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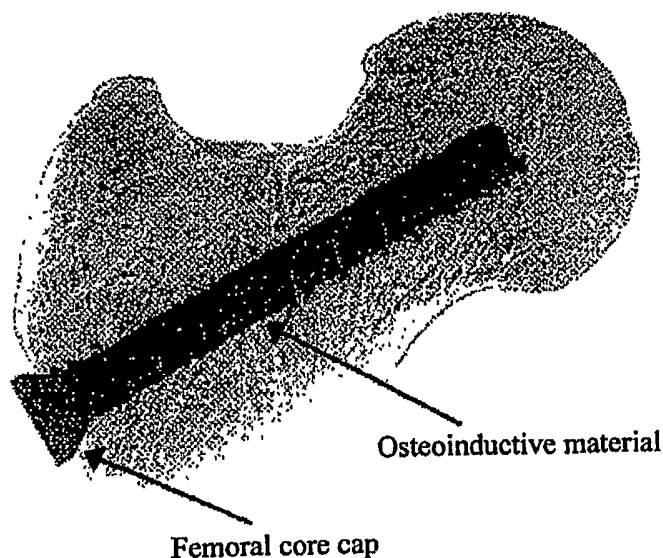
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(54) Title: A PROCESS TO TREAT AVASCULAR NECROSIS (AVN) WITH OSTEOINDUCTIVE MATERIALS



(57) Abstract: A method of treating avascular necrosis ("AVN") comprising administering one or more osteoinductive formulations to the site of AVN disease progression. The method involves the combination of a core decompression technique, followed by the introduction of one or more osteoinductive formulations into the decompression core, and concluding with capping of the lateral aspect of the decompression core with a femoral core cap. The osteoinductive formulations of the invention comprise one or more osteoinductive agents and suitable carrier molecules. The femoral core cap retains the osteoinductive formulation within the decompression core, thereby preventing leakage of the osteoinductive formulation from the decompression core. The method of the invention optionally comprises introduction of autograft or allograft with the osteoinductive formulations of the invention. The method of the invention further optionally comprises incorporation of sustained release

compositions to provide extended periods of osteogenesis.



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A PROCESS TO TREAT AVASCULAR NECROSIS (AVN) WITH OSTEOINDUCTIVE MATERIALS

Field of the Invention

The invention relates to a method of treating avascular necrosis ("AVN") comprising administering one or more osteoinductive formulations to the site of AVN disease progression. The method involves a combination of a core decompression technique, followed by the introduction of one or more osteoinductive formulations into the decompression core, and concluding with capping of the decompression core with a femoral core cap, which optionally is a biodegradable or bioabsorbable sterile polymer cap. The osteoinductive formulations of the invention comprise one or more osteoinductive agents, and optionally suitable carrier molecules. The femoral core cap retains the osteoinductive formulation within the decompression core, thereby preventing leakage of the osteoinductive formulation from the decompression core, which might otherwise induce bone formation in undesirable locations. The methods of the invention optionally comprise introduction of autograft or allograft with the osteoinductive formulations of the invention. The method of the invention further optionally comprises incorporation of sustained release compositions to provide extended periods of osteogenesis.

Background of the Invention

Avascular necrosis is a disease resulting from the temporary or permanent loss of blood supply to bones. Without an adequate blood supply, bone tissue necroses over time, losing strength and eventually resulting in collapse of either the bone itself or joint surfaces near the necrosing bone. Avascular necrosis is not restricted to any particular bone type, but is a disease that is more prevalent in certain bones. When the disease is diagnosed in a patient, it commonly affects the ends (epiphysis) of long bones such as the femur, as well as the upper arm bone, knees, shoulders, and ankles. There is no limit as to the number of bones or the timing with which one or more bones of the body becomes affected with avascular necrosis.

Avascular necrosis may be caused by a number of factors which include blunt force trauma to the area, resulting in the loss of vascularization to the affected area due to excessive pressure. Other causative agents of avascular necrosis include abuse of alcohol

or other controlled substances, the use of some medications such as steroids, increased pressure within the bone(s), as well as blood coagulation disorders, systemic lupus erythematosus (SLE), hypertension, sickle cell disease, caisson disease radiation-induced arteritis, gout and Gaucher's disease.

According to the National Institute of Arthritis and Musculoskeletal and Skin Diseases, avascular necrosis usually affects patients between the ages of 30 and 50 years of age. Furthermore, about 10,000 to 20,000 people develop avascular necrosis on a yearly basis. Therefore, a large number of patients per year are in need of treatment for avascular necrosis. (See NAIMA Questions and Answers about Avascular Necrosis, published 2001).

Typical methods of treating avascular necrosis involve a process of coring out of the diseased bone to depressurize the affected area, as well as to promote the growth of new bone tissue (See Hungerford, D., Bone marrow pressure, venography, and core depression in ischemic necrosis of the femoral head. *The Hip: Proceedings of the Seventh Open Scientific Meeting of The Hip Society*. St. Louis, C.V. Mosby, 1979, 218-237; Ficat, R., Idiopathic Bone Necrosis of the Femoral Head. Early Diagnosis and Treatment, *J. Bone Joint Surg.*, 1985, 67(1):3-9).

However, the disease may still progress in some patients, resulting in another surgical procedure such as total hip replacement (See Mont, M., *et al.*, Core Decompression Versus Nonoperative Management for Osteonecrosis of the Hip, *Clin. Orthop. and Related Research*, 1996, 324:169-178; Steinberg, M., *et al.*, Treatment of Osteonecrosis of the Femoral Head by Core Decompression, Bone Grafting, and Electrical Stimulation, *Univ. Penn. Orthop. J.*, 1997, 10:24-29).

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 improved core decompression procedures for preventing and/or treating avascular necrosis in individuals having the disease, either in its initial stages or advanced stages. A feature of the invention therefore is to provide improved core decompression techniques and follow up treatment procedures that effectively prevent and/or treat avascular necrosis.

In accordance with these and other features of embodiments of the invention, there is provided a method of treating avascular necrosis in patients suffering from the symptoms of avascular necrosis, either in its initial stages or advanced stages. The method of the invention comprises the combination of a core decompression technique, followed by the introduction of one or more osteoinductive formulations into the decompression core, and capping of the lateral aspect of the decompression core with a femoral core cap, which is optionally a biodegradable or bioabsorbable polymer cap. The femoral core cap preferably retains the osteoinductive formulation within the decompression core, thereby preventing leakage or diffusion of the osteoinductive formulation from the decompression core, which might otherwise induce bone formation in undesirable locations. The method of the invention optionally comprises the introduction of autograft or allograft with the osteoinductive formulations of the invention.

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

Brief Description of the Drawings

Figure 1A provides an image of a diseased femur bone of an individual suffering from avascular necrosis of the femur.

Figure 1B demonstrates the general concept of core decompression in the head of a diseased femur bone of an individual suffering from avascular necrosis.

Figure 1C demonstrates one embodiment of a decompression core in a diseased femur bone of an individual suffering from avascular necrosis. The decompression core is clearly shown as hollow cylinder running at an angle through a diseased portion of the femur head.

Figure 2 provides a schematic of one embodiment of the method of the invention. The osteoinductive formulation is introduced into the decompression core, followed by capping of the decompression core with a femoral core cap.

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

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, "isolated" shall mean material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

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

As used herein, "bioabsorbable" shall mean a polymer that is substantially resorbed by the body over a period of time.

The method of the invention preferably is directed to the treatment of avascular necrosis in patients having early to late-stage progression of the disease. The invention comprises the core decompression of diseased bone due to avascular necrosis, for example in the femoral neck of necrosed femur tissue, thereby relieving pressure on the diseased portion of the bone. A surgeon skilled in the art of treating avascular necrosis by core decompression would recognize techniques and devices for performing core decompression in a patient suffering from the symptoms of avascular necrosis. For example, Steinberg *et al.* describe a method of opening the femoral neck of the femur with a conical reamer, inserting an 8 mm Michele trephine, and removing the core of bone. Other examples include using a device containing a probe, a cannula and a tamp as described in U.S. Patent No. 6,679,886, or drilling the bone to be treated to form a cavity or passage in the bone, into which an inflatable balloon-like device is inserted and inflated

as described in U.S. Patent No. 6,663,647. Other devices for core decompression are available and known in the art. For example, U.S. Patent Nos. 5,409,489 (Sioufi) and 6,322,565 (Garner *et al*) describe avascular necrosis instruments having drill guide members useful with the methods of the invention.

Following core decompression of the necrotic bone tissue, osteoinductive formulations are introduced into the decompression core. Osteoinductive formulations are discussed *infra*, and further include one or more osteoinductive agent(s).

After introduction of the osteoinductive formulations, the decompression core is capped with a femoral core cap, preferably a biodegradable or bioabsorbable sterile femoral core cap, on the lateral aspect of the decompression core to seal and contain the osteoinductive formulations within the decompression core for some period of time. Capping of the lateral aspect of the decompression core is significant, as it substantially prevents release of osteoinductive formulations to surrounding tissues, including other portions of the same bone into which the decompression core was drilled. Inadvertent release of osteoinductive formulations into surrounding tissues may result in the induction of osteogenesis in undesirable locations, such as for example, the shaft of the femur bone. The inadvertent induction of osteogenesis may create unnecessary complications for the patient, ranging from pain to interference with the function of connective tissue, muscle tissue, or related tissues surrounding the bone.

The femoral core cap aspect of embodiments of the invention may comprise a bioabsorbable polymer. In another embodiment of the invention, the decompression core is generated using a cannulated reamer. Following decompression, a portion or all of the bone core removed by use of the cannulated reamer is used as the femoral core cap to close the decompression core. Optionally, the bone core used as a femoral core cap may be coated with a biodegradable or bioabsorbable polymer prior to insertion into the decompression core. The bone core used as a femoral core cap may also comprise osteoinductive formulations, alone or with a biodegradable or bioabsorbable polymer. The bone core may optionally be sterilized prior to reimplantation as a femoral core cap.

In another embodiment of the invention, the osteoinductive formulations of the invention decrease patient recovery time following core decompression surgery. In one embodiment of the invention, Bone Morphogenetic Protein (hereinafter "BMP")

osteoinductive agents present in the osteoinductive formulation promote osteogenesis and in-growth of endogenous bone. In another embodiment of the invention, osteoinductive formulations comprise a vascular endothelial growth factor (hereinafter "VEGF") that promotes vascularization of necrotic bone tissue.

In a particularly preferred embodiment of the invention, osteoinductive formulations comprise one or more BMP and one or more VEGF polynucleotides or polypeptides, thereby promoting both osteogenesis of the necrotic bone tissue as well as vasculogenesis of the necrotic bone tissue. It is believed that this particularly preferred embodiment of the invention aids in the regeneration of necrotic bone tissue while simultaneously promoting growth of vascular tissue that was damaged as a result of the development of avascular necrosis.

In another embodiment of the invention, the osteoinductive formulation provides osteoinductive agent(s) in bioavailable form immediately upon administration of the osteoinductive formulation.

In a further embodiment of the invention, the osteoinductive formulation provides osteoinductive agent(s) in bioavailable form as a sustained release formulation(s). The sustained release formulations comprise a biodegradable polymer that releases osteoinductive formulations comprising osteoinductive agent(s) in response to, and at a rate comparable to, the biodegradation of the biodegradable polymer. The osteoinductive formulation is liberated from the sustained release polymer *via* diffusion and natural fluid forces applied against the polymer composition.

Another aspect of the invention relates to osteoinductive formulations useful with the methods of the invention. Osteoinductive formulations comprise one or more osteoinductive agents, and provide the one or more agents in bioavailable form in 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.

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 activity level. Therefore, the osteoinductive formulations of the invention are available in immediate or sustained release formulations.

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.

Representative immediate release formulations are liquid formulations comprising at least osteoinductive agent(s) that are introduced into the site of core decompression, 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. Suitable liquid formulations comprise water, saline, or other acceptable fluid mediums that will not induce host immune responses.

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. 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 entireties. 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 after the introduction of the curing agent. During this period the liquid delivery composition may be introduced into the decompression core, 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 are contemplated that affect the rate of biodegradation of the polymer.

Osteoinductive formulations of the invention further contemplate the use of aqueous and non-aqueous peptide formulations to 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 introduced into the decompression core as liquid polymer sustained release compositions. An amount of the liquid composition is dispensed into the site of core decompression, 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 osteoinductive agents include, but are not limited to, gene therapy vectors harboring polynucleotides encoding the osteoinductive polypeptide 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, 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 to 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). 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 decompression core.

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-sulfamethoxazole, 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 of 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 (methotrxate), 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.

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 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 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 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 derivatives, glucose, mannose, or dextrans; chelating agents such as EDTA; sugaralcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants 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-growth of endogenous bone into the decompression core, and preferably further promote the growth of vascular tissue, or aid in preventing resorption of bone tissue 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;

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;

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;

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;

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;

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;

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;

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;

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

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.

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 core decompression 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:

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.

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.

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.

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.

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.

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.

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.

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.

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.

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 the families 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).

In one embodiment of the invention, the femoral core cap is biodegradable or bioabsorbable polymer cap and is resistant to biodegradation over extended periods of time. Examples of extended periods of time are preferably 3 months, still more preferably 6 months, still more preferably 9 months, and most preferably 12 or more months. It is understood that the biodegradation of polymers may be influenced by manipulating the ratios of the polymer composition such as, for example by adding or increasing the concentration of biostable polymers in the composition or decreasing the concentration of biodegradable polymers in the composition.

Biodegradable polymers and methods of making biodegradable polymers optionally comprising one or more active agents that may be molded into implant compositions are known in the art and described, for example, in U.S. Patent Nos. 6,461,631, 6,238,687, and 5,876,452.

Bioabsorbable polymers and methods of making bioabsorbable polymers that may be molded into implant compositions are known in the art and are described, for example, in U.S. Patent Nos. 5,984,966, 5,338,772, and 6,001,100.

One of skill in the art is readily able to determine the appropriate length and diameter of the femoral core cap, and will make these determinations in light of the anticipated diameter of the decompression core. In one embodiment of the invention, the diameter of the femoral core cap is larger than the diameter of the decompression core; in

another embodiment of the invention, the diameter of the femoral core cap is about the same as the diameter of the decompression core; in still another embodiment of the invention the diameter of the femoral core cap is smaller than the diameter of the decompression core.

