln
	Asp		
25	165	170	175
	Gly	Leu	Leu
	Gly	Lys	Glu
	Leu	Gly	Phe
	Asp	Ala	Ser
	Glu	Val	Glu
	Leu		
30	180	185	190
	Thr	Arg	Asn
	Asn	Glu	Leu
	Ile	Ala	Val
	Gly	Lys	Gly
	Ser	Ser	Leu
	Lys		
35	195	200	205
	Arg	Leu	Pro
	Val	Phe	Gly
	Met	Glu	Pro
	Arg	Ile	Leu
	Tyr	Asn	Pro
	Leu		

	210	215	220	
	Gln Gly Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser			
5	225	230	235	240
	Lys Thr Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro			
10	245	250	255	
	Glu Cys Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys			
15	260	265	270	
	Gly Gln Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys			
20	275	280	285	
	Thr Lys Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Leu			
	290	295	300	
	Ser Val Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly			
25	305	310	315	320
	Arg Cys Cys Thr Pro Gln Leu Thr Arg Thr Val Lys Met Arg Phe Arg			
30	325	330	335	
	Cys Glu Asp Gly Glu Thr Phe Ser Lys Asn Val Met Met Ile Gln Ser			

340 345 350

Cys Lys Cys Asn Tyr Asn Cys Pro His Ala Asn Glu Ala Ala Phe Pro

5 355 360 365

Phe Tyr Arg Leu Phe Asn Asp Ile His Lys Phe Arg Asp

10 370 375 380

<210> 61

<211> 2830

<212> DNA

15 <213> Homo sapiens

<400> 61

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agtacagca gcagccgcca gcaccgtcct ggccacggcc ctctctccag ccctacgac 180

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tggctgtgag tgctgtaaga tgtgcgtca gcagcttggg gacaactgca cggaggtgc 360

30 catctgtgac cccacccggg gcctctactg tgaactacag ggggaccgcc cgaggtacgc 420

aataggagtg tgtgcacagg tggtcggtgt gggtgcgtc ctggatgggg tgcgtacaa 480

caacggccag tcctccage ctaactgcaa gtacaactgc acgtgcatcg acggcgcggt 540

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5 gcgcgtgagc atacctggcc actgctgtga gcagtgggta tgtgaggacg acgccaagag 660

gccacgcaag accgcacccc gtgacacagg agccttcgat gctgtgggtg aggtggagge 720

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15 gaagtgtctg gctgtgtacc agccagagge atccatgaac ttacacttg cgggctgcat 960

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5 aagactcttt ggggtccattc agatgaatag atggaatttg gaacaataga ataactctatt 1620

atttgagacc tgccaagagg tactgtaatg ggtaattctg acgtcagegc accaaaacta 1680

10 tectgattec aaatatgtat gcacctcaag gtcacaaac atttgccaag tgagttgaat 1740

agttgcttaa ttttgatttt taatggaaag ttgtatccat taacctgggc attgttgagg 1800

ttaagtttct cttcaccctt acactgtgaa gggtagacat taggtttgtc ccagtcagaa 1860

15 ataaaatttg ataaacattc ctgttgatgg gaaaagcccc cagttaatac tccagagaca 1920

gggaaaggte agccatttc agaaggacca attgactctc acactgaatc agctgctgac 1980

20 tggcagggct ttgggcagtt ggccaggetc ttcttgaat cttctccctt gtctgcttg 2040

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25 cactgaaatg accaagacag gttcaggtag ggggtgtgggt caaaccaaga agtgggtgcc 2220

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30 tttcaggac acatctattg cagagactca ttacacagcc ttctgtctg ctgaccaaatt 2340

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5 agggcctttt ctgtgccaga cattgctctc agtgctttgc atgtattagc tcaactgaatc 2580

