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(54) **METHODS FOR DETECTION AND DIAGNOSIS OF A BONE OR CARTILAGE DISORDER**

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(57) **ABSTRACT**

The present invention is directed to methods for the detection and diagnosis of bone and/or cartilage disorders, wherein the level of expression of a polypeptide in a test sample is measured by contacting the test sample with an antibody that specifically binds to said polypeptide and measuring the binding of said antibody to said test sample.

Figure 1A

EPYC - Recognition Factor

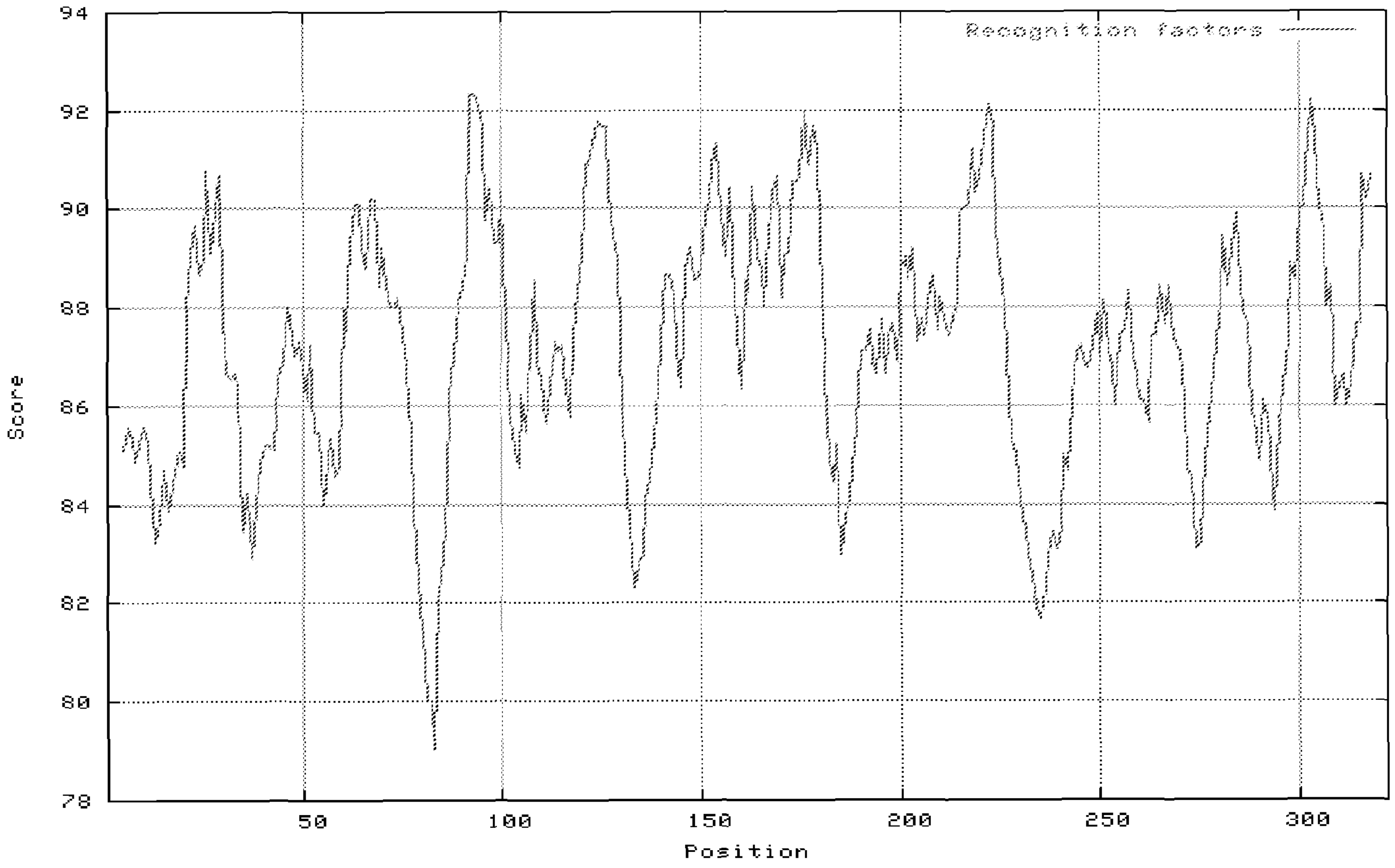


Figure 1B

EPYC - Accessibility

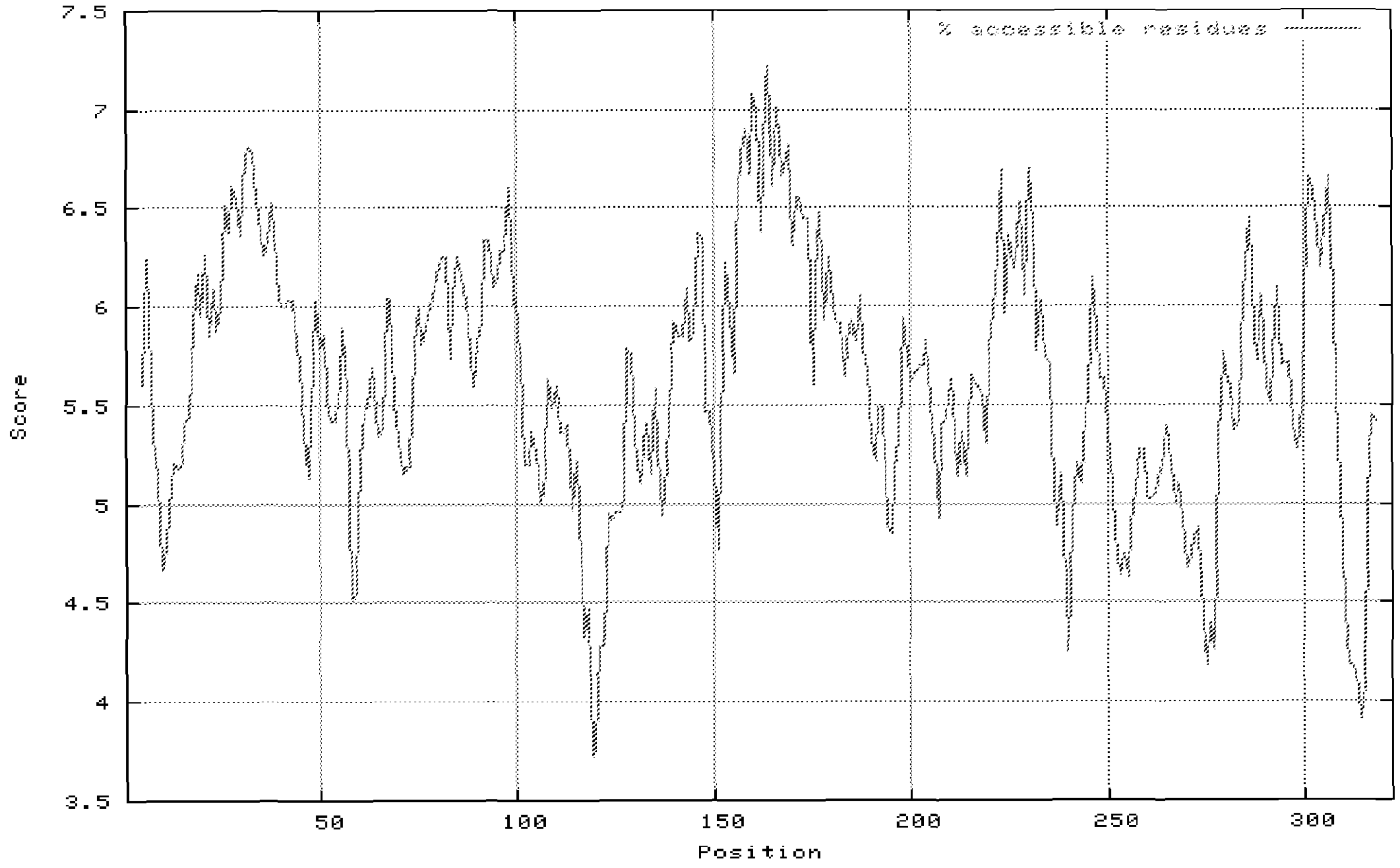


Figure 1C

EPYC - Polarity

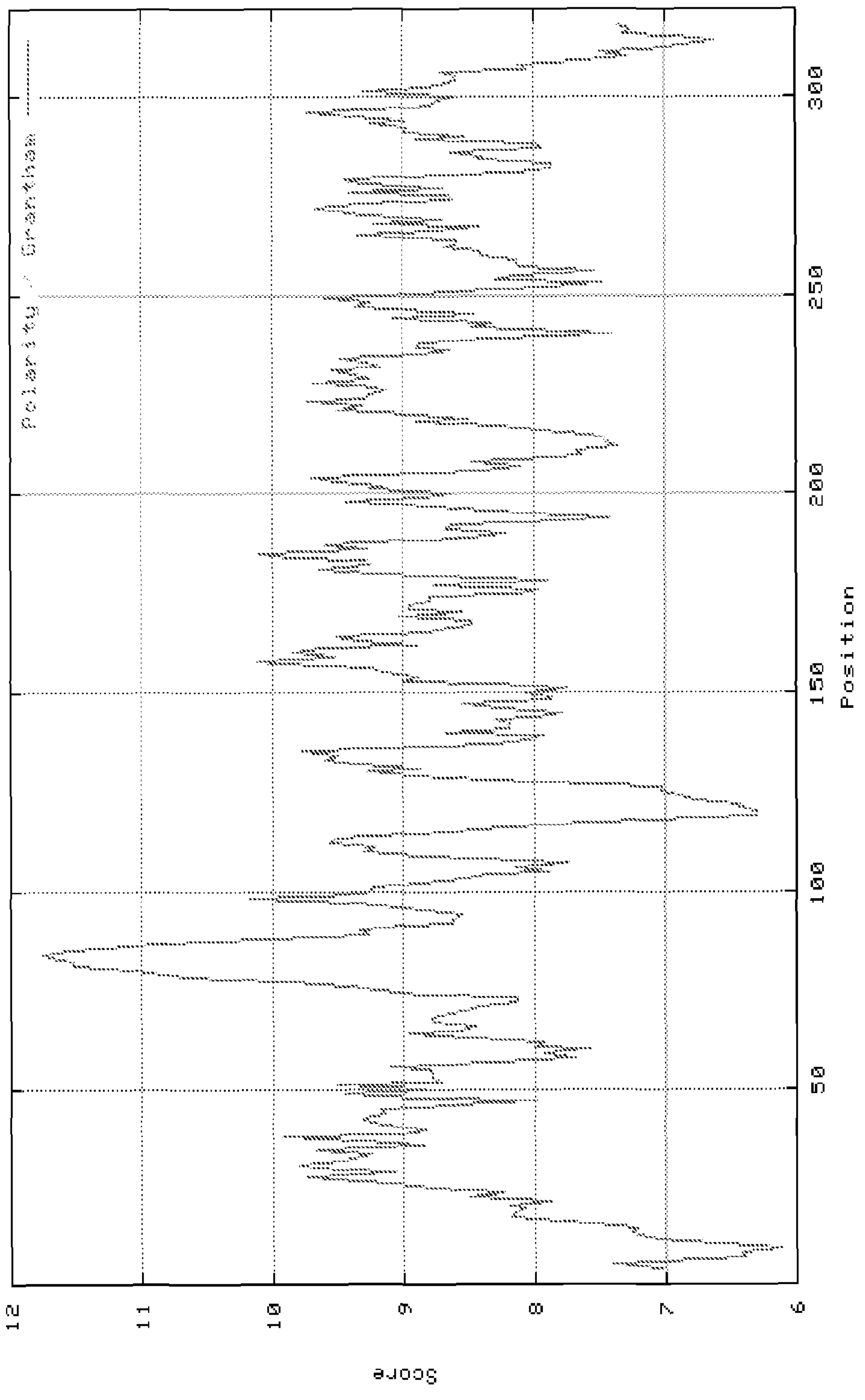


Figure 2A

ASPN - Recognition Factor

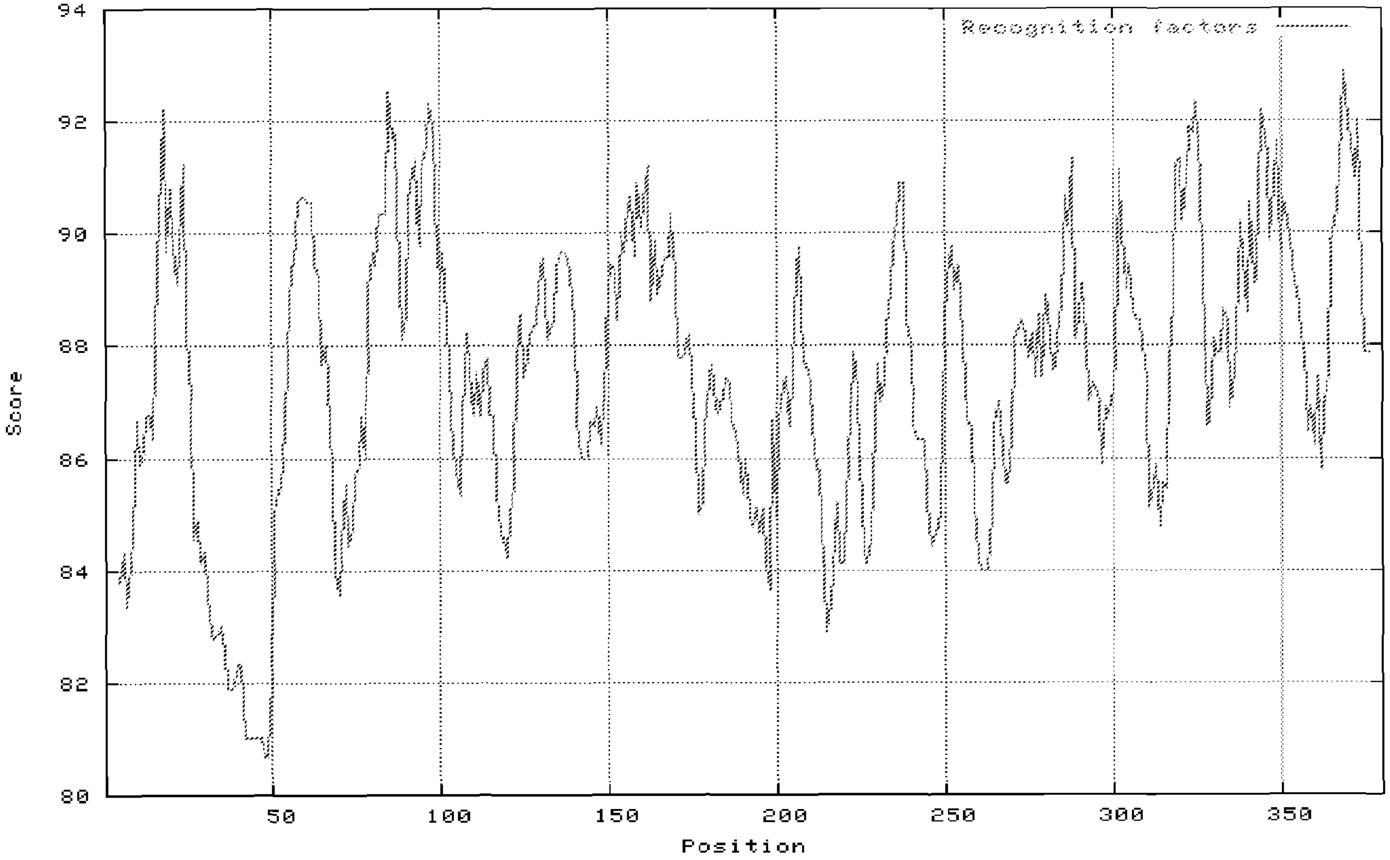


Figure 2B

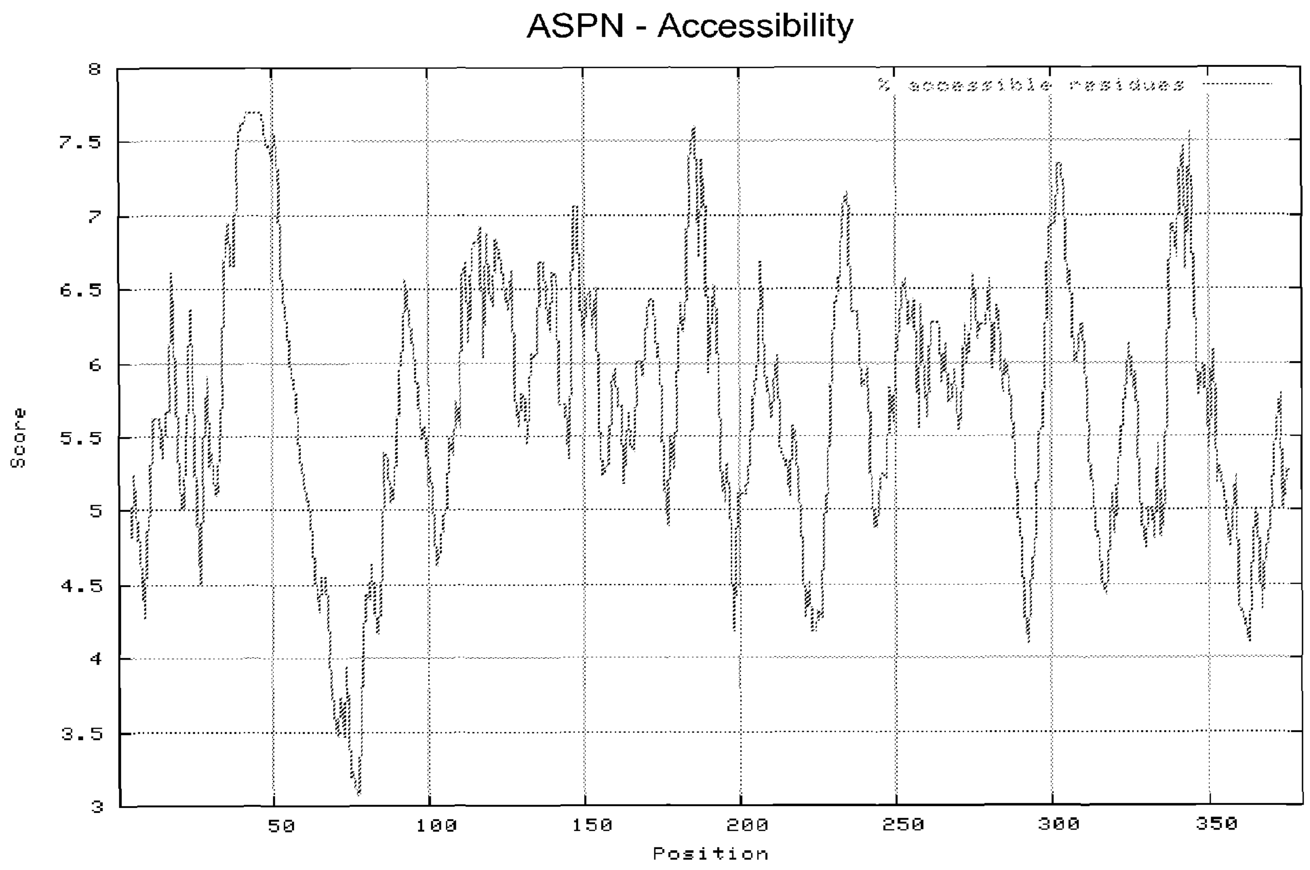

ASPN - Accessibility
% accessible residues
Score
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
50
100
150
200
250
300
350
Position