In another embodiment of the invention, the femoral core cap retains about a consistent diameter throughout the length of the cap. In another embodiment of the invention, the femoral core cap contains a tapered end.

Surgical methods for producing decompression cores are well known in the art, for example, *See* Hungerford, D., Bone marrow pressure, venography, and core depression in ischemic necrosis of the femoral head. *The Hip: Proceedings of the Seventh Open Scientific Meeting of The Hip Society*. St. Louis, C.V. Mosby, 1979, 218-237; Ficat, R., *Idiopathic Bone Necrosis of the Femoral Head. Early Diagnosis and Treatment*, *J. Bone Joint Surg.*, 1985, 67(1):3-9.

Sustained release polymer compositions used with the invention can be produced following the teachings known in the art, for example, in U.S. Patent Nos. 5,744,153, 4,938,763, 5,278,201, and 5,278,202, each of which is incorporated herein by reference. Formulations that increase the stability of osteoinductive agents over time and are useful with the osteoinductive formulations of the invention are known in the art and are described, for example, in U.S. Patent Nos. 5,916,582, 5,932,547, and 5,981,489, each of which is incorporated herein by reference.

In one embodiment of the invention, the osteoinductive formulations of the invention comprising one or more osteoinductive agent(s) are admixed with the sustained release polymers recited *supra* prior to administration in the decompression core. 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 femoral core cap may be produced using techniques known in the art, for example, by following the teachings of U.S. Patent Nos. 6,461,631, 6,238,687, 5,876,452, 5,984,966, 5,338,772, and 6,001,100, the disclosures of each of which are herein incorporated by reference in their entireties.

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 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 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 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. 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, 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 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 Champion™, 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).

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.

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. 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.

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.

Certain diagnostic or therapeutic procedures require the formation of a cavity in a bone mass to treat a pathological bone, which due to osteoporosis, avascular necrosis, or trauma, is fractured or is prone to compression fracture or collapse. These conditions, if not successfully treated, can result in deformities, chronic complications, and an overall adverse impact upon the quality of life.

The method of this invention provides osteoinductive formulations that promote osteogenesis of the necrotic bone tissue as well as vasculogenesis of the necrotic bone tissue, thereby helping to strengthen the femoral head or other relevant, critical portions of bone structures, and preventing fracture or collapse.

The methods of the invention are particularly suited for the treatment of avascular necrosis of diseased bones present in the hips, arms, knees, shoulders, and ankles. More particularly, the methods of the invention are useful to treat the symptoms of avascular necrosis present in the femoral head, the femur at the knee, the humeral head, the body of the talus, and navicular bone.

The methods of the invention provide osteoinductive formulations that promote osteogenesis of the necrotic bone tissue as well as vasculogenesis of the necrotic bone tissue, thereby helping to strengthen the femoral head and prevent fracture or collapse. The methods of the invention further provide for the prolonged induction of osteogenesis and vasculogenesis in patients requiring extended periods of treatment due to extensive bone necrosis or extensive bone loss due to core decompression or progression of the symptoms of avascular necrosis.

In an additional aspect of the invention, osteoinductive formulations 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 a surgeon skilled in the art of core decompression is best able to ascertain and judge the degree and duration of osteoinductive activity desired in any given patient. Accordingly, the osteoinductive formulations are available 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 for at least about 3 months following implantation.

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 kit additionally comprises at least one femoral core cap, preferably a biodegradable or bioabsorbable sterile polymer femoral core cap designed to seal the lateral aspect of the decompression core. In one embodiment of the invention, the femoral core cap further comprises one or more osteoinductive agents.

The kits of the invention further optionally comprises instructions for the preparation and administration of the osteoinductive formulations into the decompression core.

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

Examples

Example 1 - Treatment of femur necrosis AVN

A patient suffering from AVN, specifically tissue necrosis of the femur, is treated using the methods of the invention. Following preparation for surgery, the patient is subjected to core decompression surgery of the femur head, which yields a decompression core in the femur head. Avascular necrosis instruments having drill guide members well known in the art and referenced herein are used to conduct the core decompression surgery.

Following core decompression and cleansing of the core decompression site, osteogenic formulations comprising mature BMP-2 polypeptides and mature VEGF-C polypeptides are administered to the decompression core using well known catheter devices for delivery of liquid formulations. The lateral aspect of the decompression core is immediately capped with a bioabsorbable cap comprising a bioabsorbable polymer, thereby sealing the osteoinductive formulation within the decompression core.

The patient is provided a reasonable length of time to recover and to allow for osteogenesis and vasculogenesis. At the termination of the recovery period, X-ray imaging is utilized to ascertain the extent of osteogenesis at the site of core decompression. Angiography is utilized to ascertain the extent of vasculogenesis at the site of core decompression. Extensive re-growth of bone tissue and vascular tissue will indicate a healthy prognosis for the patient.

Example 2 - Treatment of femur necrosis AVN

A patient suffering from AVN, specifically tissue necrosis of the femur, is treated using the methods of the invention. Following preparation for surgery, the patient is subjected to core decompression surgery of the femur head using a cannulated reamer, which yields a decompression core in the femur head.

Following core decompression and cleansing of the core decompression site, osteogenic formulations comprising mature BMP-2 polypeptides and mature Osteoprotegerin polypeptides are administered to the decompression core using well known catheter devices for delivery of liquid formulations. The lateral aspect of the decompression core is immediately capped with a lateral cap comprising approximately one-half to three-quarters of the length of the bone core removed using the cannulated reamer, thereby sealing the osteoinductive formulation within the decompression core.

The patient is provided a reasonable length of time to recover and to allow for osteogenesis. At the termination of the recovery period, X-ray imaging is utilized to ascertain the extent of osteogenesis at the site of core decompression. Extensive re-growth of bone tissue indicates a healthy prognosis for the patient.

The invention has been described with reference to particularly preferred embodiments and the examples. Those skilled in the art will appreciate that modifications may be made to the invention without departing from the spirit and scope thereof.

What is claimed is:

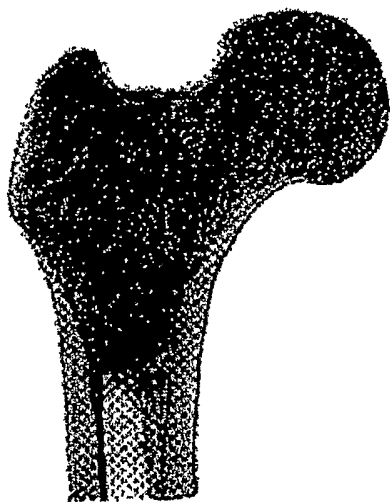
1. A method of treating avascular necrosis (AVN) comprising performing a core decompression technique on one or more necrotic bones, introducing osteoinductive formulation into the decompression core, and closing the decompression core with a core cap.
2. The method of claim 1, wherein the core cap comprises a portion of the decompression bone core.
3. The method of claim 2, wherein the core cap comprises one or more osteoinductive agents.
4. The method of claim 1, wherein the core cap comprises a biodegradable polymer.
5. The method of claim 4, wherein the biodegradable cap is resistant to biodegradation for at least 3 months.
6. The method of claim 4, wherein the biodegradable cap comprises one or more osteoinductive agents.
7. The method of claim 1, wherein the osteoinductive formulation further comprises one or more osteoinductive agents.
8. The method of claim 7, wherein the one or more osteoinductive agents comprise BMP-2.
9. The method of claim 7, 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, BMP-17, BMP-18, and any combination thereof.
10. The method of claim 7, wherein the one or more osteoinductive agents are selected from from the group consisting of CTGF-1, CTGF-2, CGTF-3, CTGF-4, and any combination thereof.
11. The method of claim 7, wherein the one or more osteoinductive agents are selected from from the group consisting of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and any combination thereof.
12. The method of claim 7, wherein the one or more osteoinductive agents is osteoprotegerin or periostin.

13. The method of claim 7, wherein the one or more osteoinductive agents are selected from the group consisting of TGF- β -1, TGF- β -2, TGF- β -3, and any combination thereof.
14. The method of claim 7, 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, periostin, one or more TGF- β s, and any combination thereof.
15. The method of claim 7, wherein the one or more osteoinductive agents are provided as therapeutic polynucleotides.
16. The method of claim 7, wherein the one or more osteoinductive agents are provided as therapeutic polypeptides.
17. The method of claim 16, wherein the therapeutic polypeptides are administered as mature polypeptides.
18. The method of claim 1, wherein the osteoinductive formulation comprises a sustained-release formulation.
19. The method of claim 7, wherein the osteoinductive formulation further comprises one or more antibiotics.
20. The method of claim 7, wherein the osteoinductive formulation further comprises demineralized bone matrix.
21. The method of claim 7, wherein the osteoinductive formulation further comprises bone marrow aspirate.
22. The method of claim 7, wherein the osteoinductive formulation further comprises bone marrow concentrate.
23. The method of claim 7, wherein the osteoinductive formulation further comprises one or more immunosuppressives.
24. The method of claim 7, wherein the osteoinductive formulation further comprises a carrier.
25. The method of claim 24, wherein the carrier is collagen.
26. The method of claim 25, wherein the collagen is recombinantly produced collagen.
27. The method of claim 1, wherein the one or more necrotic bones are selected from the group consisting of the femur, the humerus, the body of the talus, and the navicular bone

28. A kit comprising a femoral core cap device for implantation and an osteoinductive formulation comprising at least one osteoinductive agent.

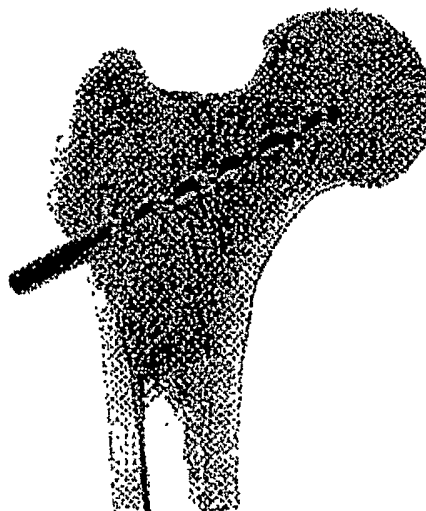
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Fig. 1A



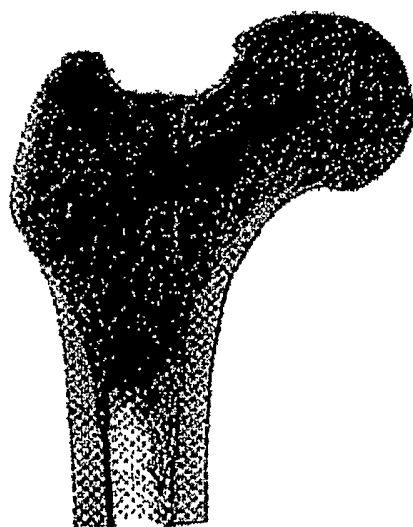
Femur w/AVN

Fig. 1B



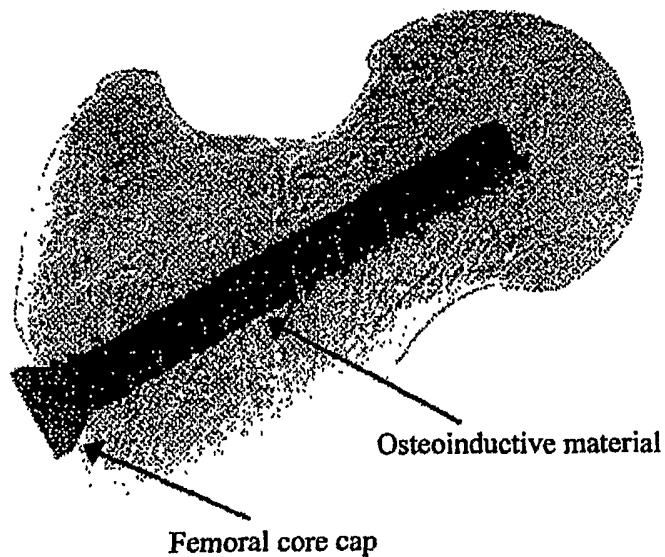
Reaming of the femoral neck

Fig. 1C



Femoral neck core

Fig. 2



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<110> Nycz, Jeffrey; McKay, Bill; Serbousek, Jon C.