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15 aaaaaaaaaa 2830

<210> 62

20 <211> 367

<212> PRT

<213> Homo sapiens

<400> 62

25 Met Arg Trp Phe Leu Pro Trp Thr Leu Ala Ala Val Thr Ala Ala Ala

1 5 10 15

30 Ala Ser Thr Val Leu Ala Thr Ala Leu Ser Pro Ala Pro Thr Thr Met

20 25 30

Asp Phe Thr Pro Ala Pro Leu Glu Asp Thr Ser Ser Arg Pro Gln Phe
35 40 45

5

Cys Lys Trp Pro Cys Glu Cys Pro Pro Ser Pro Pro Arg Cys Pro Leu
50 55 60

10

Gly Val Ser Leu Ile Thr Asp Gly Cys Glu Cys Cys Lys Met Cys Ala
65 70 75 80

Gln Gln Leu Gly Asp Asn Cys Thr Glu Ala Ala Ile Cys Asp Pro His
15 85 90 95

Arg Gly Leu Tyr Cys Asp Tyr Ser Gly Asp Arg Pro Arg Tyr Ala Ile
100 105 110

20

Gly Val Cys Ala Gln Val Val Gly Val Gly Cys Val Leu Asp Gly Val
115 120 125

25

Arg Tyr Asn Asn Gly Gln Ser Phe Gln Pro Asn Cys Lys Tyr Asn Cys
130 135 140

30

Thr Cys Ile Asp Gly Ala Val Gly Cys Thr Pro Leu Cys Leu Arg Val
145 150 155 160

Arg Pro Pro Arg Leu Trp Cys Pro His Pro Arg Arg Val Ser Ile Pro
165 170 175

5 Gly His Cys Cys Glu Gln Trp Val Cys Glu Asp Asp Ala Lys Arg Pro
180 185 190

10 Arg Lys Thr Ala Pro Arg Asp Thr Gly Ala Phe Asp Ala Val Gly Glu
195 200 205

15 Val Glu Ala Trp His Arg Asn Cys Ile Ala Tyr Thr Ser Pro Trp Ser
210 215 220

20 Pro Cys Ser Thr Ser Cys Gly Leu Gly Val Ser Thr Arg Ile Ser Asn
225 230 235 240

25 Val Asn Ala Gln Cys Trp Pro Glu Gln Glu Ser Arg Leu Cys Asn Leu
245 250 255

30 Arg Pro Cys Asp Val Asp Ile His Thr Leu Ile Lys Ala Gly Lys Lys
260 265 270

Cys Leu Ala Val Tyr Gln Pro Glu Ala Ser Met Asn Phe Thr Leu Ala
275 280 285

Gly Cys Ile Ser Thr Arg Ser Tyr Gln Pro Lys Tyr Cys Gly Val Cys
290 295 300

5

Met Asp Asn Arg Cys Cys Ile Pro Tyr Lys Ser Lys Thr Ile Asp Val
305 310 315 320

10

Ser Phe Gln Cys Pro Asp Gly Leu Gly Phe Ser Arg Gln Val Leu Trp
325 330 335

15

Ile Asn Ala Cys Phe Cys Asn Leu Ser Cys Arg Asn Pro Asn Asp Ile
340 345 350

20

Phe Ala Asp Leu Glu Ser Tyr Pro Asp Phe Ser Glu Ile Ala Asn
355 360 365

<210> 63

<211> 1723

<212> DNA

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<213> Homo sapiens

<400> 63

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ctcgggtgtg gaatttgata ttcatgtgac cgggttttat cctcttctt tttcttaaa 180

cattttttt taaaactgta ttgtttctcg ttttaattta tttttgcttg ccattcccca 240

cttgaatcgg gccgacggct tggggagatt gctctacttc cccaaatcac tgtggatttt 300

5 ggaaaccagc agaaagagga aagaggtagc aagagctcca gagagaagtc gaggaagaga 360

gagacgggggt cagagagagc gcgcggggcgt gcgagcagcg aaagcgacag gggcaaagtg 420

10 agtgacctgc ttttgggggt gaccgccgga gcgcggcggtg agccctcccc cttgggatec 480

cgagctgac cagtcgcgt gacggacaga cagacagaca ccgccccag cccagctac 540

cacctctcc ccggccggcg gcggacagtg gacgcggcgg cgagccggcg gcaggggccc 600

15 gagccccgc ccggaggcgg ggtggagggg gtcggggctc gcggcgctgc actgaaactt 660

ttctccaac ttctgggtg ttctccttc ggaggagccg tggtcgcgc gggggaagcc 720

gagccgagcg gagccgcgag aagtgtctagc tcgggccggg aggagccgca gccggaggag 780

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aagccgggct catggacggg tgaggcggcg gtgtgcgcag acagtctcc agccgcgcgc 900

25 gctccccagg ccctggcccc ggctcgggc cggggaggaa gagtagctcg ccgaggcgcc 960

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10 cagcacatag gagagatgag ctctctacag cacaacaaat gtgaatgcag accaaagaaa 1440

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15 aagcatttgt ttgtacaaga tccgcagacg tgtaaattgt cctgcaaaaa cacagactcg 1620