Figure 2C

ASPN - Polarity

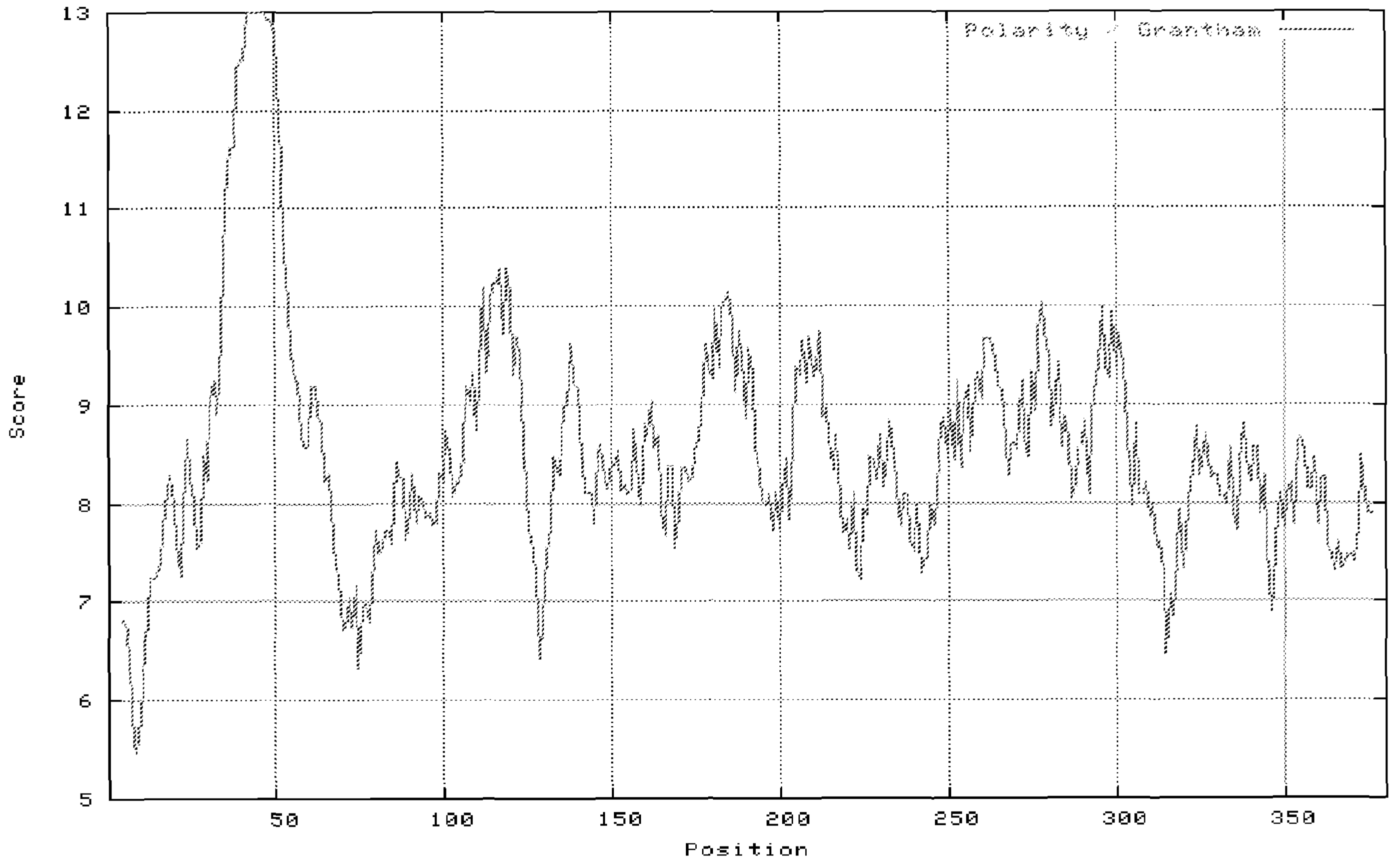


Figure 3A

LOC 646627 - Recognition Factor

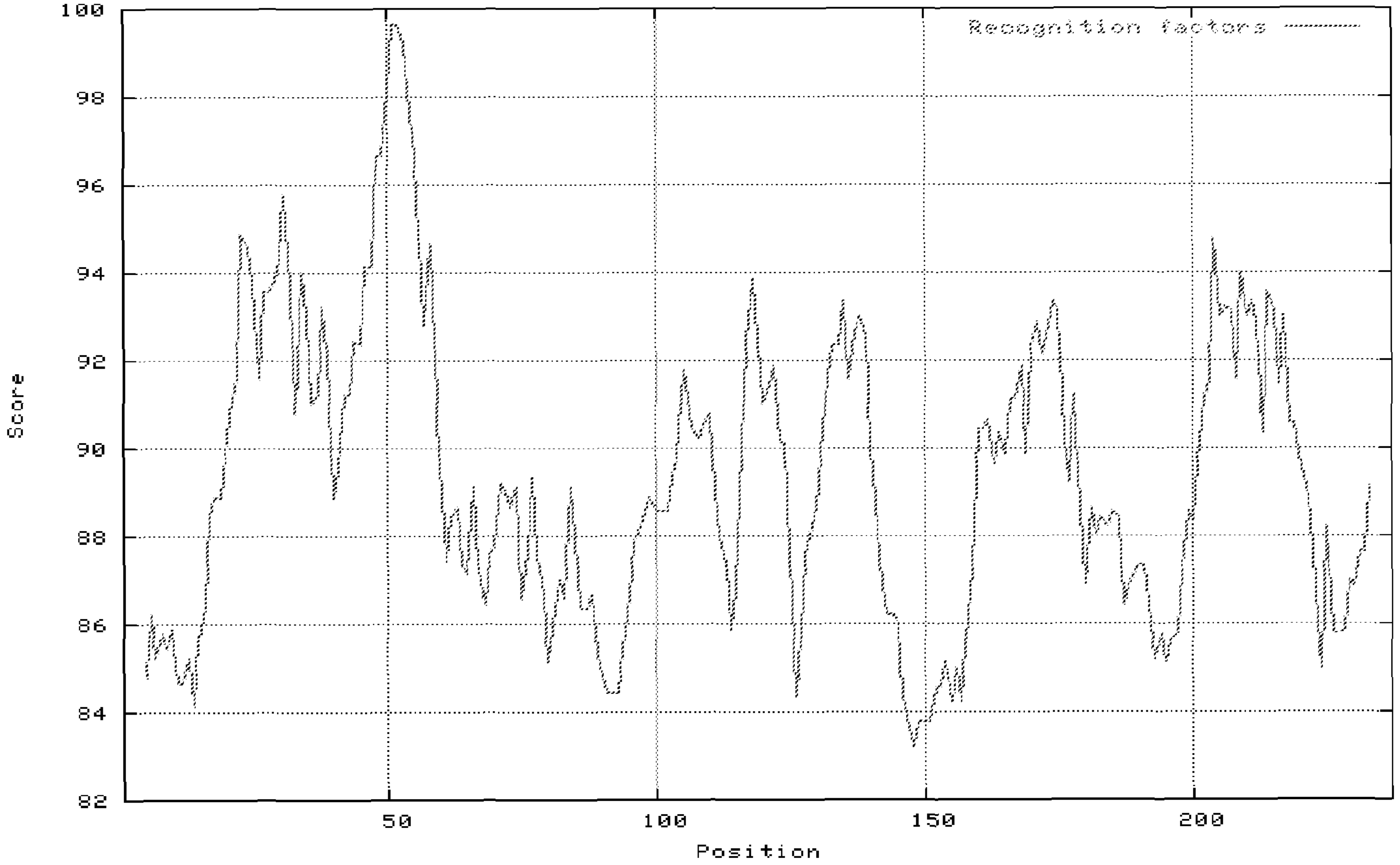


Figure 3B

LOC 646627 - Accessibility

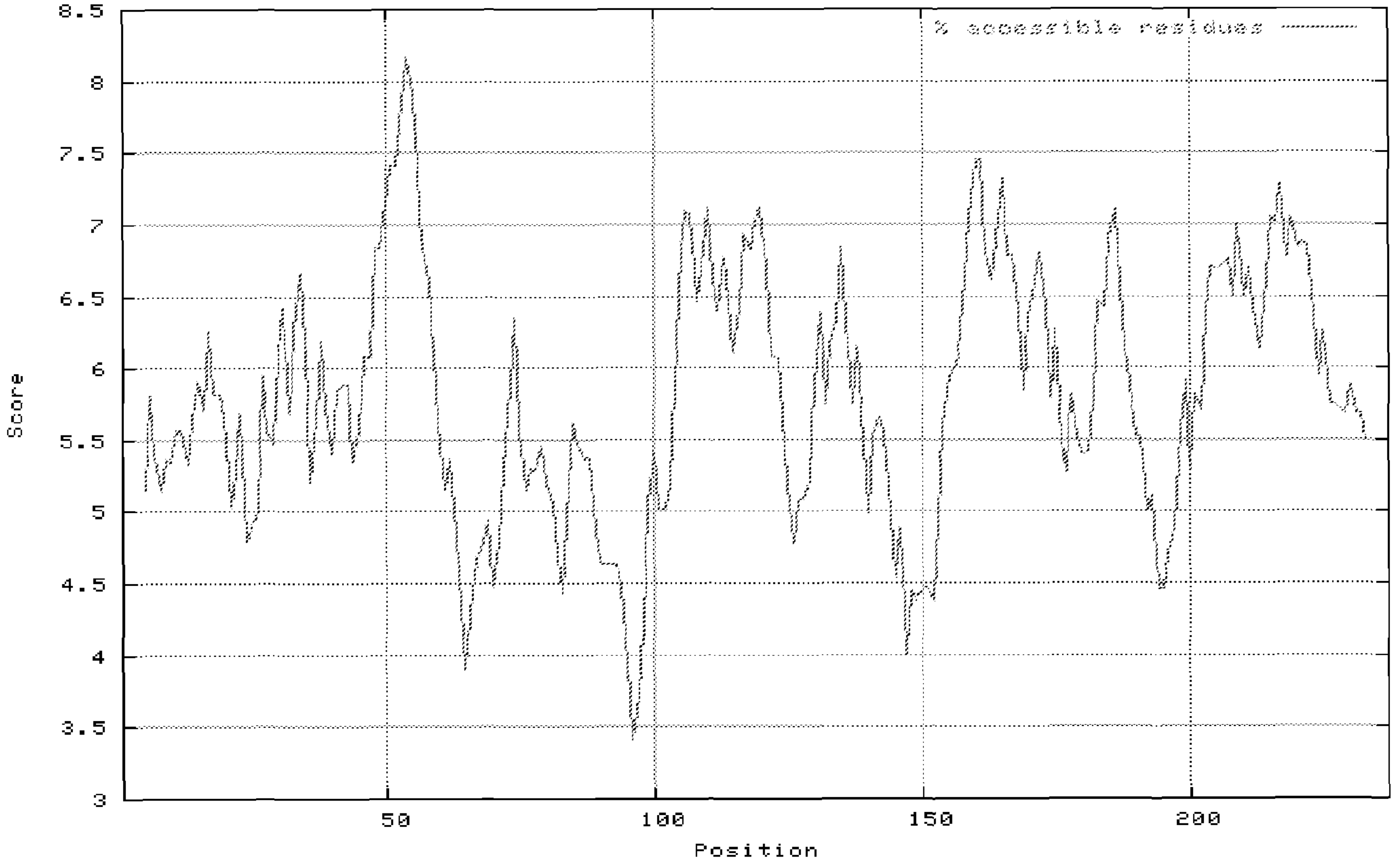