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1320

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1380

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1440

accttgacga gaatgaaaag gttgtattaa agaactatca ggacatgggt gtggaggggt
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<210> 6
<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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg
385 390 395

<210> 7

<211> 1794

<212> DNA

<213> Homo sapiens

<400> 7

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180

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300

cgccgcgcgg gtacctagcc atggctgggg cgagcaggct gctgtttctg tggctgggct
360

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420

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480

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540

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660

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720

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780

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840

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1080

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1140

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1200

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1260

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1680

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1794

<210> 8

<211> 472

<212> PRT

<213> Homo sapiens

<400> 8

Met	Ala	Gly	Ala	Ser	Arg	Leu	Leu	Phe	Leu	Trp	Leu	Gly	Cys	Phe	Cys
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Val	Ser	Leu	Ala	Gln	Gly	Glu	Arg	Pro	Lys	Pro	Pro	Phe	Pro	Glu	Leu
			20					25					30		

Arg	Lys	Ala	Val	Pro	Gly	Asp	Arg	Thr	Ala	Gly	Ala	Gly	Pro	Asp	Ser
		35					40					45			

Glu	Leu	Glu	Pro	Gln	Asp	Lys	Val	Ser	Glu	His	Met	Leu	Arg	Leu	Tyr
	50					55					60				

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

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 Glu Thr Leu Glu Arg Lys Gly
 100 105 110

Leu Tyr Ile Phe Asn Leu Thr Ser Leu Thr Lys Ser Glu Asn Ile Leu
 115 120 125

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
 145 150 155 160

Ile Gln Ile Asp Leu Ser Ala Trp Thr Leu Lys Phe Ser Arg Asn Gln
 165 170 175

Ser Gln Leu Leu Gly His Leu Ser Val Asp Met Ala Lys Ser His Arg
 180 185 190

Asp Ile Met Ser Trp Leu Ser Lys Asp Ile Thr Gln Phe Leu Arg Lys
 195 200 205

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
 225 230 235 240

Leu Val Tyr Ala Asn Asp Ala Ala Ile Ser Glu Pro Glu Ser Val Val
 245 250 255

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
 275 280 285

Arg Ser Thr Gly Leu Leu Leu Pro Leu Gln Asn Asn Glu Leu Pro Gly
 290 295 300

Ala Glu Tyr Gln Tyr Lys Lys Asp Glu Val Trp Glu Glu Arg Lys Pro
 305 310 315 320

Tyr Lys Thr Leu Gln Ala Gln Ala Pro Glu Lys Ser Lys Asn Lys Lys
 325 330 335

Lys Gln Arg Lys Gly Pro His Arg Lys Ser Gln Arg Leu Gln Phe Asp
 340 345 350

Glu Gln Thr Leu Lys Lys Ala Arg Arg Lys Gln Trp Ile Glu Pro Arg
 355 360 365

Asn Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala Asp Ile Gly Trp
 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
 405 410 415

Ala Thr Ile Gln Ser Ile Val Arg Ala Val Gly Val Val Pro Gly Ile
 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
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<210> 9

<211> 1999

<212> DNA

<213> Homo sapiens

<400> 9

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120

ccggcccgga agctaggtga gtgtggcatc cgagctgagg gacgcgagcc tgagaacggc
180

ctgctgctcc ggctgagtat ctagcttgtc tccccgatgg gattcccgtc caagctatct
240

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360

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720

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780

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840

caogaagaac atctggagaa catcccagg accagtgaac actctgcttt tcgtttcctc
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tttaacctca gcagcatccc tgagaacgag gcgatctcct ctgcagagct tcggctcttc
960

cgggagcagg tggaccaggg ccctgattgg gaaaggggct tccaccgtat aaacatttat
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1080

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1560

aattctgtca attccagtat ccccaaagcc tgttgtgtgc ccactgaact gagtgccatc
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1860

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1980

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<210> 10

<211> 408

<212> PRT

<213> Homo sapiens

<400> 10

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Leu Leu Gly Gly Ala Ser His Ala Ser Leu Ile Pro Glu Thr Gly Lys	20	25	30
Lys Lys Val Ala Glu Ile Gln Gly His Ala Gly Gly Arg Arg Ser Gly	35	40	45
Gln Ser His Glu Leu Leu Arg Asp Phe Glu Ala Thr Leu Leu Gln Met	50	55	60
Phe Gly Leu Arg Arg Arg Pro Gln Pro Ser Lys Ser Ala Val Ile Pro	65	70	75
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
Arg Ala Asn Thr Val Arg Ser Phe His His Glu Glu His Leu Glu Asn	115	120	125
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	145	150	155
Phe Arg Glu Gln Val Asp Gln Gly Pro Asp Trp Glu Arg Gly Phe His	165	170	175
Arg Ile Asn Ile Tyr Glu Val Met Lys Pro Pro Ala Glu Val Val Pro	180	185	190
Gly His Leu Ile Thr Arg Leu Leu Asp Thr Arg Leu Val His His Asn	195	200	205
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
 Leu His Gln Thr Arg Thr His Gln Gly Gln His Val Arg Ile Ser Arg
 245 250 255
 Ser Leu Pro Gln Gly Ser Gly Asn Trp Ala Gln Leu Arg Pro Leu Leu
 260 265 270
 Val Thr Phe Gly His Asp Gly Arg Gly His Ala Leu Thr Arg Arg Arg
 275 280 285
 Arg Ala Lys Arg Ser Pro Lys His His Ser Gln Arg Ala Arg Lys Lys
 290 295 300
 Asn Lys Asn Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val
 305 310 315 320
 Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr
 325 330 335
 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
 Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu
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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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<210> 11
 <211> 2207
 <212> DNA
 <213> Homo sapiens

<400> 11

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120

tgaatagtac aacctagagt attatitttac actaagacga cacaaaagat gttaaagtta
180

tcaccaagct gccggacaga tatatatcc aacaccaagg tgcagatcag catagatctg
240

tgattcagaa atcaggattt gttttggaaa gagctcaagg gttgagaaga actcaaaagc
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aagtgaagat tactttggga actacagttt atcagaagat caacttttgc taattcaa
360

accaaggcc tgattatcat aaattcatat aggaatgcat aggtcatctg atcaaataat
420

attagccgtc ttctgctaca tcaatgcagc aaaaactctt aacaactgtg gataattgga
480

aatctgagtt tcagctttct tagaaataac tactcttgac atattccaaa atatttaaaa
540

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1920

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1980

attaaatgcc atctctgttc tgtaacttga tgacagctcc aatgtcattt tgaaaaata
2040

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2160

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2207

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

<400> 12

Met His Leu Thr Val Phe Leu Leu Lys Gly Ile Val Gly Phe Leu Trp
1 5 10 15

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

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

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

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

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

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

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
145 150 155 160

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Arg Ser Cys Gly Cys His
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<210> 13
<211> 396
<212> DNA
<213> Homo sapiens

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120

cgggatctgg gatggcagga ctggattata gcaccagaag gatacgctgc attttattgt
180

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cagactctgg ttcatctgat gtttcttgac caggtaccaa agccttggtg tgctccaacc
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tatagaaata tggtagtacg ctcatgtggc tgccac
396

<210> 14
<211> 132
<212> PRT
<213> Homo sapiens

<400> 14

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

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

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
 85 90 95

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

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

Cys Gly Cys His
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<210> 15
 <211> 2943
 <212> DNA
 <213> Homo sapiens

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 120

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1980

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<211> 513
<212> PRT
<213> Homo sapiens

<400> 16

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			20					25						30	

Ala	Ala	Ala	Ala	Ala	Ala	Ala	Gly	Gly	Gln	Leu	Leu	Gly	Asp	Gly	Gly
			35					40					45		

Ser	Pro	Gly	Arg	Thr	Glu	Gln	Pro	Pro	Pro	Ser	Pro	Gln	Ser	Ser	Ser
	50					55					60				

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
 85 90 95

His Gly Leu Gln Gln Pro Gln Pro Pro Ala Leu Arg Gln Gln Glu Glu
 100 105 110

Gln Gln Gln Gln Gln Gln Leu Pro Arg Gly Glu Pro Pro Pro Gly Arg
 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
 145 150 155 160

Trp Pro His Glu Ala Ala Ser Ser Ser Gln Arg Arg Gln Pro Pro Pro
 165 170 175

Gly Ala Ala His Pro Leu Asn Arg Lys Ser Leu Leu Ala Pro Gly Ser
 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
 210 215 220

Asp Lys Glu Phe Ser Pro Arg Gln Arg His His Lys Glu Phe Lys Phe
 225 230 235 240

Asn Leu Ser Gln Ile Pro Glu Gly Glu Val Val Thr Ala Ala Glu Phe
 245 250 255

Arg Ile Tyr Lys Asp Cys Val Met Gly Ser Phe Lys Asn Gln Thr Phe
 260 265 270

Leu Ile Ser Ile Tyr Gln Val Leu Gln Glu His Gln His Arg Asp Ser

275	280	285
Asp Leu Phe Leu Leu Asp Thr Arg Val Val Trp Ala Ser Glu Glu Gly		
290	295	300
Trp Leu Glu Phe Asp Ile Thr Ala Thr Ser Asn Leu Trp Val Val Thr		
305	310	315
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		
340	345	350
Tyr Asp Lys Gln Pro Phe Met Val Ala Phe Phe Lys Val Ser Glu Val		
355	360	365
His Val Arg Thr Thr Arg Ser Ala Ser Ser Arg Arg Arg Gln Gln Ser		
370	375	380
Arg Asn Arg Ser Thr Gln Ser Gln Asp Val Ala Arg Val Ser Ser Ala		
385	390	395
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		
420	425	430
Pro Lys Gly Tyr Ala Ala Asn Tyr Cys Asp Gly Glu Cys Ser Phe Pro		
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		
465	470	475
Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Asn Ser Asn		
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<210> 17
<211> 420
<212> DNA
<213> Homo sapiens
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120

aagcatgagc tgtatgtgag tttccaagac ctgggatggc aggactggat cattgcaccc
180

aagggctatg ctgccaaatta ctgtgatgga gaatgctcct tcccaactcaa cgcacacatg
240

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300

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<210> 18
<211> 140
<212> PRT
<213> Homo sapiens
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<400> 18

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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
 85 90 95

Pro Glu Tyr Val Pro Lys Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala
 100 105 110

Ile Ser Val Leu Tyr Phe Asp Asp Asn Ser Asn Val Ile Leu Lys Lys
 115 120 125

Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
 130 135 140

<210> 19
 <211> 1878
 <212> DNA
 <213> Homo sapiens

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 120

cgatgcacgt gcgctcactg cgagctgcgg cgccgcacag ctctgtggcg ctctgggcac
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ccctgttctt gctgcgctcc gccctggccg acttcagcct ggacaacgag gtgcactcga
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gcttcatcca ccggcgcctc cgagccagg agcggcgga gatgcagcg gagatcctct
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600

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660

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<210> 20
<211> 431
<212> PRT
<213> Homo sapiens

<400> 20

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			20					25					30		

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

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

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

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

Gly	Pro	Gly	Gly	Gln	Gly	Phe	Ser	Tyr	Pro	Tyr	Lys	Ala	Val	Phe	Ser
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

100					105					110					
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				
Glu	Phe	Phe	His	Pro	Arg	Tyr	His	His	Arg	Glu	Phe	Arg	Phe	Asp	Leu
145					150					155					160
Ser	Lys	Ile	Pro	Glu	Gly	Glu	Ala	Val	Thr	Ala	Ala	Glu	Phe	Arg	Ile
				165					170						175
Tyr	Lys	Asp	Tyr	Ile	Arg	Glu	Arg	Phe	Asp	Asn	Glu	Thr	Phe	Arg	Ile
			180					185					190		
Ser	Val	Tyr	Gln	Val	Leu	Gln	Glu	His	Leu	Gly	Arg	Glu	Ser	Asp	Leu
		195					200					205			
Phe	Leu	Leu	Asp	Ser	Arg	Thr	Leu	Trp	Ala	Ser	Glu	Glu	Gly	Trp	Leu
	210					215					220				
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		
Lys	Gln	Pro	Phe	Met	Val	Ala	Phe	Phe	Lys	Ala	Thr	Glu	Val	His	Phe
		275					280					285			
Arg	Ser	Ile	Arg	Ser	Thr	Gly	Ser	Lys	Gln	Arg	Ser	Gln	Asn	Arg	Ser
	290					295					300				
Lys	Thr	Pro	Lys	Asn	Gln	Glu	Ala	Leu	Arg	Met	Ala	Asn	Val	Ala	Glu
305					310					315					320

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

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

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

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

Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His
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<210> 21
<211> 417
<212> DNA
<213> Homo sapiens
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120

cacgagctgt atgtcagctt cagagacctg ggctggcagg actggatcat cgcgcctgaa
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240

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<210> 22
<211> 139
<212> PRT
<213> Homo sapiens

<400> 22

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20 25 30

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

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

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

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

Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr
115 120 125

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

<210> 23
<211> 3536
<212> DNA
<213> Homo sapiens

<400> 23

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120

tgagcgcccc aggcctgcca tgaccgcgct ccccgggccc ctctggctcc tgggcctggc
180

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360

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420

cgcgagcgcg cgcctgggcc gcgcgcacct ggtcatgagc ttcgtaaca tggtgagcg
480

agaccgtgcc ctgggcccacc aggagcccca ttggaaggag ttccgctttg acctgaccca
540

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660

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900

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1380

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2340

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aaagtacgtg tcaccctgga tgcccagcag ccctgtcctg tgtcttgggc ctgtgagtc
2520

aagaaaaggt ccttttcagg gagtgacaag tagtaattag gctgagttgg gtggagaggt
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agtccagctg cccaaaccgt gtcattaaaa gcagatcctg cggccgcccc atccacaggc
2760

acagcccggc agagtgggtc cacctcccca tgggccaag gatgcgcctc tctggagttc
2820

acgtgctgca ccccaggga ggggcctggg gaaagctggt ccagcagcag gggtaggagc
2880

tggggccaca ctgcgggaca gcagcccctc cacctggacc agggagggcc tccatgtgca
2940

agcgcagagg aagagaccct cccatgtacg caaagggcag cccaggctg tctggaagtt
3000

ggagaattcc ctatcagcac agggatctca gctctggcct ggaggtgaag agacctgcct
3060

tgtagggtggc ttocctatct ggcctccat tttctatctg cactttttga tctccaaaca
3120

accttcagcc aaagaatctg tctaccaact cctcatagtg agccagaagc agcctcataa
3180

ccctgaatgt ggggctctgg tggtgtcac gaagcagagt tggcacataa catggaacct
3240

ggccaggcat ggtggctcac acctataacc ccagcacttt gggaggccaa ggcaggcaga
3300

tcacctgaag tcaggagttc aagaccatcc tggccaacac agtgaaaccc catctgtact
3360

aaaaatacaa gattacctgg gcatgggtgt gcatgcctat aatcccagct actcaggagg
3420

ctgaggcaga attgcttgaa cctgggaggt ggagggttgca gtgagcagag atcacaacat
3480

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3536

<210> 24
<211> 402
<212> PRT
<213> Homo sapiens

<400> 24

Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys
1 5 10 15

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

47

340 345 350
 Leu Val His Leu Met Met Pro Asp Ala Val Pro Lys Ala Cys Cys Ala
 355 360 365
 Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn
 370 375 380
 Asn Val Ile Leu Arg Lys His Arg Asn Met Val Val Lys Ala Cys Gly
 385 390 395 400
 Cys His

<210> 25
 <211> 417
 <212> DNA
 <213> Homo sapiens

<400> 25
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 cgactcccag ggatctttga tgacgtccac ggctcccacg gccggcaggt ctgccgtcgg
 120
 cacgagctct acgtcagctt ccaggacctc ggctggctgg actgggtcat cgctcccca
 180
 ggctactcgg cctattactg tgagggggag tgctccttcc cactggactc ctgcatgaat
 240
 gccaccaacc acgccatcct gcagtccctg gtgcacctga tgatgccaga cgcagtcccc
 300
 aaggcgtgct gtgcaccac caagctgagc gccacctctg tgctctacta tgacagcagc
 360
 aacaatgtca tcctgcgcaa gcaccgcaac atggtggtca aggcctgcgg ctgccac
 417