cgttgcaagg cgaggcagct tgagttaaac gaacgtactt gcagatgtga caagccgagg 1680

20 cggcagccg ggcaggagga aggagcctcc ctcagggttt cgg 1723

<210> 64

<211> 215

25 <212> PRT

<213> Homo sapiens

<400> 64

30 Met Asn Phe Leu Leu Ser Trp Val His Trp Ser Leu Ala Leu Leu Leu

1 5 10 15

Tyr Leu His His Ala Lys Trp Ser Gln Ala Ala Pro Met Ala Glu Gly
20 25 30

5

Gly Gly Gln Asn His His Glu Val Val Lys Phe Met Asp Val Tyr Gln
35 40 45

10

Arg Ser Tyr Cys His Pro Ile Glu Thr Leu Val Asp Ile Phe Gln Glu
50 55 60

15

Tyr Pro Asp Glu Ile Glu Tyr Ile Phe Lys Pro Ser Cys Val Pro Leu
65 70 75 80

20

Met Arg Cys Gly Gly Cys Cys Asn Asp Glu Gly Leu Glu Cys Val Pro
85 90 95

25

Thr Glu Glu Ser Asn Ile Thr Met Gln Ile Met Arg Ile Lys Pro His
100 105 110

30

Gln Gly Gln His Ile Gly Glu Met Ser Phe Leu Gln His Asn Lys Cys
115 120 125

Glu Cys Arg Pro Lys Lys Asp Arg Ala Arg Gln Glu Lys Lys Ser Val
130 135 140

Arg Gly Lys Gly Lys Gly Gln Lys Arg Lys Arg Lys Lys Ser Arg Tyr
145 150 155 160

5

Lys Ser Trp Ser Val Pro Cys Gly Pro Cys Ser Glu Arg Arg Lys His
 165 170 175

10

Leu Phe Val Gln Asp Pro Gln Thr Cys Lys Cys Ser Cys Lys Asn Thr
 180 185 190

15

Asp Ser Arg Cys Lys Ala Arg Gln Leu Glu Leu Asn Glu Arg Thr Cys
 195 200 205

20

Arg Cys Asp Lys Pro Arg Arg
 210 215

<210> 65

<211> 1172

<212> DNA

25

<213> Homo sapiens

<400> 65

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tgccctggc caccagagga aagtgggtgc atggatagat gtgtatactc gcgtacctg 180

ccagccccgg gaggtgggtgg tgccttgac tgtggagctc atgggcaccg tggccaaaca 240

gctggtgccc agctgcgtga ctgtgcagcg ctgtggtggc tgetgacctg acgatggcct 300

5 ggagtgtgtg cccactgggc agcaccaagt cgggatgcag atctcatga tccggtacct 360

gagcagtcag ctgggggaga tgccttgga agaacacagc cagtgtgaat gcagacctaa 420

10 aaaaaaggac agtgctgtga agccagacag ggctgccact ccccaccacc gtccccagcc 480

ccgttctgtt cggggtggg actctgccc cggagcacc tcccagctg acatcacca 540

tccactcca gcccaggcc cctctgccc cgtgcaccc agcaccacca ggcacctgac 600

15 ccccggaact gccgtgcgc ctgccagc cgcagcttc tccgttgcca agggcggggc 660

ttagagctca acccagacac ctgcaggctc cggaagctgc gaaggtaga catggcttt 720

20 cagactcagc agggtgactt gctcagagg ctatatcca gtgggggaac aaagaggagc 780

ctggtaaaaa acagccaagc cccaagacc tcagcccagg cagaagctgc tctaggacct 840

gggcctctca gagggctctt ctgccatcc ttgtctcct gaggccatca tcaaacagga 900

25 cagagttgga agaggagact gggaggcagc aagaggggtc acataccagc tcaggggaga 960

atggagtact gtctcagttt ctaaccactc tgtgcaagta agcatcttac aactggctct 1020

30 tctccccctc actaagaaga cccaaacctc tgcataatgg gatttgggct ttggtacaag 1080

aactgtgacc cccaacctg ataaaagaga tggaaggaaa aaaaaaaaaa aaaaaaaaaa 1140

aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa

1172

5

<210> 66

<211> 207

<212> PRT

<213> Homo sapiens

10

<400> 66

Met Ser Pro Leu Leu Arg Arg Leu Leu Leu Ala Ala Leu Leu Gln Leu

1 5 10 15

15

Ala Pro Ala Gln Ala Pro Val Ser Gln Pro Asp Ala Pro Gly His Gln

20 25 30

20

Arg Lys Val Val Ser Trp Ile Asp Val Tyr Thr Arg Ala Thr Cys Gln

35 40 45

Pro Arg Glu Val Val Val Pro Leu Thr Val Glu Leu Met Gly Thr Val

25

50 55 60

Ala Lys Gln Leu Val Pro Ser Cys Val Thr Val Gln Arg Cys Gly Gly

65 70 75 80

30

Cys Cys Pro Asp Asp Gly Leu Glu Cys Val Pro Thr Gly Gln His Gln

85 90 95

5 Val Arg Met Gln Ile Leu Met Ile Arg Tyr Pro Ser Ser Gln Leu Gly
100 105 110

10 Glu Met Ser Leu Glu Glu His Ser Gln Cys Glu Cys Arg Pro Lys Lys
115 120 125

15 Lys Asp Ser Ala Val Lys Pro Asp Arg Ala Ala Thr Pro His His Arg
130 135 140

Pro Gln Pro Arg Ser Val Pro Gly Trp Asp Ser Ala Pro Gly Ala Pro
145 150 155 160

20 Ser Pro Ala Asp Ile Thr His Pro Thr Pro Ala Pro Gly Pro Ser Ala
165 170 175

25 His Ala Ala Pro Ser Thr Thr Ser Ala Leu Thr Pro Gly Pro Ala Ala
180 185 190

30 Ala Ala Ala Asp Ala Ala Ala Ser Ser Val Ala Lys Gly Gly Ala
195 200 205

<210> 67

<211> 2076

<212> DNA

<213> Homo sapiens

5

<400> 67

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gtcgggttc ctgtgaggt ttacctgac accgcgcgc tttccccgc actggtggg 240