Figure 3C

LOC 646627 - Polarity

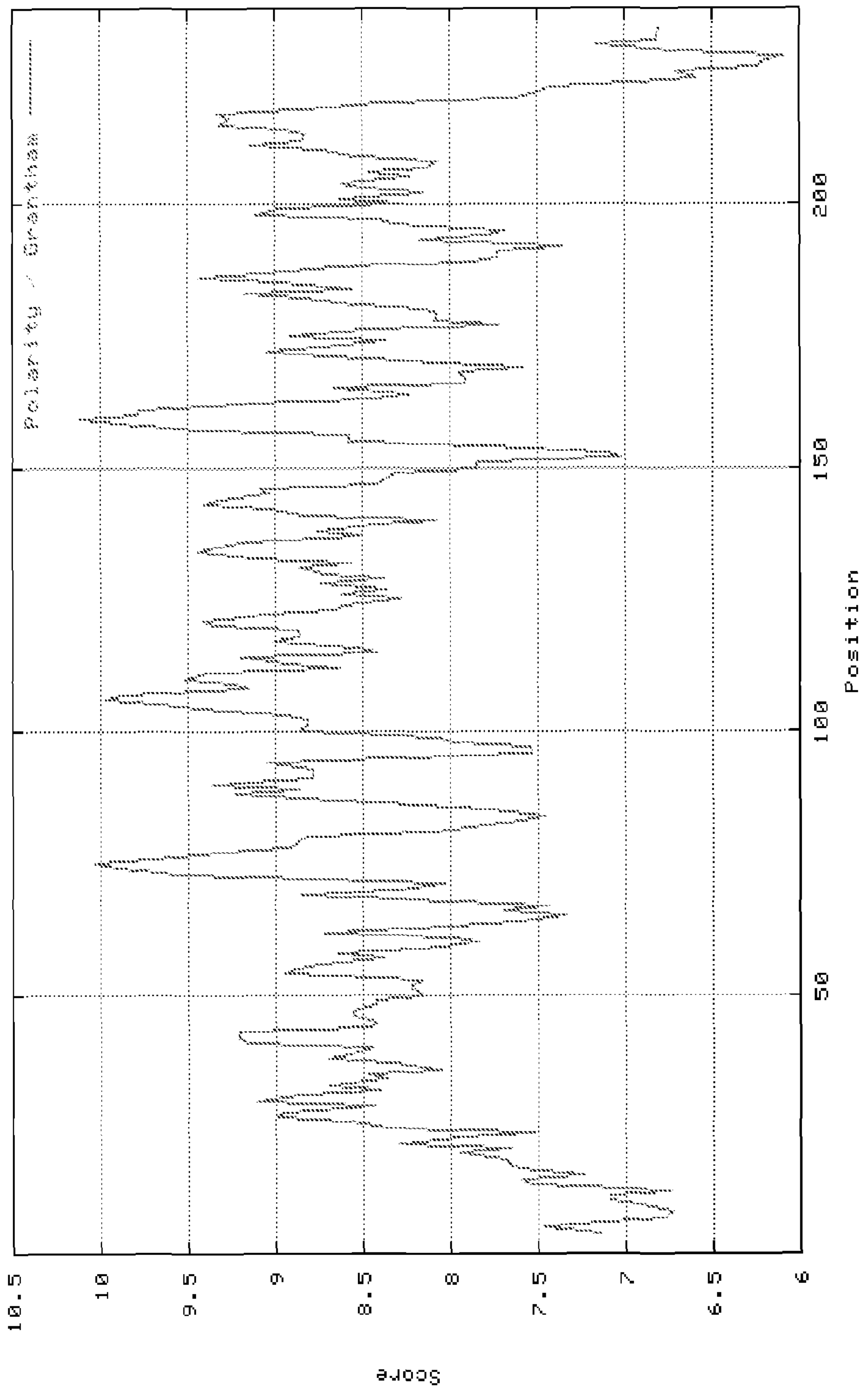


Figure 4A

LOXL3 - Recognition Factor

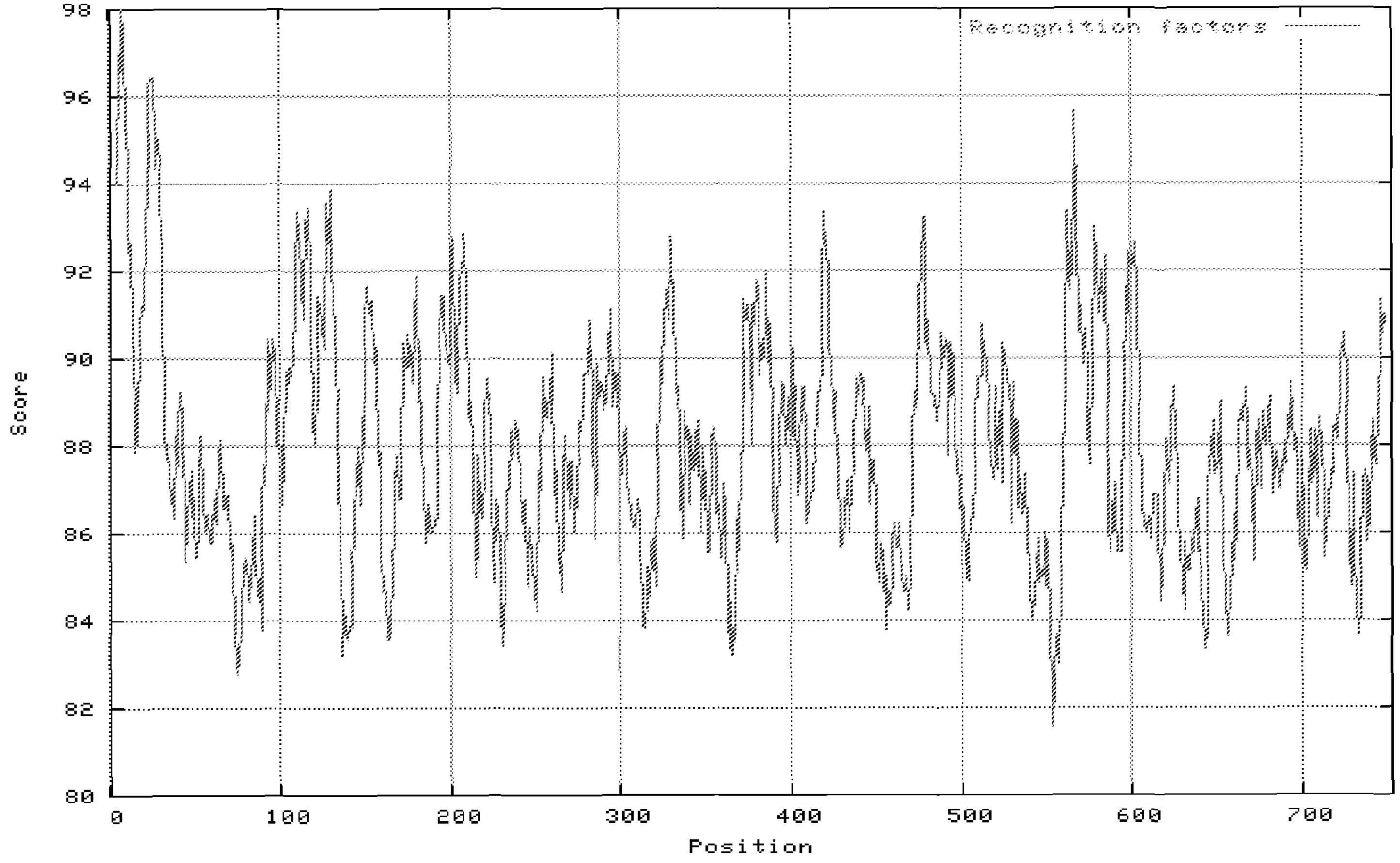


Figure 4B

LOXL3 - Accessibility

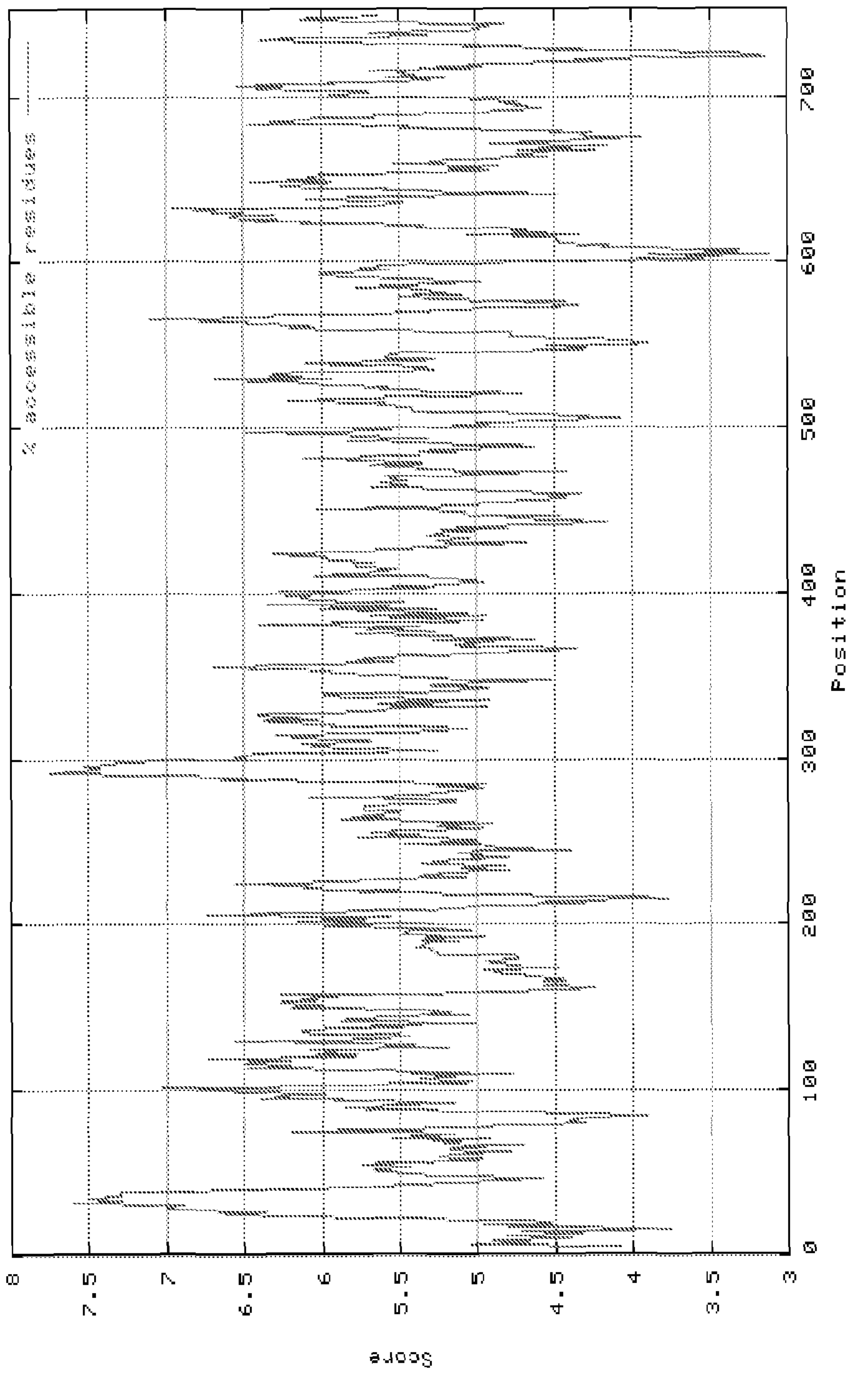


Figure 4C