<210> 26
 <211> 139
 <212> PRT
 <213> Homo sapiens
 <400> 26

48

Ala Val Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu
1 5 10 15

Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser
20 25 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

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

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

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

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

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

<210> 27
<211> 1942
<212> DNA
<213> Homo sapiens

<400> 27
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60

cagcagggag atgccggccc gctccttccc agtcctccc cgtgcccgt aacacagcac
120

ggccgcctgc agtctcctct ctgggtgatt gcgcgggcct aagatgtgtc ctggggcact
180

gtgggtggcc ctgcccctgc tgccctgct ggctggctcc ctacagggga agccactgca
240

gagctgggga cgaggggtctg ctgggggaaa cgcccacagc ccactggggg tgcctggagg
300

tgggctgcct gagcacacct tcaacctgaa gatgtttctg gagaacgtga aggtggattt
360

cctgcgcagc cttaacctga gtgggggtccc ttgcaggac aaaaccaggg tggagccgcc
420

gcagtacatg attgacctgt acaacaggta cacgtccgat aagtogacta cgccagcgtc
480

caacattgtg cggagcttca gcatggaaga tgccatctcc ataactgcc aagaggactt
540

ccccttcag aagcacatct tgctcttcaa catctccatt cctagggatg agcagatcac
600

cagagctgag ctccgactct atgtctcctg tcaaaatcac gtggaccctt ctcatgacct
660

gaaaggaagc gtggtcattt atgatgttct ggatggaaca gatgcctggg atagtgttac
720

agagaccaag accttcctgg tgtcccagga cattcaggat gagggtggg agaccttggg
780

agtgtccagc gccgtgaagc gctgggtccg gtccgactcc accaagagca aaaataagct
840

ggaagtgact gtggagagcc acaggaaggg ctgcgacacg ctggacatca gtgtcccccc
900

aggttcaga aacctgccct tctttgttgt cttctccaat gaccacagca gtgggaccaa
960

ggagaccagg ctggagctga gggagatgat cagccatgaa caagagagcg tgcctcaagaa
1020

gctgtccaag gacggctcca cagaggcagg tgagagcagt cacgaggagg acacggatgg
1080

ccacgtggct gcgggggtcga ctttagccag gcggaaaagg agcgccgggg ctggcagcca
1140

ctgtcaaaag acctccctgc gggtaaactt cgaggacatc ggctgggaca gctggatcat
1200

tgcaccaag gagtatgaag cctacgagtg taagggcggc tgcttcttcc ccttggctga
1260

cgatgtgacg ccgacgaaac acgctatcgt gcagaccctg gtgcatctca agttccccac
1320

aaaggtgggc aaggcctgct gtgtgccac caaactgagc cccatctccg tcctctacaa
1380

ggatgacatg ggggtgccca ccctcaagta ccattacgag ggcatgagcg tggcagagtg
1440

tgggtgcagg tagtatctgc ctgcggggct ggggaggcag gccaaagggg ctccacatga
1500

gaggtcctgc atgcccctgg gcacaacaag gactgattca atctgcatgc cagcctggag
1560

gaggaaaggg agcctgctct ccctccccac accccaccca aagcatacac cgctgagctc
1620

aactgccagg gaaggctaag gaaatgggga tttgagcaca acaggaaagc ctgggagggg
1680

tgttgggatg caaggaggtg atgaaaagga gacaggggga aaaataatcc atagtcagca
1740

gaaaacaaca gcagtgagcc agaggagcac aggcggggcag gtcactgcag agactgatgg
1800

aagttagaga ggtggaggag gccagctcgc tccaaaaccc ttggggagta gagggaagga
1860

gcaggccgcg tgtcacaccc atcattgtat gttatttccc acaaccagcagg ttgaggggga
1920

tggcttccaa tttagagacc cg
1942

<210> 28

<211> 429

<212> PRT

<213> Homo sapiens

<400> 28

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
20 25 30

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

Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val

50	55	60
Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys		
65	70	75 80
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
Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe		
	115	120 125
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		
145	150	155 160
Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu		
	165	170 175
Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu		
	180	185 190
Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser		
	195	200 205
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
Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val		
	245	250 255
Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu		
	260	265 270

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

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

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

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

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

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

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

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

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

<210> 29

<211> 1584

<212> DNA

<213> Homo sapiens

<400> 29

ggggagagga agagtggtag ggggagggag agagagagga agagtttcca aacttgtctc
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cagtgcacagg agacatttac gttccacaag ataaaactgc cacttagagc ccaggggaagc
 120

taaaccttcc tggcttgGCC taggagctcg agcggagtca tgggctctct ggtcctgaca
180

ctgtgcgctc ttttctgcct ggcagcttac ttggtttctg gcagcccat catgaaccta
240

gagcagtctc ctctggaaga agatatgtcc ctctttggtg atgttttctc agagcaagac
300

ggtgtcgact ttaacacact gctccagagc atgaaggatg agttttctta gacactaaac
360

ctctctgaca tccccacgca ggattcagcc aagggtggacc caccagagta catgttgga
420

ctctacaaca aatttgcaac agatcggacc tccatgccct ctgccaacat cattaggagt
480

ttcaagaatg aagatctgtt ttcccagcgc gtcagtttta atgggctccg aaaatacccc
540

ctcctottca atgtgtccat tctcaccat gaagagggtca tcatggctga acttaggcta
600

tacacactgg tgcaaaggga tcgtatgata tacgatggag tagaccgga aattaccatt
660

tttgaagtgc tggagagcaa aggggataat gagggagaaa gaaacatgct ggtcttggtg
720

tctggggaga tatatggaac caacagtgcg tgggagaact ttgatgtcac agatgccatc
780

agacgttggc aaaagtcagg ctcatccacc caccagctgg aggtccacat tgagagcaaa
840

cacgatgaag ctgaggatgc cagcagtgga cggctagaaa tagataccag tgcccagaat
900

aagcataacc ctttgctcat cgtgttttct gatgaccaa gcagtgaca ggagaggaag
960

gaggaactga atgaaatgat ttcccatgag caacttccag agctggacaa cttgggcctg
1020

gatagctttt ccagtggacc tggggaagag gctttgttgc agatgagatc aaacatcatc
1080

tatgactcca ctgcccgaat cagaaggaac gccaaaggaa actactgtaa gaggaccccg
1140

ctctacatcg acttcaagga gattgggtg gactcctgga tcatcgctcc gcctggatac
1200

gaagcctatg aatgccgtgg tgtttgtaac taccccctgg cagagcatct cacaccacaca
1260

aagcatgcaa ttatccaggc cttggtccac ctcaagaatt cccagaaagc ttccaaagcc
1320

tgctgtgtgc ccacaaagct agagcccac tcctcctct atttagacaa aggcgtcgtc
1380

acctacaagt ttaaatacga aggcattggc gtctccgaat gtggctgtag atagaagaag
1440

agtcctatgg cttattttaat aactgtaaat gtgtatattt ggtgttccta tttaatgaga
1500

ttattttaata aggggtgtaca gtaatagagg cttgctgcct tcaggaaatg gacaggtcag
1560

tttggtgtag gaaatgcata tttt
1584

<210> 30

<211> 424

<212> PRT

<213> Homo sapiens

<400> 30

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

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

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

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

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

100					105					110					
Leu	Phe	Ser	Gln	Pro	Val	Ser	Phe	Asn	Gly	Leu	Arg	Lys	Tyr	Pro	Leu
		115						120				125			
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	
Asn	Glu	Gly	Glu	Arg	Asn	Met	Leu	Val	Leu	Val	Ser	Gly	Glu	Ile	Tyr
			180					185					190		
Gly	Thr	Asn	Ser	Glu	Trp	Glu	Thr	Phe	Asp	Val	Thr	Asp	Ala	Ile	Arg
		195					200					205			
Arg	Trp	Gln	Lys	Ser	Gly	Ser	Ser	Thr	His	Gln	Leu	Glu	Val	His	Ile
	210					215					220				
Glu	Ser	Lys	His	Asp	Glu	Ala	Glu	Asp	Ala	Ser	Ser	Gly	Arg	Leu	Glu
225					230					235					240
Ile	Asp	Thr	Ser	Ala	Gln	Asn	Lys	His	Asn	Pro	Leu	Leu	Ile	Val	Phe
				245					250					255	
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				
Asn	Ile	Ile	Tyr	Asp	Ser	Thr	Ala	Arg	Ile	Arg	Arg	Asn	Ala	Lys	Gly
305					310					315					320

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

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

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

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

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
405 410 415

Ala Val Ser Glu Cys Gly Cys Arg
420

<210> 31

<211> 324

<212> DNA

<213> Homo sapiens

<400> 31

aacgccaaag gaaactactg taagaggacc ccgctctaca tcgacttcaa ggagattggg
60

tgggactcct ggatcatcgc tccgcctgga tacgaagcct atgaatgccg tgggtgtttgt
120

aactaccccc tggcagagca tctcacaccc acaaagcatg caattatcca ggccttggtc
180

cacctcaaga attcccagaa agcttccaaa gcctgctgtg tgcccacaaa gctagagccc
240

atctocatcc tctatttaga caaaggcgtc gtcacctaca agtttaaata cgaaggcatg
300

gcogtctcgc aatgtggctg taga
324

<210> 32
<211> 108
<212> PRT
<213> Homo sapiens

<400> 32

Asn Ala Lys Gly Asn Tyr Cys Lys Arg Thr Pro Leu Tyr Ile Asp Phe
1 5 10 15

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

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

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

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

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

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

<210> 33
<211> 1443
<212> DNA
<213> Homo sapiens

<400> 33

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tgctgggctt cctgctctc gccctggagc tgcggccccg gggggaggcg gccgagggcc
120

ccgcggcggc ggcggcggcg gcggcggcgg cggcagcggc gggggtcggg ggggagcgct
180

ccagccggcc agccccgtcc gtggcgcccc agccggacgg ctgccccgtg tgcgtttggc
240

ggcagcacag cgcgagctg cgcctagaga gcatcaagtc gcagatcttg agcaaactgc
300

ggctcaagga ggcgccaac atcagccgcg aggtggtgaa gcagctgctg cccaaggcgc
360

cgcgctgca gcagatcctg gacctacacg acttccaggg cgacgcgctg cagcccaggg
420

acttcctgga ggaggacgag taccacgcca ccaccgagac cgtcattagc atggcccagg
480

agacggaccc agcagtacag acagatggca gccctctctg ctgccatttt cacttcagcc
540

ccaaggtgat gttcacaaag gtactgaagg ccagctgtg ggtgtaccta cggcctgtac
600

ccgccccagc cacagtctac ctgcagatct tgcgactaaa acccctaact ggggaaggga
660

ccgcaggggg agggggcgga ggocggcgtc acatccgtat ccgctcactg aagattgagc
720

tgcactcacg ctcaggccat tggcagagca tcgacttcaa gcaagtgcta cacagctggt
780

tccgccagcc acagagcaac tggggcatcg agatcaacgc ctttgatccc agtggcacag
840

acctggctgt cacctccctg gggcggggag ccgagggggt gcatccattc atggagcttc
900

gagtcctaga gaacacaaaa cgttcccggc ggaacctggg totggactgc gacgagcact
960

caagcgagtc ccgctgctgc cgatatcccc tcacagtgga ctttgagggt ttcggtggg
1020

actggatcat cgcacctaag cgctacaagg ccaactactg ctccggccag tgogagtaca
1080

tgttcattgca aaaatatccg catacccatt tggcgcagca ggccaatcca agaggctctg
1140

ctgggccctg ttgtaccccc accaagatgt cccaatcaa catgctctac ttcaatgaca
1200

agcagcagat tatctacggc aagatccctg gcatggtggt ggatcgctgt ggctgctctt
1260

aaggtggggg atagaggatg cctccccac agaccctacc ccaagacccc tagccctgcc
1320

cccatccccc caagccctag agctccctcc actcttcccg cgaacatcac accgttcccc
1380

gaccaagccg tgtgcaatac aacagaggga ggcaggtggg aattgagggg gaggggtttg
1440

ggg
1443

<210> 34
<211> 407
<212> PRT
<213> Homo sapiens

<400> 34

Met Val Leu Ala Ala Pro Leu Leu Leu Gly Phe Leu Leu Leu Ala Leu
1 5 10 15

Glu Leu Arg Pro Arg Gly Glu Ala Ala Glu Gly Pro Ala Ala Ala Ala
20 25 30

Ala Ala Ala Ala Ala Ala Ala Ala Gly Val Gly Gly Glu Arg Ser
35 40 45

Ser Arg Pro Ala Pro Ser Val Ala Pro Glu Pro Asp Gly Cys Pro Val
50 55 60

Cys Val Trp Arg Gln His Ser Arg Glu Leu Arg Leu Glu Ser Ile Lys
65 70 75 80

Ser Gln Ile Leu Ser Lys Leu Arg Leu Lys Glu Ala Pro Asn Ile Ser
85 90 95

Arg Glu Val Val Lys Gln Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln
100 105 110

Ile Leu Asp Leu His Asp Phe Gln Gly Asp Ala Leu Gln Pro Glu Asp
115 120 125

Phe Leu Glu Glu Asp Glu Tyr His Ala Thr Thr Glu Thr Val Ile Ser
130 135 140

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

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

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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Phe Asn Asp Lys Gln Gln Ile Ile Tyr Gly Lys Ile Pro Gly Met Val
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Val Asp Arg Cys Gly Cys Ser
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<212> DNA

<213> Homo sapiens

<400> 35

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600

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<210> 36

<211> 453

<212> PRT

<213> Homo sapiens

<400> 36

Met	Asp	Leu	Ser	Ala	Ala	Ala	Ala	Leu	Cys	Leu	Trp	Leu	Leu	Ser	Ala
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Cys	Arg	Pro	Arg	Asp	Gly	Leu	Glu	Ala	Ala	Ala	Val	Leu	Arg	Ala	Ala
			20					25					30		