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gccaggggg ggctgcgggg aggagcccg gggagagggg ccaggagggg cccgcggcct 360

cgcagggggc cccgcgcgc caccctgcc cccgccagc gaccggtccc ccaccccg 420

20

tcttcacc atgcattgc tgggttctt ctctgtggcg tgttctctgc tcgcctgc 480

gtgtctccc ggctctgcg aggcgcgcgc cgcgcgcgc gccttcgagt ccgactcga 540

cctctcggac gggagcccg acgcggggga ggccacggct tatgaagca aagatctgga 600

25

ggagcagtta cggctgtgt ccagtgtaga tgaactcatg actgtactct acccagaata 660

ttggaaaatg tacaagtgc agctaaggaa aggaggctgg caacataaca gagaacagge 720

30

caacctcaac tcaaggacag aagagactat aaaatttget gcagcacatt ataatacaga 780

gatcttgaag agtattgata atgagtggag aaagactcaa tgcattccac gggaggtgtg 840

tatagatgtg gggaaggagt ttggagtcgc gacaaacacc ttctttaaac ctccatgtgt 900

gtccgtctac agatgtgggg gttgctgcaa tagtgagggg ctgcagtgca tgaacaccag 960

5 cagcagctac ctgagcaaga cggtatttga aattacagtg cctctctctc aaggcccaaa 1020

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10 ttacagacaa gttcattcca ttattagacg ttccctgcca gcaaacctac cacagtgtca 1140

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15 tgacatctgt ggaccaaaca aggagctgga tgaagagacc tgctagtgtg tctgcagagc 1320

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atgtgcctgt gaatgtacag aaagtcaca gaaatgcttg ttaaaaggaa agaagtcca 1560

25 ccaccaaaca tgcagctgtt acagacggcc atgtacgaac cgccagaagg cttgtgagcc 1620

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30 aatgagctaa gattgtactg tttccagtt catcgatttt ctattatgga aaactgtgtt 1740

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aagtctgtct ttctgaacc atgtggataa ctttacagaa atggactgga gctcatctgc 1860

aaaaggcctc ttgtaaagac tggttttctg ccaatgacca aacageccaag attttctct 1920

5 tgtgatttct ttaaaagaat gactatataa tttatttcca ctaaaaatat tgtttctgca 1980

ttcattttta tagcaacaac aattggtaaa actcactgtg atcaatattt ttatatcatg 2040

10 caaaatatgt ttaaaataaa atgaaaattg tattat 2076

<210> 68

<211> 419

15 <212> PRT

<213> Homo sapiens

<400> 68

20 Met His Leu Leu Gly Phe Phe Ser Val Ala Cys Ser Leu Leu Ala Ala

1 5 10 15

Ala Leu Leu Pro Gly Pro Arg Glu Ala Pro Ala Ala Ala Ala Phe

25 20 25 30

Glu Ser Gly Leu Asp Leu Ser Asp Ala Glu Pro Asp Ala Gly Glu Ala

35 40 45

30 Thr Ala Tyr Ala Ser Lys Asp Leu Glu Glu Gln Leu Arg Ser Val Ser

	50	55	60	
	Ser Val Asp Glu Leu Met Thr Val Leu Tyr Pro Glu Tyr Trp Lys Met			
5	65	70	75	80
	Tyr Lys Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln			
	85	90	95	
10				
	Ala Asn Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala			
	100	105	110	
15				
	His Tyr Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys			
	115	120	125	
20				
	Thr Gln Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe			
	130	135	140	
25				
	Gly Val Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr			
	145	150	155	160
30				
	Arg Cys Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr			
	165	170	175	
	Ser Thr Ser Tyr Leu Ser Lys Thr Leu Phe Glu Ile Thr Val Pro Leu			

	180	185	190
	Ser Gln Gly Pro Lys Pro Val Thr Ile Ser Phe Ala Asn His Thr Ser		
5	195	200	205
	Cys Arg Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile		
10	210	215	220
	Ile Arg Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn		
	225	230	235 240
15			
	Lys Thr Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys		
	245	250	255
20	Leu Ala Gln Glu Asp Phe Met Phe Ser Ser Asp Ala Gly Asp Asp Ser		
	260	265	270
	Thr Asp Gly Phe His Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu		
25	275	280	285
	Glu Thr Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys		
30	290	295	300
	Gly Pro His Lys Glu Leu Asp Arg Asn Ser Cys Gln Cys Val Cys Lys		

305 310 315 320

Asn Lys Leu Phe Pro Ser Gln Cys Gly Ala Asn Arg Glu Phe Asp Glu

5 325 330 335

Asn Thr Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro

 340 345 350

10

Leu Asn Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys

 355 360 365

15

Cys Leu Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr

 370 375 380

20

Arg Arg Pro Cys Thr Asn Arg Gln Lys Ala Cys Glu Pro Gly Phe Ser

385 390 395 400

Tyr Ser Glu Glu Val Cys Arg Cys Val Pro Ser Tyr Trp Lys Arg Pro

25 405 410 415

Gln Met Ser

30

<210> 69

<211> 2029

<212> DNA

<213> Homo sapiens

5

<400> 69

gttgggttcc agctttctgt agctgtaagc attggtggcc acaccacctc cttacaaage 60

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10

ttagagtgtt ttctaatttc aggtagaaga catgtccacc ttctgattat ttttgagaa 180

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agtgggtagt ggtgaatggt ttcattgatgt tgtacgtcca gctgggtcag ggtccagta 480

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atcggtccac taggtttgcg gcaactttct atgacattga aacactaaaa gttatagatg 720

30

aagaatggca aagaactcag tgcagcccta gagaaacgtg cgtggagggtg gccagtgage 780

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gctgttgcaa tgaagagagc cttatctgta tgaacaccag cacctcgtac atttccaaac 900