LOXL3 - Polarity

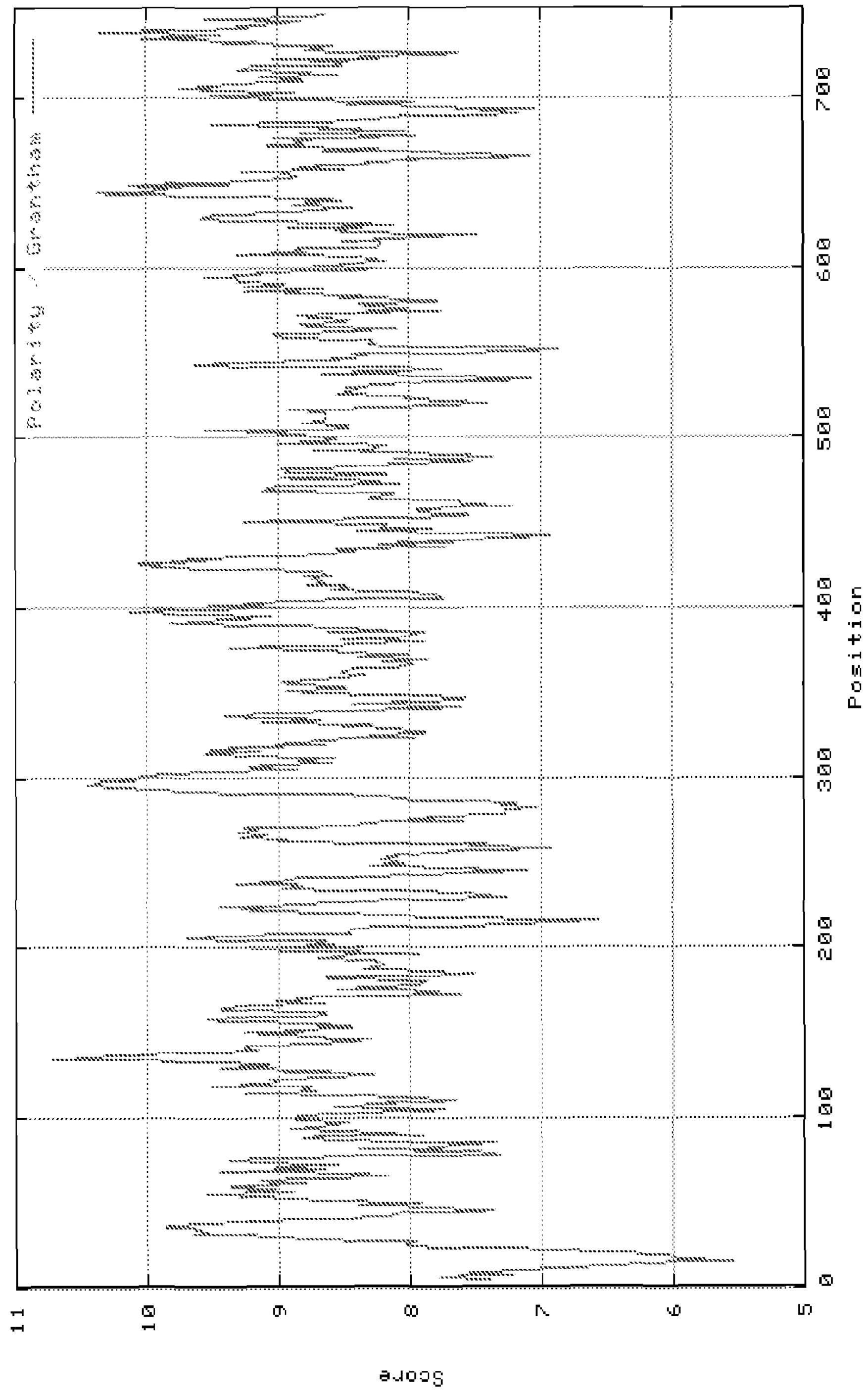


Figure 5A

TWIST2 - Recognition Factor

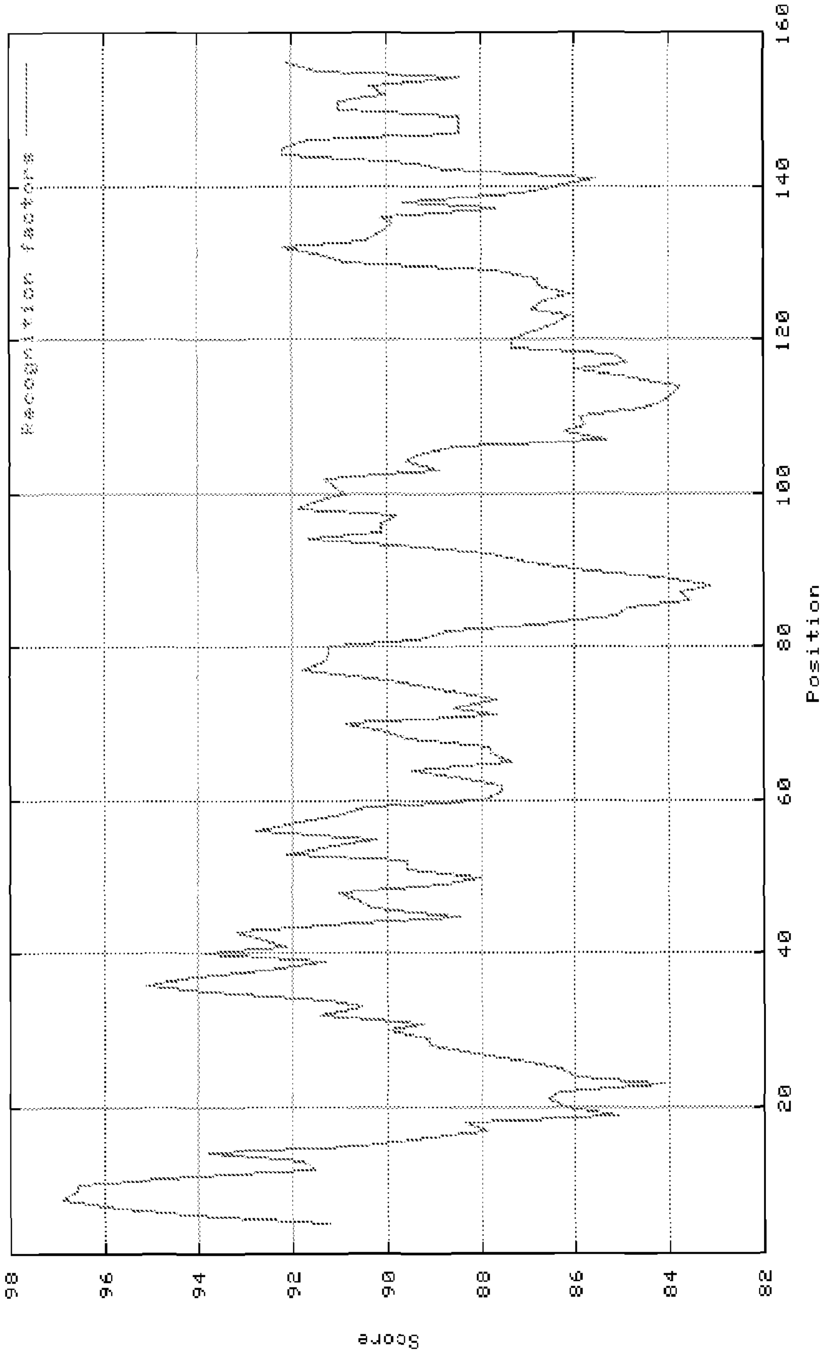


Figure 5B

TWIST2 - Accessibility

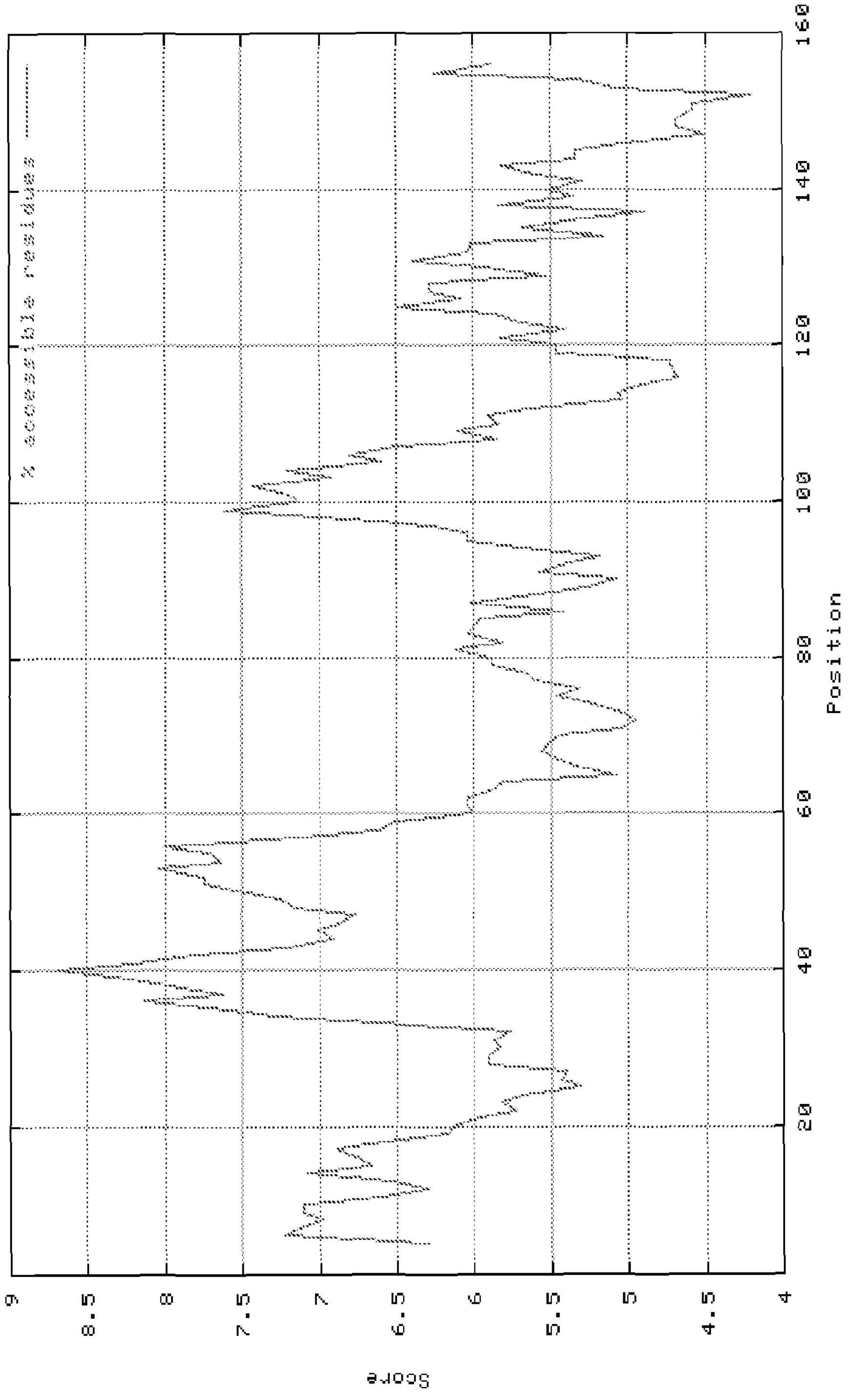


Figure 5C