Gly Ala Gly Pro Val Arg Ser Pro Gly Gly Gly Gly Gly Gly Gly Gly
 35 40 45

Gly Gly Gly Gly Gly Arg Thr Leu Ala Gln Ala Ala Gly Ala Ala Ala
 50 55 60

Val Pro Ala Ala Ala Val Pro Arg Ala Arg Ala Ala Arg Arg Ala Ala
 65 70 75 80

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
 130 135 140

Leu Phe Asp Val Ser Ser Leu Asn Asp Ala Asp Glu Val Val Gly Ala
 145 150 155 160

Glu Leu Arg Val Leu Arg Arg Gly Ser Pro Glu Ser Gly Pro Gly Ser
 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
 195 200 205

Gln Arg Trp Glu Ala Phe Asp Val Ala Asp Ala Met Arg Arg His Arg
 210 215 220

Arg Glu Pro Arg Pro Pro Arg Ala Phe Cys Leu Leu Leu Arg Ala Val
 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
 260 265 270

Val Ser Ser Arg Thr Gln Arg Lys Glu Ser Leu Phe Arg Glu Ile Arg
 275 280 285

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

Asp Pro Gly Thr Gly Thr Ala Ser Pro Arg Ala Val Ile Gly Gly Arg
 305 310 315 320

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
 340 345 350

Ser Arg Lys Pro Leu His Val Asp Phe Lys Glu Leu Gly Trp Asp Asp
 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
 385 390 395 400

Ile Gln Thr Leu Leu Asn Ser Met Ala Pro Asp Ala Ala Pro Ala Ser
 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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<213> Homo sapiens

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

<400> 38

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Leu	Trp	Asp	Leu	Pro	Gly	Phe	Gln	Gln	Ala	Ser	Ile	Ser	Ser	Ser	Ser
			20					25					30		

Ser	Ser	Ala	Glu	Leu	Gly	Ser	Thr	Lys	Gly	Met	Arg	Ser	Arg	Lys	Glu
		35					40					45			

Gly	Lys	Met	Gln	Arg	Ala	Pro	Arg	Asp	Ser	Asp	Ala	Gly	Arg	Glu	Gly
	50					55					60				

Gln	Glu	Pro	Gln	Pro	Arg	Pro	Gln	Asp	Glu	Pro	Arg	Ala	Gln	Gln	Pro
65					70					75					80

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
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Ile Asn Ala Ser Phe Phe Gln Ser Ser Lys Ser Ala Asn Thr Ile Thr
 115 120 125

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 Glu Gly Leu His Val His
 145 150 155 160

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

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

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

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
 225 230 235 240

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

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

Ser Leu Lys Arg Leu Gly Ala Pro Asp Arg Thr Gly Pro Val Val Arg
 275 280 285

Ser Cys Pro His Lys Arg Thr Pro Lys Trp Gly Lys Lys Arg Ile Leu
 290 295 300

Arg Pro Leu Arg Ala Ala Leu Pro Ala Arg Glu Ser Phe Gly Leu Ala
 305 310 315 320

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

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
 355 360 365

Lys Asn Arg Asp Asp Glu His Leu Ser Ser Thr His Phe Trp Asn Leu
 370 375 380

Val Glu Arg Ser Gly Pro Gln Gly Leu Lys Ser Arg Glu Leu Asp Phe
 385 390 395 400

Lys Gly Ser Gln Glu Lys Asp Ser Cys Gln Glu Thr Lys Ile Ser Pro
 405 410 415

Asn Pro Ala Ile Val Thr Gly Asn Val Tyr Met Ser Asn Val Gln Gln
 420 425 430

Thr Pro Leu Thr Glu Val Ser Arg Gln Gln Ala Lys Cys Leu Gln Gly
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Asn Ser Ala Trp Cys Cys Ile His Ser Pro Gly Trp Met Pro Pro Leu
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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
 485 490 495

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
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Arg Gln Ala Pro Ser Ala Pro Trp Gly Pro Pro Ala Gly Pro Leu His
 545 550 555 560

Val Gln Leu Phe Pro Cys Leu Ser Pro Leu Leu Leu Asp Ala Arg Thr
 565 570 575

Leu Asp Pro Gln Gly Ala Pro Pro Ala Gly Trp Glu Val Phe Asp Val
 580 585 590

Trp Gln Gly Leu Arg His Gln Pro Trp Lys Gln Leu Cys Leu Glu Leu
 595 600 605

Arg Ala Ala Trp Gly Glu Leu Asp Ala Gly Glu Ala Glu Ala Arg Ala
 610 615 620

Arg Gly Pro Gln Gln Pro Pro Pro Asp Leu Arg Ser Leu Gly Phe
 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
 660 665 670

Gly Ser Ala Glu Ala Ala Gly Pro Gly Ala Gly Ala Glu Gly Ser Trp
 675 680 685

Pro Pro Pro Ser Gly Ala Pro Asp Ala Arg Pro Trp Leu Pro Ser Pro
 690 695 700

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

Asn Phe Lys Glu Leu Gly Trp Asp Asp Trp Ile Ile Ala Pro Leu Glu
 740 745 750

Tyr Glu Ala Tyr His Cys Glu Gly Val Cys Asp Phe Pro Leu Arg Ser
 755 760 765

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
 785 790 795 800

Thr Pro Ile Ser Ile Leu Tyr Ile Asp Ala Gly Asn Asn Val Val Tyr
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Lys Gln Tyr Glu Asp Met Val Val Glu Ser Cys Gly Cys Arg
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<212> PRT

<213> Homo sapiens

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

Ile	Ala	Leu	Leu	Ala	Glu	Ala	Pro	Thr	Leu	Pro	Leu	Ile	Glu	Glu	Leu
			35				40					45			

Leu Glu Glu Ser Pro Gly Glu Gln Pro Arg Lys Pro Arg Leu Leu Gly
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His Ser Leu Arg Tyr Met Leu Glu Leu Tyr Arg Arg Ser Ala Asp Ser
 65 70 75 80

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

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

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

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

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

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

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
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Met Glu Arg Glu Ser Leu Leu Arg Arg Thr Arg Gln Ala Asp Gly Ile
 260 265 270

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
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Trp Asp His Trp Ile Ile Ala Pro Pro Phe Tyr Thr Pro Asn Tyr Cys
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Lys Gly Thr Cys Leu Arg Val Leu Arg Asp Gly Leu Asn Ser Pro Asn
 325 330 335

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Pro Arg Pro Ser Cys Val Pro Tyr Lys Tyr Val Pro Ile Ser Val Leu
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 120

tggatcattg ctcccccttt ctacacccca aactactgta aaggaacttg tctcogagta
 180

ctacgcgatg gtctcaattc cccaatcac gccattattc agaaccttat caatcagttg
 240

gtggaccaga gtgtcccccg gccctcctgt gtcccggtata agtatgttcc aattagtgtc
300

cttatgattg aggcaaatgg gagtattttg tacaaggagt atgaggggtat gattgctgag
360

tcttgtacat gcaga
375

<210> 42
<211> 125
<212> PRT
<213> Homo sapiens

<400> 42

Gln	Ala	Asp	Gly	Ile	Ser	Ala	Glu	Val	Thr	Ala	Ser	Ser	Ser	Lys	His
1				5					10					15	

Ser	Gly	Pro	Glu	Asn	Asn	Gln	Cys	Ser	Leu	His	Pro	Phe	Gln	Ile	Ser
			20					25					30		

Phe	Arg	Gln	Leu	Gly	Trp	Asp	His	Trp	Ile	Ile	Ala	Pro	Pro	Phe	Tyr
		35					40					45			

Thr	Pro	Asn	Tyr	Cys	Lys	Gly	Thr	Cys	Leu	Arg	Val	Leu	Arg	Asp	Gly
	50					55					60				

Leu	Asn	Ser	Pro	Asn	His	Ala	Ile	Ile	Gln	Asn	Leu	Ile	Asn	Gln	Leu
65					70					75					80

Val	Asp	Gln	Ser	Val	Pro	Arg	Pro	Ser	Cys	Val	Pro	Tyr	Lys	Tyr	Val
				85					90					95	

Pro	Ile	Ser	Val	Leu	Met	Ile	Glu	Ala	Asn	Gly	Ser	Ile	Leu	Tyr	Lys
			100					105					110		

Glu	Tyr	Glu	Gly	Met	Ile	Ala	Glu	Ser	Cys	Thr	Cys	Arg
	115						120					125

<210> 43
<211> 1744
<212> DNA
<213> Homo sapiens

<400> 43

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120

ctggcgtaga tgctgagcct ctaccgcgac ccgctgccga gggcagacat catccgcagc
180

ctacaggcag aagatgtggc agtggatggg cagaactgga cgtttgcttt tgactttctc
240

ttcctgagcc aacaagagga tctggcatgg gctgagctcc ggctgcagct gtccagccct
300

gtggacctcc cactgaggg ctcacttgcc attgagattt tccaccagcc aaagcccgac
360

acagagcagg cttcagacag ctgcttagag cggtttcaga tggacctatt cactgtcact
420

ttgtcccagg tcaccttttc cttgggcagc atggttttgg aggtgaccag gcctctctcc
480

aagtggctga agcgccctgg ggcctggag aagcagatgt ccagggtagc tggagagtgc
540

tggccgcggc cccccacacc gcctgccacc aatgtgctcc ttatgctcta ctccaacctc
600

tgcaggagc agaggcagct ggggtgggtcc accttgctgt gggaagccga gagctcctgg
660

cgggcccagg agggacagct gtcttgggag tggggcaaga ggcaccgtcg acatcacttg
720

ccagacagaa gtcaactgtg tcggaaggtc aagttccagg tggacttcaa cctgatcgga
780

tggggctcct ggatcatcta cccaagcag tacaacgcct atcgctgtga gggcgagtgt
840

cctaactctg ttggggagga gtttcatccg accaaccatg catacatcca gagtctgctg
900

aaacgttacc agccccaccg agtcccttcc acttggtgtg cccagtgaa gaccaagccg
960

ctgagcatgc tgtatgtgga taatggcaga gtgctcctag atcaccataa agacatgato
1020

gtggaagaat gtgggtgcct ctgatgacat cctggagggg gactggattt gcctgcactc
1080

tggaaggctg ggaaactcct ggaagacatg ataaccatct aatccagtaa ggagaaacag
1140

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1200

tgaagggtct agtggagtct ggccaagcac agaggctgct gtcaggaaga gggaggaaga
1260

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1320

cacaagtgca tgagttcttt actggatttt ttaaaaacct gtgaaccccc cgaaactgta
1380

tgtgaaagtt gagacatatg tgcattgtatt ttggagggtg gatgaagtca cctatagctt
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1500

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1560

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1620

gttctctgct aatgagctgt acaacaataa agccattgtc tagttaaaaa aaaaaaaaaa
1680

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1740

aaaa
1744

<210> 44
<211> 347
<212> PRT
<213> Homo sapiens

<400> 44

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

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

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

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

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

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

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
 340 345

<210> 45
 <211> 504
 <212> DNA
 <213> Homo sapiens

<400> 45
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 120
 cgggcccagg agggacagct gtcctgggag tggggcaaga ggcaccgtcg acatcaactg
 180
 ccagacagaa gtcaactgtg tcggaaggtc aagttccagg tggacttcaa cctgatcgga
 240
 tggggctcct ggatcatcta cccaagcag tacaacgcct atcgctgtga gggcgagtgt
 300
 cctaatacctg ttggggagga gtttcatccg accaaccatg catacatcca gagtctgctg
 360
 aaacgttacc agccccaccg agtcccttcc acttggtgtg cccagtgaa gaccaagccg
 420
 ctgagcatgc tgtatgtgga taatggcaga gtgctcctag atcaccataa agacatgatc
 480

gtggaagaat gtgggtgcct ctga
504

<210> 46
<211> 167
<212> PRT
<213> Homo sapiens

<400> 46

Trp Pro Arg Pro Pro Thr Pro Pro Ala Thr Asn Val Leu Leu Met Leu
1 5 10 15

Tyr Ser Asn Leu Ser Gln Glu Gln Arg Gln Leu Gly Gly Ser Thr Leu
20 25 30

Leu Trp Glu Ala Glu Ser Ser Trp Arg Ala Gln Glu Gly Gln Leu Ser
35 40 45

Trp Glu Trp Gly Lys Arg His Arg Arg His His Leu Pro Asp Arg Ser
50 55 60

Gln Leu Cys Arg Lys Val Lys Phe Gln Val Asp Phe Asn Leu Ile Gly
65 70 75 80

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
115 120 125

Pro Ser Thr Cys Cys Ala Pro Val Lys Thr Lys Pro Leu Ser Met Leu
130 135 140

Tyr Val Asp Asn Gly Arg Val Leu Leu Asp His His Lys Asp Met Ile
145 150 155 160

Val Glu Glu Cys Gly Cys Leu
165

<210> 47
<211> 1101
<212> DNA
<213> Homo sapiens

<400> 47

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120

cccaccctgg acagggccga catggaggag ctggtcatcc ccaccacgt gagggcccag
180

tacgtggccc tgctgcagcg cagccacggg gaccgctccc gcggaagag gttcagccag
240

agcttccgag aggtggccgg caggttcctg gcgttgagg ccagcacaca cctgctggctg
300

ttcggcatgg agcagcggct gccgcccaac agcgagctgg tgcaggccgt gctgcggctc
360

ttccaggagc cgggtcccaa ggccgcgctg cacaggcacg ggccgctgtc cccgcgcagc
420

gccccggccc gggtgaccgt cgagtggctg cgcgtccgcg acgacggctc caaccgcacc
480

tccctcatcg actccaggct ggtgtccgtc cacgagagcg gctggaaggc cttcgacgtg
540

accgaggccg tgaacttctg gcagcagctg agccggcccc ggagccgct gctgctacag
600

gtgtcggtgc agaggagca tctgggcccg ctggcgtccg gcgccacaa gctggtccgc
660

tttgccctgc agggggcgcc agccgggctt ggggagcccc agctggagct gcacaccctg
720

gaccttgggg actatggagc tcagggcgac tgtgacctg aagcaccaat gaccgagggc
780

accgctgct gcgcgcagga gatgtacatt gacctgcagg ggatgaagtg ggccgagaac
840

tgggtgctgg agccccggg cttcctggct tatgagtgtg tgggcacctg ccggcagccc
900

cggaggccc tggccttcaa gtggcgttt ctggggcctc gacagtgcac cgcctcggag
960

actgcctcgc tgcccatgat cgtcagcatc aaggaggag gcaggaccag gcccagggtg
1020

gtcagcctgc ccaacatgag ggtgcagaag tgcagctgtg cctcggatgg tgcgctcgtg
1080

ccaaggaggc tccagccata g
1101

<210> 48

<211> 366

<212> PRT

<213> Homo sapiens

<400> 48

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

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

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

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

Leu Gln 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 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
115 120 125