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gaagatccat ccagatccct gaagaagatc gctgttccca ttccaagaaa ctctgtccta 1080

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<210> 70

<211> 354

<212> PRT

<213> Homo sapiens

15

<400> 70

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1 5 10 15

20

Gln Leu Val Gln Gly Ser Ser Asn Glu His Gly Pro Val Lys Arg Ser

20 25 30

25

Ser Gln Ser Thr Leu Glu Arg Ser Glu Gln Gln Ile Arg Ala Ala Ser

35 40 45

30

Ser Leu Glu Glu Leu Leu Arg Ile Thr His Ser Glu Asp Trp Lys Leu

50 55 60

Trp Arg Cys Arg Leu Arg Leu Lys Ser Phe Thr Ser Met Asp Ser Arg
65 70 75 80

5

Ser Ala Ser His Arg Ser Thr Arg Phe Ala Ala Thr Phe Tyr Asp Ile
 85 90 95

10

Glu Thr Leu Lys Val Ile Asp Glu Glu Trp Gln Arg Thr Gln Cys Ser
 100 105 110

15

Pro Arg Glu Thr Cys Val Glu Val Ala Ser Glu Leu Gly Lys Ser Thr
 115 120 125

20

Asn Thr Phe Phe Lys Pro Pro Cys Val Asn Val Phe Arg Cys Gly Gly
 130 135 140

25

Cys Cys Asn Glu Glu Ser Leu Ile Cys Met Asn Thr Ser Thr Ser Tyr
145 150 155 160

30

Ile Ser Lys Gln Leu Phe Glu Ile Ser Val Pro Leu Thr Ser Val Pro
 165 170 175

Glu Leu Val Pro Val Lys Val Ala Asn His Thr Gly Cys Lys Cys Leu
 180 185 190

Pro Thr Ala Pro Arg His Pro Tyr Ser Ile Ile Arg Arg Ser Ile Gln
195 200 205

5
Ile Pro Glu Glu Asp Arg Cys Ser His Ser Lys Lys Leu Cys Pro Ile
210 215 220

10
Asp Met Leu Trp Asp Ser Asn Lys Cys Lys Cys Val Leu Gln Glu Glu
225 230 235 240

15
Asn Pro Leu Ala Gly Thr Glu Asp His Ser His Leu Gln Glu Pro Ala
245 250 255

20
Leu Cys Gly Pro His Met Met Phe Asp Glu Asp Arg Cys Glu Cys Val
260 265 270

25
Cys Lys Thr Pro Cys Pro Lys Asp Leu Ile Gln His Pro Lys Asn Cys
275 280 285

30
Ser Cys Phe Glu Cys Lys Glu Ser Leu Glu Thr Cys Cys Gln Lys His
290 295 300

30
Lys Leu Phe His Pro Asp Thr Cys Ser Cys Glu Asp Arg Cys Pro Phe
305 310 315 320

His Thr Arg Pro Cys Ala Ser Gly Lys Thr Ala Cys Ala Lys His Cys

325 330 335

5

Arg Phe Pro Lys Glu Lys Arg Ala Ala Gln Gly Pro His Ser Arg Lys

340 345 350

10

Asn Pro

<210> 71

15

<211> 2825

<212> DNA

<213> Homo sapiens

20

<220>

<221> misc_feature

<222> (2689)..(2689)

<223> n is a, c, g, or t

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<400> 71

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<211> 345

<212> PRT

30 <213> Homo sapiens

<400> 72

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Ser Ser Asn Lys Glu Gln Asn Gly Val Gln Asp Pro Gln His Glu Arg
 35 40 45