TWIST2 - Polarity

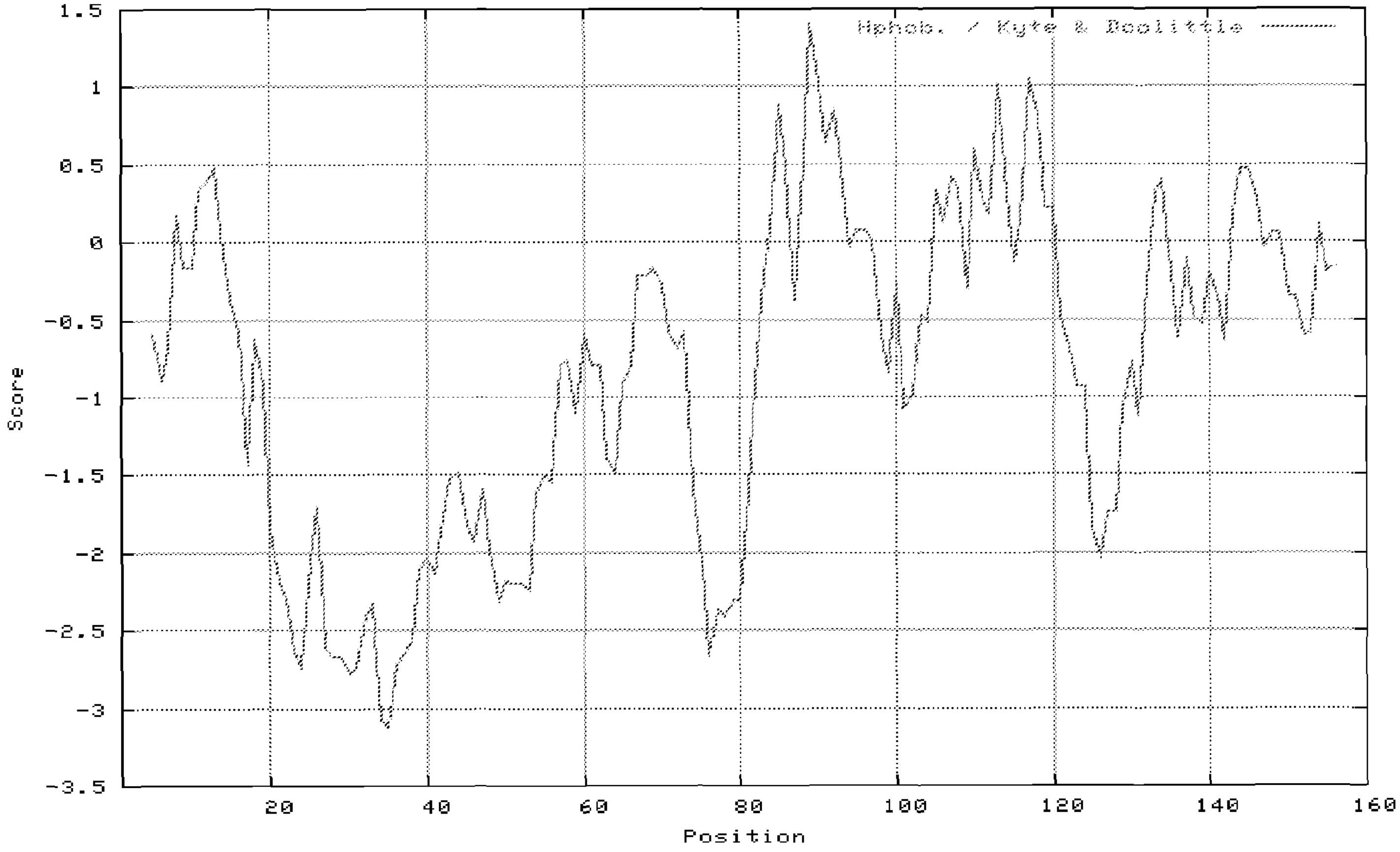


Figure 6A

CRTAC1 - Recognition Factor

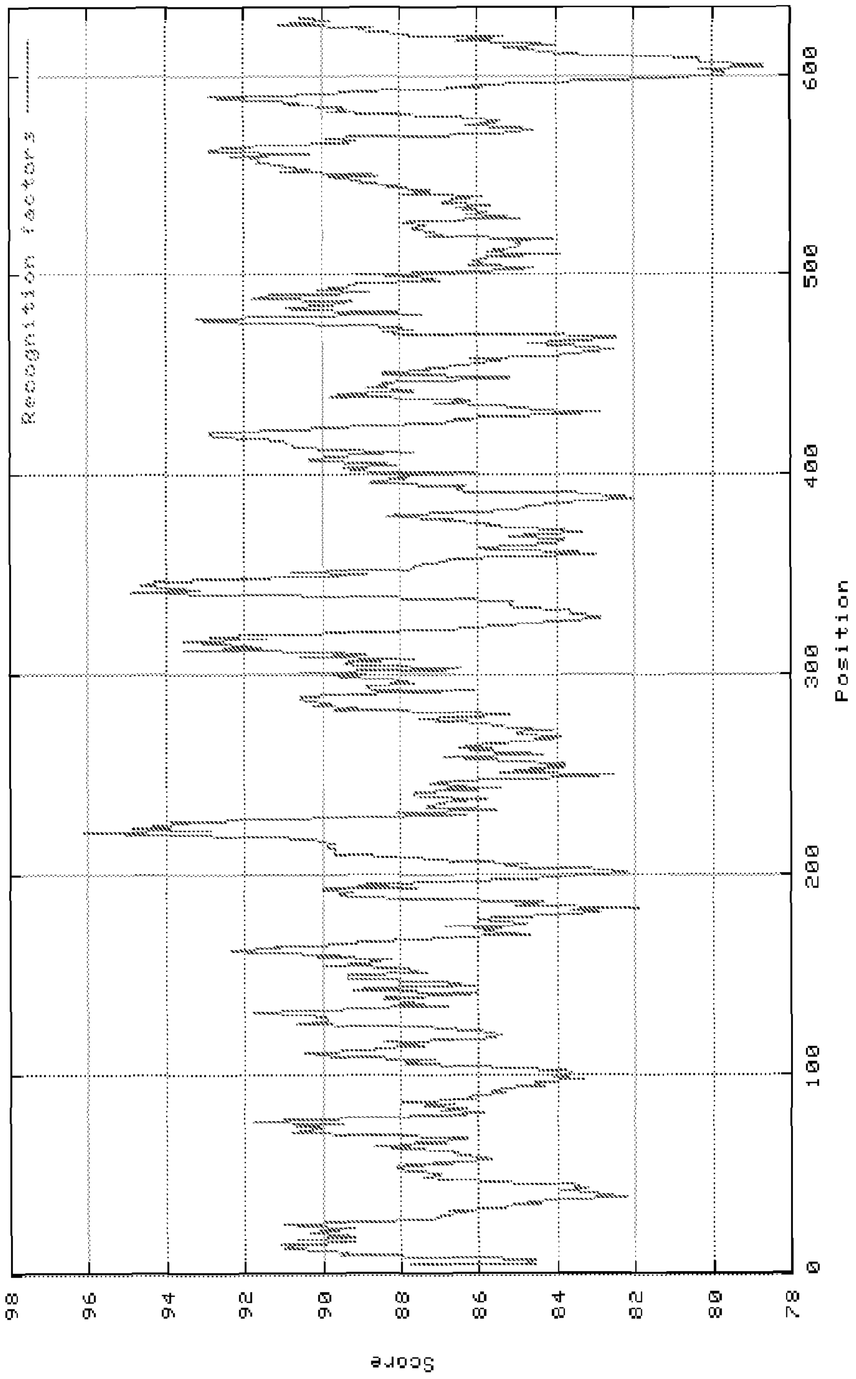


Figure 6B

CRTAC1 - Accessibility

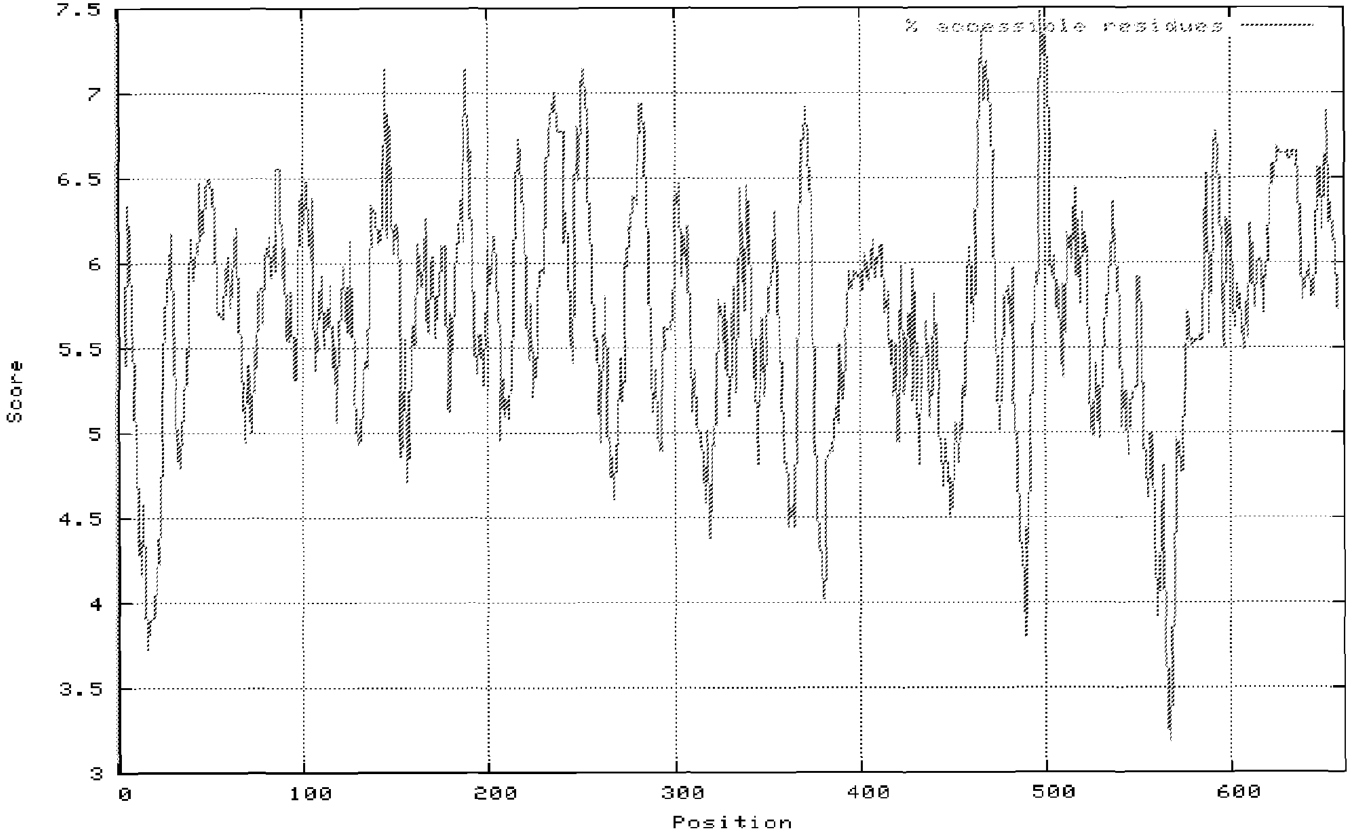
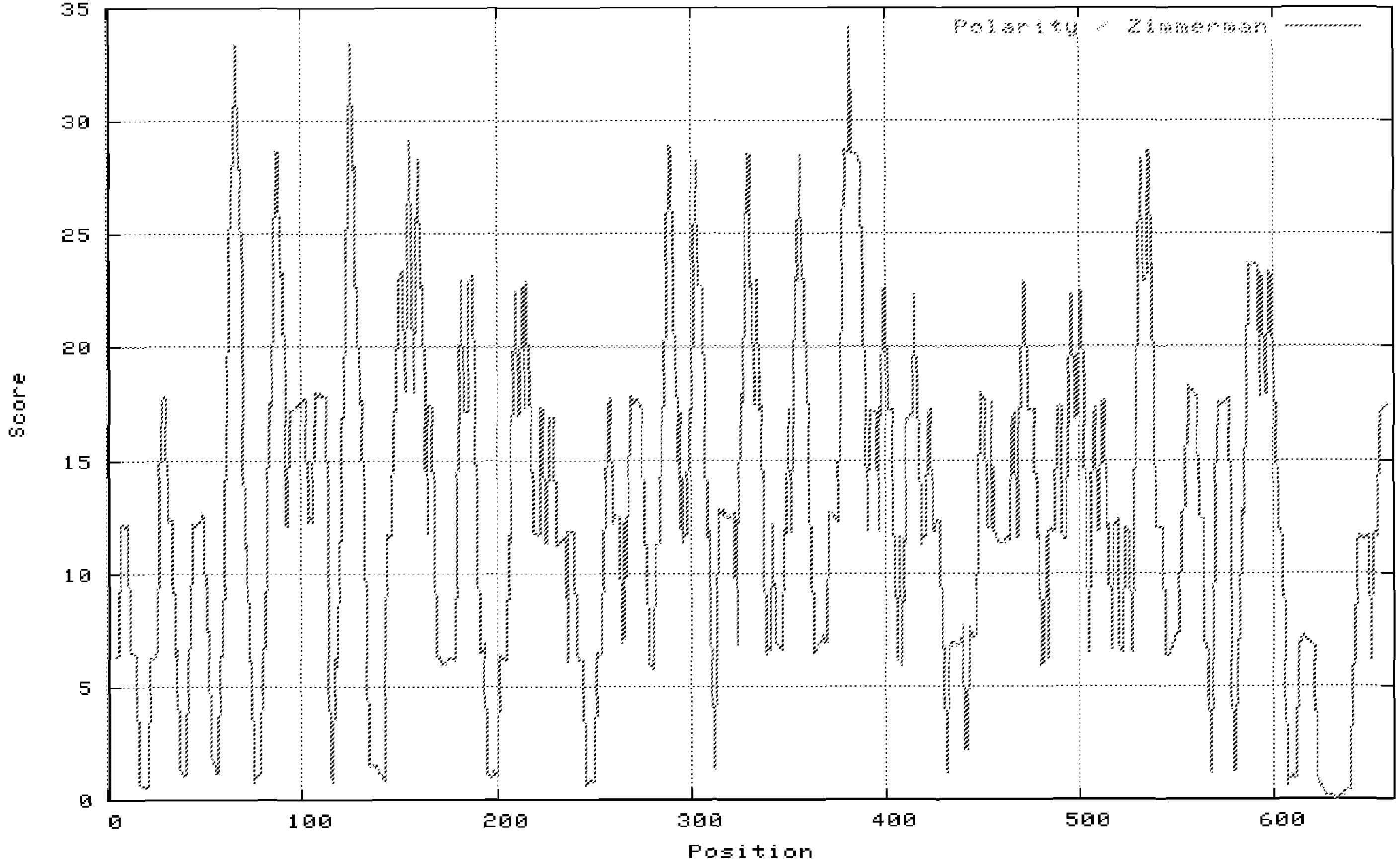