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

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
			180					185					190		
Pro	Arg	Gln	Pro	Leu	Leu	Leu	Gln	Val	Ser	Val	Gln	Arg	Glu	His	Leu
		195					200					205			
Gly	Pro	Leu	Ala	Ser	Gly	Ala	His	Lys	Leu	Val	Arg	Phe	Ala	Ser	Gln
	210					215					220				
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
				245					250					255	
Met	Thr	Glu	Gly	Thr	Arg	Cys	Cys	Arg	Gln	Glu	Met	Tyr	Ile	Asp	Leu
			260					265					270		
Gln	Gly	Met	Lys	Trp	Ala	Glu	Asn	Trp	Val	Leu	Glu	Pro	Pro	Gly	Phe
		275					280					285			
Leu	Ala	Tyr	Glu	Cys	Val	Gly	Thr	Cys	Arg	Gln	Pro	Pro	Glu	Ala	Leu
	290					295					300				
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
				325					330					335	
Arg	Pro	Gln	Val	Val	Ser	Leu	Pro	Asn	Met	Arg	Val	Gln	Lys	Cys	Ser
			340					345					350		

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

<210> 49

<211> 1098

<212> DNA

<213> Homo sapiens

<400> 49

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120

cccgtactgg acagggccga catggagaag ctggcatcc ccgcccacgt gagggcccag
180

tatgtagtcc tgctgoggcg cagccacggg gaccgctccc gcggaaagag gttcagccag
240

agcttcagag aggtggccgg caggttcctg gcgtcggagg ccagcacaca cctgctggcg
300

ttcggcatgg agcagcggct gccgccaac agcgagctgg tgcaggcctg gctgcggctc
360

ttccaggagc cggccccaa ggccgcgctg cacaggcacg ggcggtgtc ccgcgcagc
420

gccaggccc gggtgaccgt cgagtggctg cggtccgag acgacggctc caaccgcacc
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tccctcatcg actccaggct ggtgtccgtc cagcagagcg gctggaaggc cttcgacgtg
540

accgaggccg tgaacttctg gcagcagctg agccggcccc ggcagccgct gctgctacag
600

gtgtcggctg agagggagca tctgggcccg ctggcgtccg gcgcccacaa gctggctccg
660

tttgctcgc agggggcgcc agccgggctt ggggagcccc agctggagct gcacaccctg
720

gacctcaggg actatggagc tcagggcgac tgtgaccctg aagcaccaat gaccgagggc
780

accgctgct gccgccagga gatgtacatt gacctgcagg ggatgaagtg ggccaagaac
840

tgggtgctgg agccccggg cttcctggct tacgagtgtg tgggcacctg ccagcagccc
900

ccggaggccc tggccttcaa ttggccattt ctggggccgc gacagtgtat cgcctcggag
960

actgcctcgc tgcccatgat cgtcagcacc aaggagggag gcaggaggcc ccaggtggtc
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1080

aggaggctcc agccatag
1098

<210> 50
<211> 365
<212> PRT
<213> Homo sapiens

<400> 50

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

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

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

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

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

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
115 120 125

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

130		135		140
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				
	180	185		190
Pro Arg Gln Pro Leu Leu Leu Gln Val Ser Val Gln Arg Glu His Leu				
	195	200	205	
Gly Pro Leu Ala Ser Gly Ala His Lys Leu Val Arg Phe Ala Ser Gln				
210		215	220	
Gly Ala Pro Ala Gly Leu Gly Glu Pro Gln Leu Glu Leu His Thr Leu				
225		230	235	240
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				
	260	265		270
Gln Gly Met Lys Trp Ala Lys Asn Trp Val Leu Glu Pro Pro Gly Phe				
	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				
305		310	315	320
Thr Ala Ser Leu Pro Met Ile Val Ser Ile Lys Glu Gly Gly Arg Arg				
	325	330		335
Pro Gln Val Val Ser Leu Pro Asn Met Arg Val Gln Lys Cys Ser Cys				
	340	345	350	

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

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

<400> 51
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120

gatcaaaggc aggcgatact tctgtttgcc gggacgctat atataacgtg atgagcgcac
180

gggctgcgga gacgcaccgg agcgctcgcc cagccgccgc ctccaagccc ctgaggtttc
240

cggggaccac aatgaacaag ttgctgtgct gcgcgctcgt gtttctggac atctcatta
300

agtggaccac ccaggaaacg tttcctccaa agtaccttca ttatgacgaa gaaacctctc
360

atcagctggt gtgtgacaaa tgcctcctg gtacctacct aaaacaacac tgtacagcaa
420

agtgaagac cgtgtgcgcc cttgccctg accactacta cacagacagc tggcacacca
480

gtgacgagt tctatactgc agccccgtgt gcaaggagct gcagtacgtc aagcaggagt
540

gcaatcgcac ccacaaccgc gtgtgcgaat gcaaggaagg gcgctacctt gagatagagt
600

tctgcttgaa acataggagc tgccctcctg gatttgaggt ggtgcaagct ggaaccccag
660

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720

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780

gaaatgcaac acacgacaac atatgttccg gaaacagtga atcaactcaa aaatgtggaa
840

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900

ctaactggct tagtgtcttg gtagacaatt tgccctggcac caaagtaaac gcagagagtg
960

tagagaggat aaaacggcaa cacagctcac aagaacagac tttccagctg ctgaagttat
1020

ggaaacatca aaacaaagac caagatatag tcaagaagat catccaagat attgacctct
1080

gtgaaaacag cgtgcagcgg cacattggac atgctaacct caccttogag cagcttcgta
1140

gcttgatgga aagcttaccg ggaaagaaag tgggagcaga agacattgaa aaaacaataa
1200

aggcatgcaa acccagtgac cagatcctga agctgctcag tttgtggoga ataaaaaatg
1260

gcgaccaaga caccttgaag ggcctaatagc acgcactaaa gcactcaaag acgtaccact
1320

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1380

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1440

aaataagctg cttataactg gaaatggcca ttgagctggt tcctcacaat tggcgagatc
1500

ccatggatga gtaaactggt tctcaggcac ttgaggcttt cagtgatatc tttctcatta
1560

ccagtgacta attttgccac aggggtactaa aagaaactat gatgtggaga aaggactaac
1620

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1680

gactatattt tcccttatta ctgcttgcag taattcaact ggaaattaaa aaaaaaaaaa
1740

tagactccat tgtgccttac taaatatggg aatgtctaac ttaaataagct ttgagatttc
1800

agotatgcta gaggcctttta ttagaaagcc atattttttt ctgtaaaagt tactaatata
1860

tctgtaacac tattacagta ttgctattta tattcattca gatataagat ttgtacatat
1920

tatcatoccta taaagaaacg gtatgactta attttagaaa gaaaattata ttctgtttat
1980

tatgacaaat gaaagagaaa atatataattt ttaatggaaa gtttgtagca tttttctaata
2040

aggtactgcc atatTTTTtct gtgtggagta tttttataat tttatctgta taagctgtaa
2100

tatcattttta tagaaaatgc attatttagt caattgttta atgttggaac acatatgaaa
2160

tataaattat ctgaatatta gatgctotga gaaattgaat gtacottatt taaaagattt
2220

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2280

aaaaaaaaa a
2291

<210> 52
<211> 401
<212> PRT
<213> Homo sapiens

<400> 52

Met	Asn	Lys	Leu	Leu	Cys	Cys	Ala	Leu	Val	Phe	Leu	Asp	Ile	Ser	Ile
1				5					10					15	

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
		35					40					45			

Tyr	Leu	Lys	Gln	His	Cys	Thr	Ala	Lys	Trp	Lys	Thr	Val	Cys	Ala	Pro
	50					55					60				

Cys	Pro	Asp	His	Tyr	Tyr	Thr	Asp	Ser	Trp	His	Thr	Ser	Asp	Glu	Cys
65					70					75					80

Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu	Gln	Tyr	Val	Lys	Gln	Glu
				85					90					95	

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

100	105	110
Leu Glu Ile Glu Phe Cys Leu Lys His Arg Ser Cys Pro Pro Gly Phe		
115	120	125
Gly Val Val Gln Ala Gly Thr Pro Glu Arg Asn Thr Val Cys Lys Arg		
130	135	140
Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro Cys		
145	150	155
Arg Lys His Thr Asn Cys Ser Val Phe Gly Leu Leu Leu Thr Gln Lys		
165	170	175
Gly Asn Ala Thr His Asp Asn Ile Cys Ser Gly Asn Ser Glu Ser Thr		
180	185	190
Gln Lys Cys Gly Ile Asp Val Thr Leu Cys Glu Glu Ala Phe Phe Arg		
195	200	205
Phe Ala Val Pro Thr Lys Phe Thr Pro Asn Trp Leu Ser Val Leu Val		
210	215	220
Asp Asn Leu Pro Gly Thr Lys Val Asn Ala Glu Ser Val Glu Arg Ile		
225	230	235
Lys Arg Gln His Ser Ser Gln Glu Gln Thr Phe Gln Leu Leu Lys Leu		
245	250	255
Trp Lys His Gln Asn Lys Asp Gln Asp Ile Val Lys Lys Ile Ile Gln		
260	265	270
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		
290	295	300
Lys Lys Val Gly Ala Glu Asp Ile Glu Lys Thr Ile Lys Ala Cys Lys		
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
 340 345 350

Lys Thr Tyr His Phe Pro Lys Thr Val Thr Gln Ser Leu Lys Lys Thr
 355 360 365

Ile Arg Phe Leu His Ser Phe Thr Met Tyr Lys Leu Tyr Gln Lys Leu
 370 375 380

Phe Leu Glu Met Ile Gly Asn Gln Val Gln Ser Val Lys Ile Ser Cys
 385 390 395 400

Leu

<210> 53
 <211> 1014
 <212> DNA
 <213> Homo sapiens

<400> 53
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 60

agccccgtgt gcaaggagct gcagtacgtc aagcaggagt gcaatcgcac ccacaaccgc
 120

gtgtgcgaat gcaaggaagg gcgctacctt gagatagagt tctgcttgaa acataggagc
 180

tgccctcctg gatttggagt ggtgcaagct ggaaccccag agcgaaatac agtttgcaaa
 240

agatgtocag atgggttctt ctcaaagag acgtcatcta aagcaccctg tagaaaacac
 300

acaaattgca gtgtcttttg tctcctgcta actcagaaag gaaatgcaac acacgacaac
 360

atatgttccg gaaacagtga atcaactcaa aaatgtggaa tagatgttac cctgtgtgag
 420

gaggcattct tcaggtttgc tgttcttaca aagtttacgc ctaactggct tagtgtcttg
 480

gtagacaatt tgcctggcac caaagtaaac gcagagagtg tagagaggat aaaacggcaa
540

cacagctcac aagaacagac tttccagctg ctgaagttat ggaaacatca aaacaaagac
600

caagatatag tcaagaagat catccaagat attgacctct gtgaaaacag cgtgcagcgg
660

cacattggac atgctaacct caccttcgag cagcttcgta gcttgatgga aagcttacgg
720

ggaaagaaag tgggagcaga agacattgaa aaaacaataa aggcattgcaa acccagtgac
780

cagatcctga agctgctcag tttgtggcga ataaaaaatg gcgaccaaga caccttgaag
840

ggcctaattgc acgcactaaa gcactcaaag acgtaccact ttcccaaaac tgtcactcag
900

agtctaaaga agaccatcag gttccttcac agcttcacaa tgtacaaatt gtatcagaag
960

ttatttttag aaatgatagg taaccaggtc caatcagtaa aaataagctg ctta
1014

<210> 54

<211> 338

<212> PRT

<213> Homo sapiens

<400> 54

Pro	Cys	Pro	Asp	His	Tyr	Tyr	Thr	Asp	Ser	Trp	His	Thr	Ser	Asp	Glu
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Cys	Leu	Tyr	Cys	Ser	Pro	Val	Cys	Lys	Glu	Leu	Gln	Tyr	Val	Lys	Gln
			20					25					30		

Glu	Cys	Asn	Arg	Thr	His	Asn	Arg	Val	Cys	Glu	Cys	Lys	Glu	Gly	Arg
		35					40					45			