15

Ile Ile Thr Val Ser Thr Asn Gly Ser Ile His Ser Pro Arg Phe Pro
 50 55 60

20

His Thr Tyr Pro Arg Asn Thr Val Leu Val Trp Arg Leu Val Ala Val
65 70 75 80

25

Glu Glu Asn Val Trp Ile Gln Leu Thr Phe Asp Glu Arg Phe Gly Leu
 85 90 95

30

Glu Asp Pro Glu Asp Asp Ile Cys Lys Tyr Asp Phe Val Glu Val Glu
 100 105 110

30

Glu Pro Ser Asp Gly Thr Ile Leu Gly Arg Trp Cys Gly Ser Gly Thr
 115 120 125

Val Pro Gly Lys Gln Ile Ser Lys Gly Asn Gln Ile Arg Ile Arg Phe
130 135 140

5

Val Ser Asp Glu Tyr Phe Pro Ser Glu Pro Gly Phe Cys Ile His Tyr
145 150 155 160

10

Asn Ile Val Met Pro Gln Phe Thr Glu Ala Val Ser Pro Ser Val Leu
165 170 175

Pro Pro Ser Ala Leu Pro Leu Asp Leu Leu Asn Asn Ala Ile Thr Ala
15 180 185 190

Phe Ser Thr Leu Glu Asp Leu Ile Arg Tyr Leu Glu Pro Glu Arg Trp
195 200 205

20

Gln Leu Asp Leu Glu Asp Leu Tyr Arg Pro Thr Trp Gln Leu Leu Gly
210 215 220

25

Lys Ala Phe Val Phe Gly Arg Lys Ser Arg Val Val Asp Leu Asn Leu
225 230 235 240

30

Leu Thr Glu Glu Val Arg Leu Tyr Ser Cys Thr Pro Arg Asn Phe Ser
245 250 255

Val Ser Ile Arg Glu Glu Leu Lys Arg Thr Asp Thr Ile Phe Trp Pro

260 265 270

5

Gly Cys Leu Leu Val Lys Arg Cys Gly Gly Asn Cys Ala Cys Cys Leu

275 280 285

10

His Asn Cys Asn Glu Cys Gln Cys Val Pro Ser Lys Val Thr Lys Lys

290 295 300

15

Tyr His Glu Val Leu Gln Leu Arg Pro Lys Thr Gly Val Arg Gly Leu

305 310 315 320

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His Lys Ser Leu Thr Asp Val Ala Leu Glu His His Glu Glu Cys Asp

325 330 335

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Cys Val Cys Arg Gly Ser Thr Gly Gly

340 345

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<210> 73

<211> 2745

<212> DNA

<213> Homo sapiens

<400> 73

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30 <211> 391

<212> PRT

<213> Homo sapiens

<400> 74

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

Ile Arg Gly Gln Ile Leu Ser Lys Leu Arg Leu Ala Ser Pro Pro Ser
50 55 60

Gln Gly Glu Val Pro Pro Gly Pro Leu Pro Glu Ala Val Leu Ala Leu
65 70 75 80

Tyr Asn Ser Thr Arg Asp Arg Val Ala Gly Glu Ser Ala Glu Pro Glu
85 90 95

Pro Glu Pro Glu Ala Asp Tyr Tyr Ala Lys Glu Val Thr Arg Val Leu
100 105 110

Met Val Glu Thr His Asn Glu Ile Tyr Asp Lys Phe Lys Gln Ser Thr

	115	120	125
	His Ser Ile Tyr Met Phe Phe Asn Thr Ser Glu Leu Arg Glu Ala Val		
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	Pro Glu Pro Val Leu Leu Ser Arg Ala Glu Leu Arg Leu Leu Arg Arg		
10	145	150	155 160
	Leu Lys Leu Lys Val Glu Gln His Val Glu Leu Tyr Gln Lys Tyr Ser		
	165	170	175
15	Asn Asn Ser Trp Arg Tyr Leu Ser Asn Arg Leu Leu Ala Pro Ser Asp		
	180	185	190
20	Ser Pro Glu Trp Leu Ser Phe Asp Val Thr Gly Val Val Arg Gln Trp		
	195	200	205
	Leu Ser Arg Gly Gly Glu Ile Glu Gly Phe Arg Leu Ser Ala His Cys		
25	210	215	220
	Ser Cys Asp Ser Arg Asp Asn Thr Leu Gln Val Asp Ile Asn Gly Phe		
	225	230	235 240
30	Thr Thr Gly Arg Arg Gly Asp Leu Ala Thr Ile His Gly Met Asn Arg		

245 250 255

Pro Phe Leu Leu Leu Met Ala Thr Pro Leu Glu Arg Ala Gln His Leu
5 260 265 270

Gln Ser Ser Arg His Arg Arg Ala Leu Asp Thr Asn Tyr Cys Phe Ser
10 275 280 285

Ser Thr Glu Lys Asn Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg
15 290 295 300

Lys Asp Leu Gly Trp Lys Trp Ile His Glu Pro Lys Gly Tyr His Ala
305 310 315 320

Asn Phe Cys Leu Gly Pro Cys Pro Tyr Ile Trp Ser Leu Asp Thr Gln
20 325 330 335

Tyr Ser Lys Val Leu Ala Leu Tyr Asn Gln His Asn Pro Gly Ala Ser
25 340 345 350

Ala Ala Pro Cys Cys Val Pro Gln Ala Leu Glu Pro Leu Pro Ile Val
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Tyr Tyr Val Gly Arg Lys Pro Lys Val Glu Gln Leu Ser Asn Met Ile

370 375 380

Val Arg Ser Cys Lys Cys Ser

5 385 390

<210> 75

<211> 336

10 <212> DNA

<213> Homo sapiens

<400> 75

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gccaacttet gcctggggcc ctgccctac atttgagcc tggacagca gtacagcaag 180

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25 <210> 76

<211> 112

<212> PRT

30 <213> Homo sapiens

<400> 76

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Val Arg Gln Leu Tyr Ile Asp Phe Arg Lys Asp Leu Gly Trp Lys Trp
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Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly Pro Cys
35 40 45

15

Pro Tyr Ile Trp Ser Leu Asp Thr Gln Tyr Ser Lys Val Leu Ala Leu
50 55 60

20

Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys Val Pro
65 70 75 80

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Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg Lys Pro
85 90 95

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Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys Cys Ser
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<213> Homo sapiens

<400> 77

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gcaaattttt taaa 1695

30 <210> 78

<211> 414

<212> PRT

<213> Homo sapiens

<400> 78

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Met His Tyr Cys Val Leu Ser Ala Phe Leu Ile Leu His Leu Val Thr

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Val Ala Leu Ser Leu Ser Thr Cys Ser Thr Leu Asp Met Asp Gln Phe