Figure 6C



CRTAC1 - Polarity

Figure 7A

CHAD - Recognition Factor

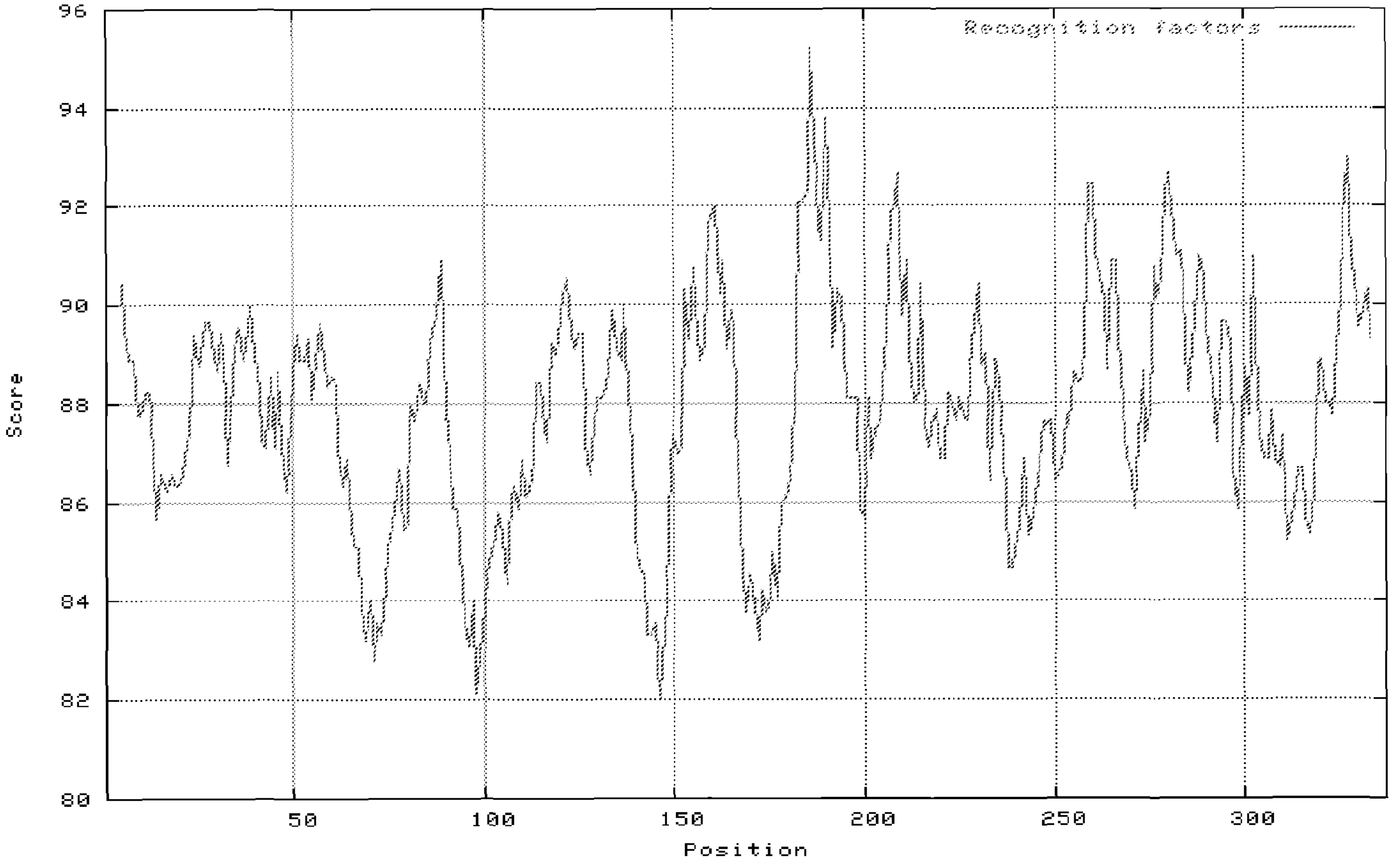


Figure 7B

CHAD - Accessibility

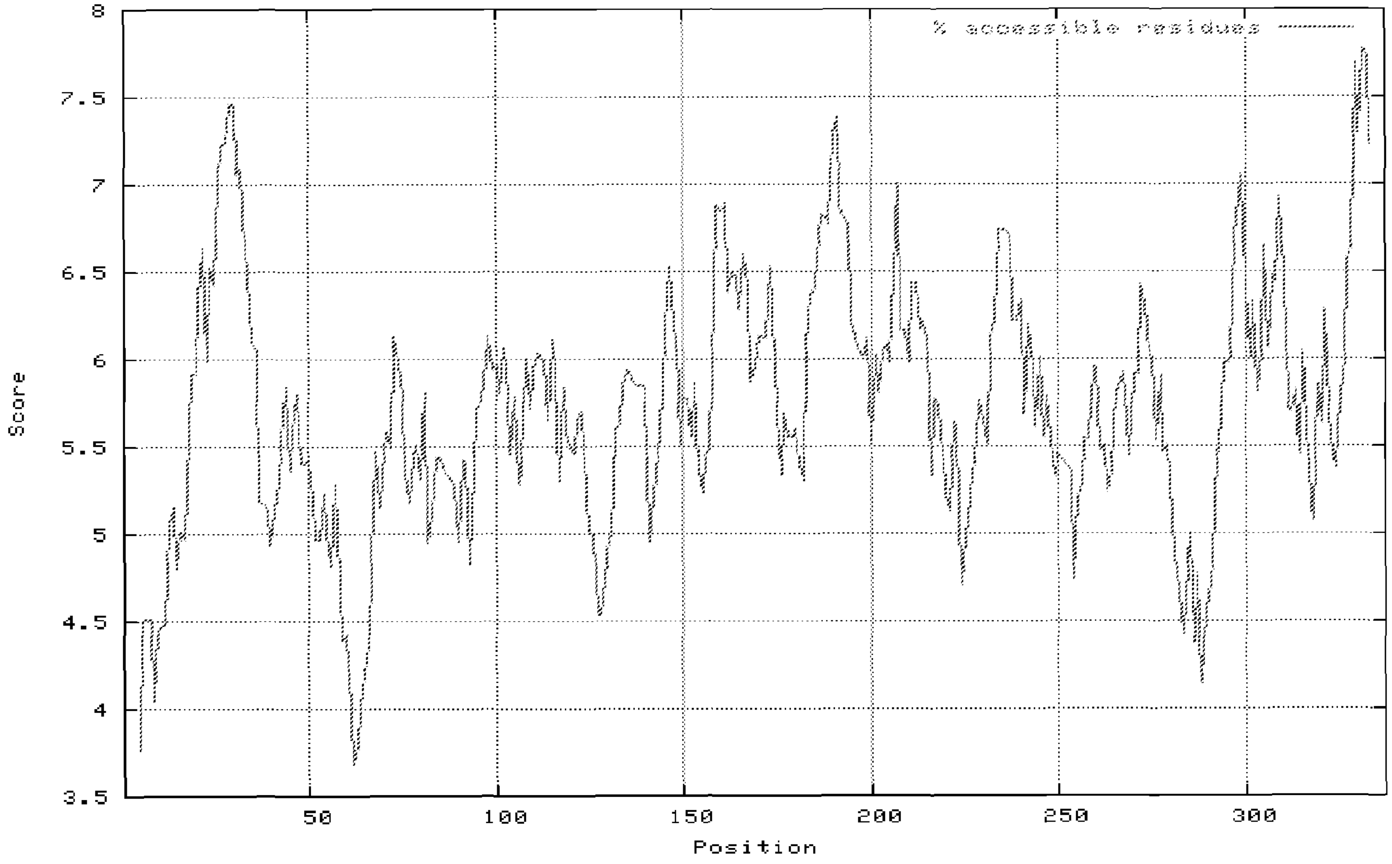
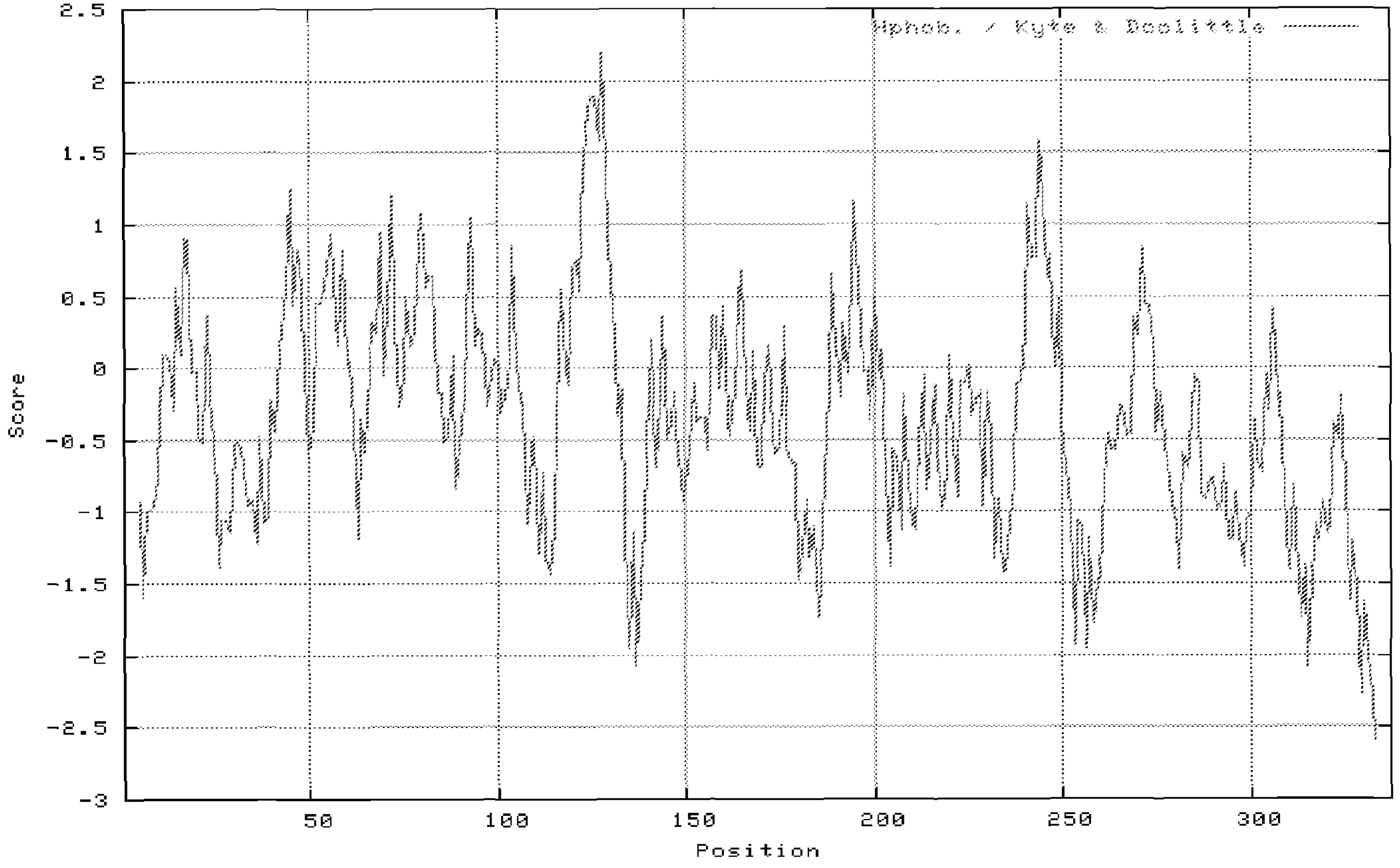