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

Arg Cys Pro Asp Gly Phe Phe Ser Asn Glu Thr Ser Ser Lys Ala Pro
 85 90 95

Cys Arg Lys His Thr Asn Cys Ser Val Phe Gly Leu Leu Leu Thr Gln
 100 105 110

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

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

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

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

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

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

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

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

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

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

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

Cys Leu

<210> 55
 <211> 2312
 <212> DNA
 <213> Homo sapiens

<400> 55
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 60

ccacctccga ccaccgccag cgctccaggc ccgcgcgtcc ccgctcgccg ccaccgcgcc
 120

ctccgctccg ccgcgcgtgc caaccatgac cgccgccagt atgggccccg tccgcgtcgc
 180

cttcgtggtc ctactgccc tctgcagccg gccggccgtc ggccagaact gcagcgggac
 240

gtgccggtgc ccggacgagc cggcgccgcg ctgcccgccg ggcgtagacc tcgtgctgga
 300

cggctgcggc tgctgccgcg tctgcgcaa gcagctgggc gagctgtgca ccgagcgcga
 360

cccctgcgac ccgcacaagg gcctcttctg tgacttcggc tccccggcca accgcaagat
 420

cggcggtgtgc accgccaaag atggtgctcc ctgcatcttc ggtggtacgg tgtaccgcag
 480

cggagagtcc ttccagagca gctgcaagta ccagtgcacg tgccctggacg gggcggtggg
 540

ctgcatgccc ctgtgcagca tggacgttcg tctgccagc cctgactgcc cttccccgag
 600

gagggtaag ctgcccgga aatgctgcga ggagtgggtg tgtgacgagc ccaaggacca
 660

aaccgtgggtt gggcctgccc tcgcggctta ccgactggaa gacacgtttg gccagagccc
720

aactatgatt agagccaact gcctgggtcca gaccacagag tggagcgctt gttccaagac
780

ctgtgggatg ggcattctcca cccgggttac caatgacaac gcctcctgca ggctagagaa
840

gcagagccgc ctgtgcatgg tcaggccttg cgaagctgac ctggaagaga acattaagaa
900

gggcaaaaag tgcattccgta ctcccaaaat ctccaagcct atcaagtttg agctttctgg
960

ctgcaccagc atgaagacat accgagctaa attctgtgga gtatgtaccg acggccgatg
1020

ctgcaccccc cacagaacca ccaccctgcc ggtggagttc aagtgccctg acggcgaggt
1080

catgaagaag aacatgatgt tcatcaagac ctgtgcctgc cattacaact gtcccggaga
1140

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1200

gagagtgaga gacattaact cattagactg gaacttgaac tgattcacat ctcatTTTTc
1260

cgtaaaaatg atttcagtag cacaagttat ttaaattctgt ttttctaact gggggaaaag
1320

attcccaccc aattcaaaac attgtgccat gtcaaacaaa tagtctatct tcccagaca
1380

ctggtttgaa gaatgttaag acttgacagt ggaactacat tagtacacag caccagaatg
1440

tatattaagg tgtggcttta ggagcagtgg gagggtagca gcagaaagggt tagtatcatc
1500

agatagctct tatacgagta atatgcctgc tatttgaagt gtaattgaga aggaaaattt
1560

tagcgtgctc actgaacctg ctgtagcccc agtgacagct aggatgtgca ttctccagcc
1620

atcaagagac tgagtcaagt tgttcoctaa gtcagaacag cagactcagc tctgacatto
1680

tgattcgaat gacactgttc aggaatcgga atcctgtcga ttagactgga cagcttgtgg
1740

caagtgaatt tcctgtaaca agccagattt tttaaaattt atattgtaaa tattgtgtgt
1800

gtgtgtgtgt gtgtatatat atatatatat gtacagttat ctaagttaat ttaaagttgt
1860

ttgtgccttt ttatTTTTgt ttttaatgct ttgatatttc aatgttagcc tcaattttctg
1920

aacaccatag gtagaatgta aagcttgtct gatcggttcaa agcatgaaat ggatacttat
1980

atggaaattc tctcagatag aatgacagtc cgtcaaaaaca gattgtttgc aaaggggagg
2040

catcagtgtc cttggcaggc tgatttctag gtaggaaatg tggtagctca cgtcacttt
2100

taatgaacaa atggccttta ttaaaaactg agtgactcta tatagctgat cagttttttc
2160

acctggaagc atttgtttct actttgatat gactgttttt cggacagttt atttgttgag
2220

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2280

aaaaaaaaa aaaaacgaca gcaacggaat tc
2312

<210> 56

<211> 349

<212> PRT

<213> Homo sapiens

<400> 56

Met	Thr	Ala	Ala	Ser	Met	Gly	Pro	Val	Arg	Val	Ala	Phe	Val	Val	Leu
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Leu	Ala	Leu	Cys	Ser	Arg	Pro	Ala	Val	Gly	Gln	Asn	Cys	Ser	Gly	Pro
			20						25				30		

Cys	Arg	Cys	Pro	Asp	Glu	Pro	Ala	Pro	Arg	Cys	Pro	Ala	Gly	Val	Ser
		35					40					45			

Leu	Val	Leu	Asp	Gly	Cys	Gly	Cys	Cys	Arg	Val	Cys	Ala	Lys	Gln	Leu
	50						55				60				

Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
 65 70 75 80

Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
 85 90 95

Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
 100 105 110

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
 165 170 175

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

Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
 195 200 205

Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
 210 215 220

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
 245 250 255

Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
 260 265 270

Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr

100

275 280 285

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

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

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

<210> 57

<211> 1069

<212> DNA

<213> Homo sapiens

<400> 57

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120

ctgtgcaccg agcgcgaccc ctgcgacccg cacaagggcc tcttctgtga cttcggctcc
180

ccggccaacc gcaagatcgg cgtgtgcacc gccaaagatg gtgctccctg catcttcggt
240

ggtacggtgt accgcagcgg agagtccttc cagagcagct gcaagtacca gtgcacgtgc
300

ctggacgggg cggtgggctg catgcccctg tgcagcatgg acgttcgtct gccagccct
360

gactgcccct tcccgaggag ggtcaagctg cccgggaaat gctgcgagga gtgggtgtgt
420

gacgagccca aggaccaaac cgtgggttggg cctgcccctg cggcttaccg actggaagac
480

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540

agcgctgttt ccaagacctg tgggatgggc atctccaccc gggttaccaa tgacaacgcc
600

tcctgcaggc tagagaagca gagccgcctg tgcattggtca ggccttgcca agctgacctg
660

gaagagaaca ttaagaaggc caaaaagtgc atccgtactc ccaaaatctc caagcctatc
720

aagtttgagc tttctggctg caccagcatg aagacatacc gagctaaatt ctgtggagta
780

tgtaccgacg gccgatgctg cccccccac agaaccacca ccctgcccgt ggagttcaag
840

tgccctgacg gcgaggctcat gaagaagaac atgatgttca tcaagacctg tgccctgcat
900

tacaactgtc ccggagacaa tgacatcttt gaatcgtgt actacaggaa gatgtacgga
960

gacatggcat gaagccagag agtgagagac attaactcat tagactggaa cttgaactga
1020

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1069

<210> 58

<211> 323

<212> PRT

<213> Homo sapiens

<400> 58

Gln	Asn	Cys	Ser	Gly	Pro	Cys	Arg	Cys	Pro	Asp	Glu	Pro	Ala	Pro	Arg
1				5					10					15	

Cys	Pro	Ala	Gly	Val	Ser	Leu	Val	Leu	Asp	Gly	Cys	Gly	Cys	Cys	Arg
			20					25					30		

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

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

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

102

				85						90					95			
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						
Lys	Leu	Pro	Gly	Lys	Cys	Cys	Glu	Glu	Trp	Val	Cys	Asp	Glu	Pro	Lys			
	130					135					140							
Asp	Gln	Thr	Val	Val	Gly	Pro	Ala	Leu	Ala	Ala	Tyr	Arg	Leu	Glu	Asp			
145					150					155					160			
Thr	Phe	Gly	Pro	Asp	Pro	Thr	Met	Ile	Arg	Ala	Asn	Cys	Leu	Val	Gln			
				165					170					175				
Thr	Thr	Glu	Trp	Ser	Ala	Cys	Ser	Lys	Thr	Cys	Gly	Met	Gly	Ile	Ser			
			180					185					190					
Thr	Arg	Val	Thr	Asn	Asp	Asn	Ala	Ser	Cys	Arg	Leu	Glu	Lys	Gln	Ser			
		195					200					205						
Arg	Leu	Cys	Met	Val	Arg	Pro	Cys	Glu	Ala	Asp	Leu	Glu	Glu	Asn	Ile			
	210					215					220							
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				
Phe	Cys	Gly	Val	Cys	Thr	Asp	Gly	Arg	Cys	Cys	Thr	Pro	His	Arg	Thr			
			260					265					270					
Thr	Thr	Leu	Pro	Val	Glu	Phe	Lys	Cys	Pro	Asp	Gly	Glu	Val	Met	Lys			
		275					280					285						
Lys	Asn	Met	Met	Phe	Ile	Lys	Thr	Cys	Ala	Cys	His	Tyr	Asn	Cys	Pro			
	290					295					300							

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

Asp Met Ala

<210> 59
<211> 1985
<212> DNA
<213> Homo sapiens

<400> 59
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120
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180
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360
cagccctgcg accacaccaa ggggctggaa tgcaacttcg gcgccagctc caccgctctg
420
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480
caaacgggg aaagtttcca gcccaactgt aaacatcagt gcacatgtat tgatggcgcc
540
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720
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780

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840

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900

tccacacgag ttaccaatga caaccctgag tgcgccttg tgaaagaaac ccggatttgt
960

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1020

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1080

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1140

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1200

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1320

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1380

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1500

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1560

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1740

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1800

acagaaatca ggtgttttaa gactgaatgt tttatttato aaaatgtagc ttttggggag
1860

105

ggaggggaaa tgtaatactg gaataatttg taaatgattt taattttata ttcagtgaaa
1920

agattttatt tatggaatta accatttaaat aaagaaatat ttacctaata aaaaaaaaaa
1980

aaaaa
1985

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

<400> 60

Met Ser Ser Arg Ile Ala Arg Ala Leu Ala Leu Val Val Thr Leu Leu
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His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His Cys
20 25 30

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
50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe
65 70 75 80

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
100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val
115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly
130 135 140

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

145		150		155		160
Trp Val Cys Asp	Glu Asp Ser Ile Lys Asp	Pro Met Glu Asp	Gln Asp			
	165	170	175			
Gly Leu Leu Gly	Lys Glu Leu Gly Phe Asp Ala Ser	Glu Val Glu Leu				
	180	185	190			
Thr Arg Asn Asn	Glu Leu Ile Ala Val Gly Lys Gly	Ser Ser Leu Lys				
	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				
225	230	235	240			
Lys Thr Cys Gly	Thr Gly Ile Ser Thr Arg Val Thr Asn Asp	Asn Pro				
	245	250	255			
Glu Cys Arg Leu	Val Lys Glu Thr Arg Ile Cys Glu Val Arg	Pro Cys				
	260	265	270			
Gly Gln Pro Val	Tyr Ser Ser Leu Lys Lys Gly Lys Lys	Cys Ser Lys				
	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				
305	310	315	320			
Arg Cys Cys Thr	Pro Gln Leu Thr Arg Thr Val Lys Met Arg	Phe Arg				
	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				
	355	360	365			

Phe Tyr Arg Leu Phe Asn Asp Ile His Lys Phe Arg Asp
370 375 380

<210> 61
<211> 2830
<212> DNA
<213> Homo sapiens

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1740

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1920

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1980

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2100

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2160

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2340

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2400

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2700

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2830

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<211> 367
<212> PRT
<213> Homo sapiens

110

<400> 62

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

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

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
 85 90 95

Arg Gly Leu Tyr Cys Asp Tyr Ser Gly Asp Arg Pro Arg Tyr Ala Ile
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Gly Val Cys Ala Gln Val Val Gly Val Gly Cys Val Leu Asp Gly Val
 115 120 125

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

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

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

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

111

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

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

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

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

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

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

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

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 <211> 1723
 <212> DNA
 <213> Homo sapiens

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 120

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 180

catttttttt taaaactgta ttgtttctcg ttttaattta tttttgcttg ccattcccca
240

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300

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420

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480

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540

cacctcctcc ccggccggcg gcggacagtg gacgcggcgg cgagccgcgg gcaggggccg
600

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720

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840

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900

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960

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1080

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1260

113

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1320

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1380

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1723

<210> 64
<211> 215
<212> PRT
<213> Homo sapiens

<400> 64

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			20					25					30		

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

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

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

Met	Arg	Cys	Gly	Gly	Cys	Cys	Asn	Asp	Glu	Gly	Leu	Glu	Cys	Val	Pro
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

114

85

90

95

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

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

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

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

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

Arg Cys Asp Lys Pro Arg Arg
 210 215

<210> 65
 <211> 1172
 <212> DNA
 <213> Homo sapiens

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420

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960

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1172

<210> 66
<211> 207
<212> PRT
<213> Homo sapiens

116

<400> 66

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

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
 50 55 60

Ala Lys Gln Leu Val Pro Ser Cys Val Thr Val Gln Arg Cys Gly Gly
 65 70 75 80

Cys Cys Pro Asp Asp Gly Leu Glu Cys Val Pro Thr Gly Gln His Gln
 85 90 95

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

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

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

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

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

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

<400> 67

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660

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720

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119

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2076

<210> 68
<211> 419
<212> PRT
<213> Homo sapiens

<400> 68

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Glu Ser Gly Leu Asp Leu Ser Asp Ala Glu Pro Asp Ala Gly Glu Ala
35 40 45

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
65 70 75 80

Tyr Lys Cys Gln Leu Arg Lys Gly Gly Trp Gln His Asn Arg Glu Gln
85 90 95

Ala Asn Leu Asn Ser Arg Thr Glu Glu Thr Ile Lys Phe Ala Ala Ala
100 105 110

His Tyr Asn Thr Glu Ile Leu Lys Ser Ile Asp Asn Glu Trp Arg Lys
115 120 125

Thr Gln Cys Met Pro Arg Glu Val Cys Ile Asp Val Gly Lys Glu Phe
130 135 140

Gly Val Ala Thr Asn Thr Phe Phe Lys Pro Pro Cys Val Ser Val Tyr
145 150 155 160

Arg Cys Gly Gly Cys Cys Asn Ser Glu Gly Leu Gln Cys Met Asn Thr
165 170 175

120

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
 195 200 205

Cys Arg Cys Met Ser Lys Leu Asp Val Tyr Arg Gln Val His Ser Ile
 210 215 220

Ile Arg Arg Ser Leu Pro Ala Thr Leu Pro Gln Cys Gln Ala Ala Asn
 225 230 235 240

Lys Thr Cys Pro Thr Asn Tyr Met Trp Asn Asn His Ile Cys Arg Cys
 245 250 255

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
 275 280 285

Glu Thr Cys Gln Cys Val Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys
 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
 325 330 335

Asn Thr Cys Gln Cys Val Cys Lys Arg Thr Cys Pro Arg Asn Gln Pro
 340 345 350

Leu Asn Pro Gly Lys Cys Ala Cys Glu Cys Thr Glu Ser Pro Gln Lys
 355 360 365

Cys Leu Leu Lys Gly Lys Lys Phe His His Gln Thr Cys Ser Cys Tyr
 370 375 380

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

121

385

390

395

400

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Gln Met Ser

<210> 69
<211> 2029
<212> DNA
<213> Homo sapiens

<400> 69
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300

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960

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1080

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1140

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1200

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1260

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1740

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1800

123

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1920

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<211> 354

<212> PRT

<213> Homo sapiens

<400> 70

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Ser Leu Glu Glu Leu Leu Arg Ile Thr His Ser Glu Asp Trp Lys Leu
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Trp Arg Cys Arg Leu Arg Leu Lys Ser Phe Thr Ser Met Asp Ser Arg
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Ser Ala Ser His Arg Ser Thr Arg Phe Ala Ala Thr Phe Tyr Asp Ile
85 90 95