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15

Met Arg Lys Arg Ile Glu Ala Ile Arg Gly Gln Ile Leu Ser Lys Leu

35 40 45

Lys Leu Thr Ser Pro Pro Glu Asp Tyr Pro Glu Pro Glu Glu Val Pro

50 55 60

20

Pro Glu Val Ile Ser Ile Tyr Asn Ser Thr Arg Asp Leu Leu Gln Glu

65 70 75 80

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Lys Ala Ser Arg Arg Ala Ala Ala Cys Glu Arg Glu Arg Ser Asp Glu

85 90 95

30

Glu Tyr Tyr Ala Lys Glu Val Tyr Lys Ile Asp Met Pro Pro Phe Phe

100 105 110

Pro Ser Glu Asn Ala Ile Pro Pro Thr Phe Tyr Arg Pro Tyr Phe Arg
115 120 125

5
Ile Val Arg Phe Asp Val Ser Ala Met Glu Lys Asn Ala Ser Asn Leu
130 135 140

10
Val Lys Ala Glu Phe Arg Val Phe Arg Leu Gln Asn Pro Lys Ala Arg
145 150 155 160

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Val Pro Glu Gln Arg Ile Glu Leu Tyr Gln Ile Leu Lys Ser Lys Asp
165 170 175

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Leu Thr Ser Pro Thr Gln Arg Tyr Ile Asp Ser Lys Val Val Lys Thr
180 185 190

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Arg Ala Glu Gly Glu Trp Leu Ser Phe Asp Val Thr Asp Ala Val His
195 200 205

30
Glu Trp Leu His His Lys Asp Arg Asn Leu Gly Phe Lys Ile Ser Leu
210 215 220

His Cys Pro Cys Cys Thr Phe Val Pro Ser Asn Asn Tyr Ile Ile Pro
225 230 235 240

Asn Lys Ser Glu Glu Leu Glu Ala Arg Phe Ala Gly Ile Asp Gly Thr
245 250 255

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Ser Thr Tyr Thr Ser Gly Asp Gln Lys Thr Ile Lys Ser Thr Arg Lys
260 265 270

10

Lys Asn Ser Gly Lys Thr Pro His Leu Leu Leu Met Leu Leu Pro Ser
275 280 285

15

Tyr Arg Leu Glu Ser Gln Gln Thr Asn Arg Arg Lys Lys Arg Ala Leu
290 295 300

20

Asp Ala Ala Tyr Cys Phe Arg Asn Val Gln Asp Asn Cys Cys Leu Arg
305 310 315 320

25

Pro Leu Tyr Ile Asp Phe Lys Arg Asp Leu Gly Trp Lys Trp Ile His
325 330 335

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Glu Pro Lys Gly Tyr Asn Ala Asn Phe Cys Ala Gly Ala Cys Pro Tyr
340 345 350

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Leu Trp Ser Ser Asp Thr Gln His Ser Arg Val Leu Ser Leu Tyr Asn
355 360 365

Thr Ile Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Ser Gln Asp
370 375 380

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Leu Glu Pro Leu Thr Ile Leu Tyr Tyr Ile Gly Lys Thr Pro Lys Ile
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Glu Gln Leu Ser Asn Met Ile Val Lys Ser Cys Lys Cys Ser
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<210> 79

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<211> 336

<212> DNA

<213> Homo sapiens

<400> 79

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<210> 80

<211> 112

<212> PRT

<213> Homo sapiens

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<400> 80

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Leu Arg Pro Leu Tyr Ile Asp Phe Lys Arg Asp Leu Gly Trp Lys Trp

20 25 30

15

Ile His Glu Pro Lys Gly Tyr Asn Ala Asn Phe Cys Ala Gly Ala Cys

35 40 45

20

Pro Tyr Leu Trp Ser Ser Asp Thr Gln His Ser Arg Val Leu Ser Leu

50 55 60

25

Tyr Asn Thr Ile Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Ser

65 70 75 80

Gln Asp Leu Glu Pro Leu Thr Ile Leu Tyr Tyr Ile Gly Lys Thr Pro

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Lys Ile Glu Gln Leu Ser Asn Met Ile Val Lys Ser Cys Lys Cys Ser

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<210> 81

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10 agatatactg gaaaacattc acgagtgat ggaaatcaaa ttcaaaggcg tggacaatga 1020

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15 gaggaagaag cgggcttgg acaccaatta ctgtccgc aactggagg agaactgtg 1200

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20 taagggtac tatgcaact tetgtcagg ccttgcca tactccgca gtgcagacac 1320

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25 caaagtggag cagctctcca acatggtgt gaagtctgt aaatgtagt gagacccac 1500

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<212> PRT
<213> Homo sapiens

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<400> 82

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Phe Ala Thr Val Ser Leu Ser Leu Ser Thr Cys Thr Thr Leu Asp Phe
 20 25 30

15

Gly His Ile Lys Lys Lys Arg Val Glu Ala Ile Arg Gly Gln Ile Leu
 35 40 45

20

Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro Thr Val Met Thr His
 50 55 60