Figure 7C

CHAD - Polarity



METHODS FOR DETECTION AND DIAGNOSIS OF A BONE OR CARTILAGE DISORDER

FIELD OF THE INVENTION

[0001] The present invention relates to methods and kits for diagnosing and/or detecting a bone or cartilage disorder. More specifically, the present invention identifies several genes expressed at higher level in bone and/or cartilage which may be useful in the methods. The present invention also identifies several peptides occurring in body fluids, which may be useful in the methods.

BACKGROUND

[0002] Bones are rigid, dynamic organs comprising a variety of tissue types. The primary tissue of bone is osseous tissue, also called bone tissue, a relatively hard, lightweight tissue formed mostly of calcium phosphate. Other tissue types found in bone include marrow, endosteum and periosteum, nervers, blood vessels and cartilage.

[0003] Two distinct cell lineages are found in bone. Osteoblasts are bone-forming cells which descend from undifferentiated mesenchymal progenitor cells. Osteoclasts are the cells responsible for bone resorption and descend from monocyte stem cells. The continuous destruction and rebuilding of bone arises from the interplay of these two cell types. The action of osteoblasts and osteoclasts are controlled by chemical factors which either promote or inhibit the activity of these cells thus controlling the rate at which bone is made and/or destroyed.

[0004] The formation of bone during embryonic development occurs through two distinct pathways: endochondrial or intramembranous ossification. Intramembranous ossification occurs mainly during formation of bones of the skull from mesenchyme tissue. Endochondral ossification occurs in long bones (e.g. limbs) and entails the formation of bone from cartilage. Endochondrial ossification begins at primary ossification centers in the cartilage which appear during fetal development. These centers are responsible for the formation of the diaphyses of long bones. Secondary ossification occurs after birth, and forms the epiphyses of long bones. The diaphysis and both epiphyses of a long bone are separated by a growing zone of cartilage called the epiphyseal plate. When maturity is reached (about 18 years of age for humans), the cartilage is replaced by bone, fusing the diaphysis and both epiphyses together, a process termed epiphyseal closure.

[0005] A panoply of disorders arise from disturbances in the complex balance of bone resporption and build up, including but not limited to Paget's disease (osteitis deformans), inflammatory bone diseases such as rheumatoid arthritis, osteoarthritis and periodontal disease, focal osteogenesis occurring during skeletal metastases, Crouzon's syndrome, opsismodysplasia, pycnodysostosis/Toulouse-Lautrec disease, osteogenesis imperfecta (brittle bone disease) and osteoporosis. Other skeletal disorders include osteomalacia, osteopenia, osteopetrosis and osteochondritis dissecans.

[0006] Osteoporosis is one of the most prominent of the skeletal disorders. In osteoporosis, the bone mineral density is reduced, bone architecture is disrupted and the amount and variety of non-collagenous proteins in the bone is altered. The disease is most commonly observed in post-menopausal females but may also develop in men. The underlying mechanism in osteoporosis is an imbalance between bone resorption and bone formation; bone resorption is increased and/or formation of new bone is inadequate.

[0007] Cartilage is a type of dense connective tissue composed of specialized cells called chondrocytes that produce extracellular matrix. Cartilage is found in the articular surface of bones, the rib cage, the ear, the nose, the bronchial tubes and the intervertebral discs. Its mechanical properties lie between bone and dense connective tissue. Unlike other connective tissue, cartilage does not contain blood vessels.

[0008] Cartilage is classified into three groups: hyaline cartilage, elastic cartilage and fibrocartilage. Hyaline cartilage is a hard, translucent material with high concentrations of collagen and proteoglycan. It covers the ends of bones to form the smooth articular surface of joints. Elastic cartilage contains high concentrations of elastin, which provides an elasticity, and is found in the pinna of the ear, in tubular structures such as the auditory tubes and in the epioglotis. Fibrocartilage comprises a dense network of type I collagen providing high tensile strength and support, and is found in the intervertebral discs, the symphysis pubis and the attachments of certain tendons and ligaments.

[0009] Several diseases affect the cartilage including osteoarthritis, achondroplasia, and costochondritis. Osteoarthritis is a clinical syndrome in which low-grade inflammation results in pain in the joints, caused by abnormal wearing of the cartilage inside joints or a decrease of synovial fluid that lubricates the joints. The main symptom of osteoarthritis is chronic pain resulting in decreased mobility. There appears to be a hereditary susceptibility to this condition.

[0010] In recent years the palette of biomarkers to study the biological processes leading to severe bone and cartilage diseases like osteoporosis and rheumatoid arthritis has increased. Recently, the focus was drawn to several regulation molecules influencing either osteoclast or osteoblast proliferation. Despite this progress in understanding the biology of bone turnover, more biomarkers are needed for basic research and clinical studies on bone and cartilage disease.

SUMMARY

[0011] The present invention relates to methods of diagnosis and detection in the field of bone and/or cartilage disorders based on the differential expression observed for the polypeptides of the invention represented by SEQ ID NOs: 1 to 56. The present invention also relates to methods of diagnosis and detection in the field of bone and/or cartilage disorders based on the detection of body fluid peptides, represented by SEQ ID NOs: 57-193, derived from the polypeptides of the invention.

[0012] The present specification describes the identification of various polypeptides which are expressed to a greater degree in bone and/or cartilage tissue as compared to other tissues. These polypeptides are expected to serve as effective targets for the diagnosis and detection of bone and/or cartilage disorders in mammals. It appears that the polypeptides are differentially expressed in patients exhibiting a bone and/or cartilage disorder relative to healthy age and gender matched controls. The skilled artisan will recognize that such differentially expressed polypeptides have utility in the early detection, diagnosis, and/or prognosis of bone disorders, within the scope of the present invention.

[0013] The present specification also describes the identification of body fluid peptides derived from the selectively expressed polypeptides. The body fluid peptides are also found to serve as effective targets for the diagnosis and detection of bone and/or cartilage disorders in mammals. Generally, the detection for use in the diagnosis is performed in an in vitro assay.

[0014] Bone disorders which may be diagnosed according to the present invention include, without limitation, osteoporosis, osteopenia, osteomalacia, osteomyeloma, osteodystrophy, Paget's disease, osteogenesis imperfecta, bone sclerosis, aplastic bone disorder, humoral hypercalcemic myeloma, multiple myeloma, Crouzon's syndrome, opsismodysplasia, pycnodysostosis, and osteopetrosis.

[0015] Cartilage disorders which may be diagnosed according to the present invention include, without limitation, arthritis, including osteoarthritis and rheumatoid arthritis, degenerative joint disease, osteochondritis, osteochondritis dissecans, costochondritis and polychondritis.

[0016] In one embodiment, the present invention provides an antibody which binds, preferably specifically, to a polypeptide selected from SEQ ID NOs: 1 to 56. In a related embodiment, the present invention provides an antibody which binds, preferably specifically, to a peptide selected from SEQ ID NOs: 57-193. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody or single-chain antibody. For diagnostic purposes, the antibodies of the present invention may be detectably labeled, attached to a solid support, or the like. The antibody may bind to any epitope of a polypeptide selected from SEQ ID NOs: 1 to 56 and is capable of binding to at least one epitope of the polypeptide. The antibody may recognize a linear or conformational epitope of a polypeptide selected from SEQ ID NOs: 1 to 56. In one embodiment, the antibody recognizes an epitope common to a polypeptide selected from SEQ ID NOs: 1 to 56 and a peptide selected from SEQ ID NOs: 57-193.

[0017] In other embodiments, the present invention provides DNA encoding any of the herein described antibodies and vectors comprising the DNA. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells or yeast cells.

[0018] In other embodiments, the present invention provides oligopeptides which bind, preferably specifically, to a polypeptide selected from SEQ ID NOs: 1 to 56. In a related embodiment, the present invention provides oligopeptides which bind, preferably specifically, to a peptide selected from SEQ ID NOs: 57-193. The oligopeptides of the present invention may optionally be produced in CHO cells or bacterial cells. For diagnostic purposes, the oligopeptides may be detectably labeled, attached to a solid support or the like. Vectors comprising DNA encoding any oligopeptide of the invention and host cells comprising any such vector are also provided. A process for producing any of the oligopeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired oligopeptide and recovering the desired oligopeptide from the cell culture.

[0019] In another embodiment, the invention provides small organic molecules which bind, preferably specifically, to a polypeptide selected from SEQ ID NOs: 1 to 56 and/or a peptide selected from SEQ ID NOs: 57-193. For diagnostic purposes, the organic molecules of the present invention may be detectably labeled, attached to a solid support, or the like.

[0020] In another embodiment, the invention concerns a composition comprising any of the herein described antibodies, oligopeptides or small organic molecules (collectively, "specific binding agents"), in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

[0021] In yet another embodiment, the invention concerns a kit comprising a container and a composition within the container, wherein the composition may comprise any of the herein described specific binding agents (i.e. antibodies, oligopeptides or small organic molecules). The kit may further optionally comprise a label affixed to the container, or a package insert included with the container, that refers to the use of the composition for the diagnostic detection of a bone and/or cartilage disorder.

[0022] Yet another embodiment of the present invention is directed to a method of determining the level of expression of a polypeptide selected from SEQ ID NOs: 1 to 56 and/or a peptide selected from SEQ ID NOs: 57-193 in a test sample. In one aspect, the method comprises contacting the test sample with a specific binding agent (i.e. an antibody, oligopeptide or small organic molecule) that specifically binds the polypeptide and/or peptide and determining the binding of the specific binding agent to the test sample. Preferably, the specific binding agent is an antibody.

[0023] Yet another embodiment of the present invention is directed to a method of determining altered expression of a polypeptide selected from SEQ ID NOs: 1 to 56 in a test sample comprising (a) contacting a test sample with a specific binding agent that specifically binds to said polypeptide (b) measuring binding of said specific binding agent to said test sample and (c) comparing binding of step (b) to a control, whereby altered expression of said polypeptide is identified by a difference in binding of step (b) to a control. Preferably, the specific binding agent is an antibody.