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

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

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

Cys Cys Asn Glu Glu Ser Leu Ile Cys Met Asn Thr Ser Thr Ser Tyr
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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
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Pro Thr Ala Pro Arg His Pro Tyr Ser Ile Ile Arg Arg Ser Ile Gln
 195 200 205

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

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

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

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

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

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

<210> 71
<211> 2825
<212> DNA
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2825

128

<211> 345
 <212> PRT
 <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

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

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

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

Val Ser Asp Glu Tyr Phe Pro Ser Glu Pro Gly Phe Cys Ile His Tyr
 145 150 155 160

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
 180 185 190

129

Phe Ser Thr Leu Glu Asp Leu Ile Arg Tyr Leu Glu Pro Glu Arg Trp
 195 200 205

Gln Leu Asp Leu Glu Asp Leu Tyr Arg Pro Thr Trp Gln Leu Leu Gly
 210 215 220

Lys Ala Phe Val Phe Gly Arg Lys Ser Arg Val Val Asp Leu Asn Leu
 225 230 235 240

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

Gly Cys Leu Leu Val Lys Arg Cys Gly Gly Asn Cys Ala Cys Cys Leu
 275 280 285

His Asn Cys Asn Glu Cys Gln Cys Val Pro Ser Lys Val Thr Lys Lys
 290 295 300

Tyr His Glu Val Leu Gln Leu Arg Pro Lys Thr Gly Val Arg Gly Leu
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His Lys Ser Leu Thr Asp Val Ala Leu Glu His His Glu Glu Cys Asp
 325 330 335

Cys Val Cys Arg Gly Ser Thr Gly Gly
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<210> 73
 <211> 2745
 <212> DNA
 <213> Homo sapiens

<400> 73
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<210> 74

<211> 391

<212> PRT

<213> Homo sapiens

<400> 74

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			20					25					30		

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	

133

Pro Glu Pro Glu Ala Asp Tyr Tyr Ala Lys Glu Val Thr Arg Val Leu
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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
 130 135 140

Pro Glu Pro Val Leu Leu Ser Arg Ala Glu Leu Arg Leu Leu Arg Arg
 145 150 155 160

Leu Lys Leu Lys Val Glu Gln His Val Glu Leu Tyr Gln Lys Tyr Ser
 165 170 175

Asn Asn Ser Trp Arg Tyr Leu Ser Asn Arg Leu Leu Ala Pro Ser Asp
 180 185 190

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
 210 215 220

Ser Cys Asp Ser Arg Asp Asn Thr Leu Gln Val Asp Ile Asn Gly Phe
 225 230 235 240

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
 260 265 270

Gln Ser Ser Arg His Arg Arg Ala Leu Asp Thr Asn Tyr Cys Phe Ser
 275 280 285

Ser Thr Glu Lys Asn Cys Cys Val Arg Gln Leu Tyr Ile Asp Phe Arg
 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
325 330 335

Tyr Ser Lys Val Leu Ala Leu Tyr Asn Gln His Asn Pro Gly Ala Ser
340 345 350

Ala Ala Pro Cys Cys Val Pro Gln Ala Leu Glu Pro Leu Pro Ile Val
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Val Arg Ser Cys Lys Cys Ser
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<210> 75
<211> 336
<212> DNA
<213> Homo sapiens

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<210> 76
<211> 112
<212> PRT
<213> Homo sapiens

<400> 76

135

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Ile His Glu Pro Lys Gly Tyr His Ala Asn Phe Cys Leu Gly Pro Cys
 35 40 45

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

Tyr Asn Gln His Asn Pro Gly Ala Ser Ala Ala Pro Cys Cys Val Pro
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Gln Ala Leu Glu Pro Leu Pro Ile Val Tyr Tyr Val Gly Arg Lys Pro
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Lys Val Glu Gln Leu Ser Asn Met Ile Val Arg Ser Cys Lys Cys Ser
 100 105 110

<210> 77
 <211> 1695
 <212> DNA
 <213> Homo sapiens

<400> 77
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137

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<210> 78
<211> 414
<212> PRT
<213> Homo sapiens

<400> 78

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			20					25					30		

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				

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

Lys	Ala	Ser	Arg	Arg	Ala	Ala	Ala	Cys	Glu	Arg	Glu	Arg	Ser	Asp	Glu
				85					90					95	

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

Ile Val Arg Phe Asp Val Ser Ala Met Glu Lys Asn Ala Ser Asn Leu

138

130	135	140
Val Lys Ala Glu Phe Arg Val Phe Arg Leu Gln Asn Pro Lys Ala Arg 145 150 155 160		
Val Pro Glu Gln Arg Ile Glu Leu Tyr Gln Ile Leu Lys Ser Lys Asp 165 170 175		
Leu Thr Ser Pro Thr Gln Arg Tyr Ile Asp Ser Lys Val Val Lys Thr 180 185 190		
Arg Ala Glu Gly Glu Trp Leu Ser Phe Asp Val Thr Asp Ala Val His 195 200 205		
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		
Ser Thr Tyr Thr Ser Gly Asp Gln Lys Thr Ile Lys Ser Thr Arg Lys 260 265 270		
Lys Asn Ser Gly Lys Thr Pro His Leu Leu Leu Met Leu Leu Pro Ser 275 280 285		
Tyr Arg Leu Glu Ser Gln Gln Thr Asn Arg Arg Lys Lys Arg Ala Leu 290 295 300		
Asp Ala Ala Tyr Cys Phe Arg Asn Val Gln Asp Asn Cys Cys Leu Arg 305 310 315 320		
Pro Leu Tyr Ile Asp Phe Lys Arg Asp Leu Gly Trp Lys Trp Ile His 325 330 335		
Glu Pro Lys Gly Tyr Asn Ala Asn Phe Cys Ala Gly Ala Cys Pro Tyr 340 345 350		

139

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

Leu Glu Pro Leu Thr Ile Leu Tyr Tyr Ile Gly Lys Thr Pro Lys Ile
 385 390 395 400

Glu Gln Leu Ser Asn Met Ile Val Lys Ser Cys Lys Cys Ser
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<210> 79

<211> 336

<212> DNA

<213> Homo sapiens

<400> 79

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 120

gccaaacttct gtgctggagc atgcccgtat ttatggagtt cagacactca gcacagcagg
 180

gtcctgagct tatataatac cataaatoca gaagcatctg cttctccttg ctgcgtgtcc
 240

caagatttag aacctotaac cattctctac tacattggca aaacacccaa gattgaacag
 300

ctttotaata tgattgtaaa gtcttgcaaa tgcagc
 336

<210> 80

<211> 112

<212> PRT

<213> Homo sapiens

<400> 80

Ala Leu Asp Ala Ala Tyr Cys Phe Arg Asn Val Gln Asp Asn Cys Cys
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Leu Arg Pro Leu Tyr Ile Asp Phe Lys Arg Asp Leu Gly Trp Lys Trp

140

20 25 30

Ile His Glu Pro Lys Gly Tyr Asn Ala Asn Phe Cys Ala Gly Ala Cys
35 40 45

Pro Tyr Leu Trp Ser Ser Asp Thr Gln His Ser Arg Val Leu Ser Leu
50 55 60

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
85 90 95

Lys Ile Glu Gln Leu Ser Asn Met Ile Val Lys Ser Cys Lys Cys Ser
100 105 110

<210> 81
<211> 2574
<212> DNA
<213> Homo sapiens

<400> 81
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120
caccttcttg ccaagcctca gtctttggga tctggggagg ccgcctggtt ttctccctc
180
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240
tcccagctca cacatgaaga tgcacttgca aagggctctg gtggtcctgg ccctgctgaa
300
ctttgccacg gtcagcctct ctctgtccac ttgcaccacc ttggacttcg gccacatcaa
360
gaagaagagg gtggaagcca ttaggggaca gatcttgagc aagctcaggc tcaccagccc
420
ccctgagcca acggtgatga cccacgtccc ctatcaggtc ctggcccttt acaacagcac
480

ccgggagctg ctggaggaga tgcattggga gagggaggaa ggctgcaccc aggaaaacac
540

cgagtcggaa tactatgccca aagaaatcca taaattcgac atgatccagg ggctggcggga
600

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660

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720

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780

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840

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900

gtccaactta ggtctagaaa tcagcattca ctgtccatgt cacacctttc agcccaatgg
960

agatatcctg gaaaacattc acgaggtgat ggaaatcaaa ttcaaaggcg tggacaatga
1020

ggatgaccat ggccgtggag atctggggcg cctcaagaag cagaaggatc accacaaccc
1080

tcattctaac ctcatgatga ttccccaca ccggctcgac aaccggggcc aggggggtca
1140

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1200

tgtgogcccc ctctacattg acttccgaca ggatctgggc tggaagtggg tccatgaacc
1260

taagggttac tatgccaaact tctgctcagg cccttgccca tacctccgca gtgcagacac
1320

aaccacacgc acggtgctgg gactgtacaa cactctgaac cctgaagcat ctgcctcgcc
1380

ttgtgcgtg ccccgaggacc tggagcccct gaccatcctg tactatgttg ggaggacccc
1440

caaagtggag cagctctcca acatggtggg gaagtcttgt aaatgtagct gagacccac
1500

gtgcgacaga gagaggggag agagaaccac cactgcctga ctgcccgcct ctcgggaaac
1560

acacaagcaa caaacctcac tgagaggcct ggagcccaca accttcggct cggggcaa
1620

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1680

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1740

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1800

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1860

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1920

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1980

acgaagacaa agtcccagaa ttgtatctca tactgtctgg gattaagggc aaatctatta
2040

cttttgcaaa ctgtcctcta catcaattaa catcgtgggt cactacaggg agaaaatcca
2100

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2160

gaaagggtgg aaatcaaccc tctcctgtct gccctctggg tccctcctct caacctctcc
2220

tcgatcatat tcccccttgg acacttggtt agacgccttc caggtcagga tgcacatttc
2280

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2340

accctgtgtt catttggtgt tcctggaagc aggtgctaca acatgtgagg cattcgggga
2400

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2460

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2574

<210> 82

<211> 412

143

<212> PRT

<213> Homo sapiens

<400> 82

Met Lys Met His Leu Gln Arg Ala Leu Val Val Leu Ala Leu Leu Asn
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Phe Ala Thr Val Ser Leu Ser Leu Ser Thr Cys Thr Thr Leu Asp Phe
 20 25 30

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

Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro Thr Val Met Thr His
 50 55 60

Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
 65 70 75 80

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
 115 120 125

Ser Lys Val Phe Arg Phe Asn Val Ser Ser Val Glu Lys Asn Arg Thr
 130 135 140

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

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
 180 185 190

Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp Val Thr Asp Thr Val

195					200					205					
Arg	Glu	Trp	Leu	Leu	Arg	Arg	Glu	Ser	Asn	Leu	Gly	Leu	Glu	Ile	Ser
210					215						220				
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
				245					250					255	
Asp	Asp	His	Gly	Arg	Gly	Asp	Leu	Gly	Arg	Leu	Lys	Lys	Gln	Lys	Asp
			260					265					270		
His	His	Asn	Pro	His	Leu	Ile	Leu	Met	Met	Ile	Pro	Pro	His	Arg	Leu
		275					280					285			
Asp	Asn	Pro	Gly	Gln	Gly	Gly	Gln	Arg	Lys	Lys	Arg	Ala	Leu	Asp	Thr
	290					295					300				
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
			325						330					335	
Lys	Gly	Tyr	Tyr	Ala	Asn	Phe	Cys	Ser	Gly	Pro	Cys	Pro	Tyr	Leu	Arg
			340					345					350		
Ser	Ala	Asp	Thr	Thr	His	Ser	Thr	Val	Leu	Gly	Leu	Tyr	Asn	Thr	Leu
		355					360					365			
Asn	Pro	Glu	Ala	Ser	Ala	Ser	Pro	Cys	Cys	Val	Pro	Gln	Asp	Leu	Glu
	370					375					380				
Pro	Leu	Thr	Ile	Leu	Tyr	Tyr	Val	Gly	Arg	Thr	Pro	Lys	Val	Glu	Gln
385					390					395					400
Leu	Ser	Asn	Met	Val	Val	Lys	Ser	Cys	Lys	Cys	Ser				
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<210> 83
<211> 3213
<212> DNA
<213> Homo sapiens

<400> 83

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120

gggaccaagg cccaaatgtc tgtgcccttc aacagatttt gggcaccaaa aagaaatact
180

tcagcacttg taagaactgg tataaaaagt ccatctgtgg acagaaaacg actgttttat
240

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300

ccattgacca tgtttatggc actctgggca tcgtgggagc caccacaacg cagcgtatt
360

ctgacgcctc aaaactgagg gaggagatcg agggaaaggg atccttcaact tactttgcac
420

cgagtaatga ggcttgggac aacttggatt ctgatatccg tagaggtttg gagagcaacg
480

tgaatgttga attactgaat gctttacata gtcacatgat taataagaga atgttgacca
540

aggacttaaa aaatggcatg attattcctt caatgtataa caatttgggg cttttcatta
600

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660

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780

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840

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960

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1560

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1680

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1740

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1800

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1920

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2100

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2160

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2280

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2340

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2400

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2940

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3000

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3120

148

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3180

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3213

<210> 84
<211> 836
<212> PRT
<213> Homo sapiens

<400> 84

Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val
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Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
20 25 30

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

Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65 70 75 80

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

Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
115 120 125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn
130 135 140

Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu
145 150 155 160

Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr
 165 170 175

Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu
 180 185 190

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

Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr
 245 250 255

Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe
 260 265 270

Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu
 275 280 285

Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His
 290 295 300

Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val
 305 310 315 320

Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp
 325 330 335

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

Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe

150

370		375		380
Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp				
385		390		395 400
Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp				
	405		410	415
Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His				
	420		425	430
Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile				
	435		440	445
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
Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe				
	500		505	510
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				
530		535		540
Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln				
545		550		555 560
Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly				
	565		570	575
Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys				
	580		585	590

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

Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu
 625 630 635 640

Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val
 645 650 655

Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys
 660 665 670

Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser
 675 680 685

Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys
 690 695 700

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

Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly
 755 760 765

Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val
 770 775 780

Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu
 785 790 795 800

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

152

805

810

815

Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu
820 825 830

Gly Arg Ser Gln
835 01