25

Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
65 70 75 80

30

Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr Gln Glu Asn Thr
 85 90 95

Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln

	100	105	110
	Gly Leu Ala Glu His Asn Glu Leu Ala Val Cys Pro Lys Gly Ile Thr		
5	115	120	125
	Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu Lys Asn Arg Thr		
10	130	135	140
	Asn Leu Phe Arg Ala Glu Phe Arg Val Leu Arg Val Pro Asn Pro Ser		
	145	150	155 160
15	Ser Lys Arg Asn Glu Gln Arg Ile Glu Leu Phe Gln Ile Leu Arg Pro		
	165	170	175
	Asp Glu His Ile Ala Lys Gln Arg Tyr Ile Gly Gly Lys Asn Leu Pro		
20	180	185	190
	Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp Val Thr Asp Thr Val		
25	195	200	205
	Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu Gly Leu Glu Ile Ser		
	210	215	220
30	Ile His Cys Pro Cys His Thr Phe Gln Pro Asn Gly Asp Ile Leu Glu		

	225	230	235	240
	Asn Ile His Glu Val Met Glu Ile Lys Phe Lys Gly Val Asp Asn Glu			
5	245	250	255	
	Asp Asp His Gly Arg Gly Asp Leu Gly Arg Leu Lys Lys Gln Lys Asp			
	260	265	270	
10				
	His His Asn Pro His Leu Ile Leu Met Met Ile Pro Pro His Arg Leu			
	275	280	285	
15				
	Asp Asn Pro Gly Gln Gly Gly Gln Arg Lys Lys Arg Ala Leu Asp Thr			
	290	295	300	
20				
	Asn Tyr Cys Phe Arg Asn Leu Glu Glu Asn Cys Cys Val Arg Pro Leu			
	305	310	315	320
	Tyr Ile Asp Phe Arg Gln Asp Leu Gly Trp Lys Trp Val His Glu Pro			
25	325	330	335	
	Lys Gly Tyr Tyr Ala Asn Phe Cys Ser Gly Pro Cys Pro Tyr Leu Arg			
	340	345	350	
30				
	Ser Ala Asp Thr Thr His Ser Thr Val Leu Gly Leu Tyr Asn Thr Leu			

355 360 365

5 Asn Pro Glu Ala Ser Ala Ser Pro Cys Cys Val Pro Gln Asp Leu Glu
370 375 380

10 Pro Leu Thr Ile Leu Tyr Tyr Val Gly Arg Thr Pro Lys Val Glu Gln
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15 Leu Ser Asn Met Val Val Lys Ser Cys Lys Cys Ser
405 410

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<211> 3213
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25 gggaccaagg cccaaatgct tgtgcccttc aacagatttt gggcaccaaa aagaaatact 180

tcagcacttg taagaactgg tataaaaagt ccattctgtg acagaaaacg actgttttat 240

30 atgaatgttg ccctgggtat atgagaatgg aaggaatgaa aggctgcca gcagttttgc 300

ccattgacca tgtttatggc actctgggca tcgtgggagc caccacaacg cagcgtatt 360

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cgagtaatga ggcttgggac aacttggatt ctgatatccg tagaggtttg gagagcaacg 480

5 tgaatgttga attactgaat gctttacata gtcacatgat taataagaga atgttgacca 540

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10 accattatcc taatgggggt gtcactgtta attgtgctcg aatcatccat gggaaccaga 660

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25 tgatecattt gattgatcag gtctaatte ctgattctgc caaacaagtt attgagctgg 1140

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25 ttgtggaacc aaaaattaaa gtgattgaag gcagtcttca gcctattatc aaaactgaag 2100

gaccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag 2160

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tcattctgac attaaaagtt ctggctaact ttggaatcca ttgagaaaa atccttgta 2820

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25 attctatat gagggggtt actggtaa atgtgtattt ttacaacta atttgtact 3060

ctcagaatgt ttgtcatg cttcttgcaa tgcataattt ttaatctca acgtttcaat 3120

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<211> 836

5 <212> PRT

<213> Homo sapiens

<400> 84

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20 Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
35 40 45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
50 55 60

25 Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65 70 75 80

30 Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
85 90 95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
100 105 110

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Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115 120 125

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Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130 135 140

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Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145 150 155 160

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Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
165 170 175

25

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

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Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys
195 200 205

Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His
210 215 220

Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe
225 230 235 240

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Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr
245 250 255

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Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe
260 265 270

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Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu
275 280 285

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Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His
290 295 300

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Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val
305 310 315 320

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Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp
325 330 335

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Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val
340 345 350

Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp
355 360 365

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Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe
370 375 380

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Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp
385 390 395 400

15

Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp
405 410 415

20

Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His
420 425 430

25

Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile
435 440 445

30

Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr
450 455 460

Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly
465 470 475 480

Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu

485 490 495

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Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe

500 505 510

10

Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro

515 520 525

Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met

15 530 535 540

Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln

545 550 555 560

20

Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly

565 570 575

25

Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys

580 585 590

30

Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys

595 600 605

Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val
610 615 620

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Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu
625 630 635 640

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Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val
645 650 655

15

Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys
660 665 670

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Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser
675 680 685

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Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys
690 695 700

30

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

Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile
725 730 735

Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu
740 745 750

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Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly
755 760 765

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Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val
770 775 780

15

Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu
785 790 795 800

20

Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys
805 810 815

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Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu
820 825 830

30

Gly Arg Ser Gln
835