[0024] In a related embodiment, the present invention provides a method of determining altered expression of a polypeptide selected from SEQ ID NOs: 1 to 56 in a test sample comprising (a) contacting a test sample with a specific binding agent that specifically binds to a peptide of SEQ ID NOs: 57-193 (b) measuring binding of said specific binding agent to said test sample and (c) comparing binding of step (b) to a control, whereby altered expression of said polypeptide is identified by a difference in binding of step (b) to a control. Preferably, the specific binding agent is an antibody.

[0025] Yet another embodiment of the present invention is directed to a method of determining altered expression of a peptide selected from SEQ ID NOs: 57 to 193 in a test sample comprising (a) contacting a test sample with a specific binding agent that specifically binds to said peptide (b) measuring binding of said specific binding agent to said test sample and (c) comparing binding of step (b) to a control, whereby altered expression of said peptide is identified by a difference in binding of step (b) to a control. Preferably, the specific binding agent is an antibody.

[0026] In a related embodiment, the present invention provides a method of determining altered expression of a peptide selected from SEQ ID NOs: 57 to 193 in a test sample comprising (a) contacting a test sample with a specific binding agent that specifically binds to a polypeptide of SEQ ID NOs: 1-56 (b) measuring binding of said specific binding agent to said test sample and (c) comparing binding of step (b) to a control, whereby altered expression of said peptide is identified by a difference in binding of step (b) to a control. Preferably, the specific binding agent is an antibody.

[0027] Yet another embodiment of the present invention is directed to a method of diagnosing a bone and/or cartilage disorder in a mammal, comprising determining the level of a polypeptide selected from SEQ ID NOs: 1 to 56 in a test sample from said mammal suspected of having said disorder, wherein a difference in the level of said polypeptide in said mammal compared to the level of said polypeptide in a normal mammal indicates the presence of a bone and/or cartilage disorder. Preferably the mammal is a human.

[0028] In a related embodiment, the present invention provides a method of diagnosing a bone and/or cartilage disorder in a mammal, comprising determining the level of a peptide selected from SEQ ID NOs: 57-193 in a test sample from said mammal suspected of having said disorder, wherein a difference in the level of said peptide in said mammal compared to the level of said peptide in a normal mammal indicates the presence of a bond and/or cartilage disorder. Preferably the mammal is a human.

[0029] In one aspect, the diagnostic method comprises (a) contacting a test sample obtained from the mammal with a specific binding agent that binds to a polypeptide selected from SEQ ID NOs: 1 to 56 (b) measuring binding of the specific binding agent to the test sample and (c) comparing binding of step (b) to a control, whereby a bone and/or cartilage disorder is diagnosed by an increase or decrease in expression of the polypeptide in the test sample compared to control. Preferably, the specific binding agent is an antibody.

[0030] In a related aspect, the diagnostic method comprises (a) contacting a test sample obtained from the mammal with a specific binding agent that binds to a peptide selected from SEQ ID NOs: 57-193 (b) measuring binding of the specific binding agent to the test sample and (c) comparing binding of step (b) to a control, whereby a bone and/or cartilage disorder is diagnosed by an increase or decrease in binding to the test sample compared to control. Preferably, the specific binding agent is an antibody.

[0031] Yet another embodiment of the present invention is directed to a method of binding a specific binding agent to a test sample comprising a polypeptide selected from SEQ ID NOs: 1 to 56 and/or a peptide selected from SEQ ID NOs: 57-193, wherein the method comprises contacting the test sample with said specific binding agent under conditions which are suitable for binding of the specific binding agent to said polypeptide and/or peptide and allowing binding therebetween. Preferably, the specific binding agent is an antibody.

[0032] Other embodiments of the present invention are directed to the use of a herein described specific binding agent in the preparation of a medicament useful for the diagnostic detection of a bone and/or cartilage disorder. Preferably, the specific binding agent is an antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIGS. **1**A-**1**C illustrate recognition factor, accessibility and polarity profiles for epiphycan (EPYC) (SEQ ID NO: 19).

[0034] FIGS. **2**A-**2**C illustrate recognition factor, accessibility and polarity profiles for asporin (ASPN) (SEQ ID NO: 2).

[0035] FIGS. **3**A-**3**C illustrate recognition factor, accessibility and polarity profiles for LOC 646627 (SEQ ID NO: 28).

[0036] FIGS. **4**A-**4**C illustrate recognition factor, accessibility and polarity profiles for LOXL3 (SEQ ID NO: 29).

[0037] FIGS. **5**A-**5**C illustrate recognition factor, accessibility and polarity profiles for TWIST2 (SEQ ID NO: 54).

[0038] FIGS. **6**A-**6**C illustrate recognition factor, accessibility and polarity profiles for CRTAC1 (SEQ ID NO: 16).

[0039] FIGS. **7**A-**7**C illustrate recognition factor, accessibility and polarity profiles for CHAD (SEQ ID NO: 10).

DETAILED DESCRIPTION

[0040] Definitions

[0041] By "test sample" is intended any biological sample obtained from an organism, body fluids, cell line, tissue culture, or other source which contains, or is suspected to contain, a polypeptide selected from SEQ ID NOs: 1 to 56 and/or a peptide selected from SEQ ID NOs: 57-193. As indicated, biological samples include body fluids (such as the following non-limiting examples, sputum, amniotic fluid, urine, saliva, tears, sweat, breast milk, secretions, interstitial fluid, blood, synovial fluid, serum, spinal fluid, lymph, semen, vaginal fluid, cerebro-spinal fluid, cell culture supernatant, cell extract, tissue extract, etc.) which contain the polypeptides and/or peptides, and other tissue sources found to express the polypeptides and/or peptides. Methods for obtaining tissue biopsies and body fluids from organisms are well known in the art.

[0042] The term "antibody" is used in the broadest sense and specifically covers, for example, single monoclonal antibodies (including agonist, antagonist and neutralizing antibodies), antibody compositions with polyepitopic specificity, polyclonal antibodies, single chain antibodies, and antibody fragments that exhibit the desired biological or immunological activity. The term "immunoglobulin" (Ig) is used interchangeable with antibody herein.

[0043] The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contains 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150 kDa. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_H1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site.

[0044] The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobluins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α, δ, ϵ, γ, and μ, respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function.

[0045] The term “variable” refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Rather, the V regions consist of relatively invariant stretches called framework regions (FR) of 15-30 amino acids separated by shorter regions of extreme variability called “hypervariable regions” that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β-sheet configuration, connected by three hypervariable or complementarity determining region (CDR), which form loops connecting, and in some cases forming part of, the β-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity.

[0046] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogenous antibodies, i.e., the individual antibodies comprising the population are identical except for possibly naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier “monoclonal” is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology or may be made using recombinant DNA methods in bacterial, eukaryotic animals or plant cells or may be isolated from phage antibody libraries.

[0047] The monoclonal antibodies herein include “chimeric” antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. Chimeric antibodies of interest herein include “primatized” antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

[0048] An “intact” antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains C_H1, C_H2 and C_H3.

[0049] “Antibody fragments” comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0050] Papain digestion of antibodies produces two identical antigen-binding fragments, called “Fab” fragments, and a residual “Fc” fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H1). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0051] The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

[0052] “Fv” is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0053] “Single-chain Fv” also abbreviated as “sFv” or “scFv” are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding.

[0054] The term “diabodies” refers to small antibody fragments prepared by constructing sFv fragments with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two “crossover” sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains.

[0055] “Humanized” forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[0056] A "species-dependent antibody," e.g., a mammalian anti-human IgE antibody, is an antibody which has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

[0057] An antibody or other organic molecule "which binds" an antigen of interest, e.g. a polypeptide selected from SEQ ID NOs: 1 to 56 and/or a peptide selected from SEQ ID NOs: 57-193, is one that binds the antigen with sufficient affinity such that the antibody or other organic molecule is useful as a diagnostic agent in a cell, tissue and/or body fluid expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody or other organic molecule to a "non-target" protein will be less than about 10% of the binding of the antibody or other organic molecule to its particular target protein as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of an antibody or other organic molecule to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a Kd for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope

[0058] The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody, oligopeptide or other organic molecule so as to generate a "labeled" antibody, oligopeptide or other organic molecule. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

[0059] The terms "Western blot," "Western immunoblot" "immunoblot" and "Western" refer to the immunological analysis of protein(s), polypeptides or peptides that have been immobilized onto a membrane support. The proteins are first resolved by polyacrylamide gel electrophoresis (i.e., SDS-PAGE) to separate the proteins, followed by transfer of the protein from the gel to a solid support, such as nitrocellulose or a nylon membrane. The immobilized proteins are then exposed to an antibody having reactivity towards an antigen of interest. The binding of the antibody (i.e., the primary antibody) is detected by use of a secondary antibody which specifically binds the primary antibody. The secondary antibody is typically conjugated to an enzyme which permits visualization of the antigen-antibody complex by the production of a colored reaction product or catalyzes a luminescent enzymatic reaction (e.g., the ECL reagent, Amersham).

[0060] As used herein, the term "ELISA" refers to enzyme-linked immunosorbent assay (or EIA). Numerous ELISA methods and applications are known in the art, and are described in many references (See, e.g., Crowther, "Enzyme-Linked Immunosorbent Assay (ELISA)," in *Molecular Biomethods Handbook,* Rapley et al. [eds.], pp. 595-617, Humana Press, Inc., Totowa, N.J. [1998]; Harlow and Lane (eds.), *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory Press [1988]; Ausubel et al. (eds.), *Current Protocols in Molecular Biology,* Ch. 11, John Wiley & Sons, Inc., New York [1994]). In addition, there are numerous commercially available ELISA test systems.

[0061] One ELISA method is a "direct ELISA," where an antigen (e.g., a polypeptide selected from SEQ ID Nos: 1-56 and/or a peptide selected from SEQ ID Nos: 57-193) in a sample is detected. In one embodiment of the direct ELISA, a sample containing antigen is exposed to a solid (i.e., stationary or immobilized) support (e.g., a microtiter plate well). The antigen within the sample becomes immobilized to the stationary phase, and is detected directly using an enzyme-conjugated antibody specific for the antigen.

[0062] In an alternative embodiment, an antibody specific for an antigen is detected in a sample. In this embodiment, a sample containing an antibody (e.g., an antibody specific for a polypeptide selected from SEQ ID Nos: 1-56 or a peptide selected from SEQ ID Nos: 57-193) is immobilized to a solid support (e.g., a microtiter plate well). The antigen-specific antibody is subsequently detected using purified antigen and an enzyme-conjugated antibody specific for the antigen.

[0063] In an alternative embodiment, an "indirect ELISA" is used. In one embodiment, an antigen (or antibody) is immobilized to a solid support (e.g., a microtiter plate well) as in the direct ELISA, but is detected indirectly by first adding an antigen-specific antibody (or antigen), then followed by the addition of a detection antibody specific for the antibody that specifically binds the antigen, also known as "species-specific" antibodies (e.g., a goat anti-rabbit antibody), which are available from various manufacturers known to those in the art.

[0064] In other embodiments, a "sandwich ELISA" is used, where the antigen (e.g. contained in a test sample) is immobilized on a solid support (e.g., a microtiter plate) via an antibody (i.e., a capture antibody) that is immobilized on the solid support and is able to bind the antigen of interest. Following the affixing of a suitable capture antibody to the immobilized phase, a sample is then added to the microtiter plate well, followed by washing. If the antigen of interest is present in the sample, it is bound to the capture antibody present on the support. In some embodiments, a sandwich ELISA is a "direct sandwich" ELISA, where the captured antigen is detected directly by using an enzyme-conjugated antibody directed against the antigen. Alternatively, in other embodiments, a sandwich ELISA is an "indirect sandwich" ELISA, where the captured antigen is detected indirectly by using an antibody directed against the antigen, which is then detected by another enzyme-conjugated antibody which binds the antigen-specific antibody, thus forming an antibody-antigen-antibody-antibody complex. Suitable reporter reagents are then added to detect the third antibody. Alternatively, in some embodiments, any number of additional antibodies are added as necessary, in order to detect the antigen-antibody complex. In some preferred embodiments, these additional antibodies are labelled or tagged, so as to permit their visualization and/or quantitation.

[0065] As used herein, the term "capture antibody" refers to an antibody that is used in a sandwich ELISA to bind (i.e., capture) an antigen in a sample prior to detection of the antigen. For example, in some embodiments, a polyclonal antibody against a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 serves as a capture antibody when immobilized in a microtiter plate well. This capture antibody binds the polypeptide and/or peptide present in a sample added to the well. In one embodiment of the present invention, biotinylated capture antibodies are used in the present invention in conjunction with avidin-coated solid support. Another antibody (i.e., the detection antibody) is then used to bind and detect the antigen-antibody complex, in effect forming a "sandwich" comprised of antibody-antigen-antibody (i.e., a sandwich ELISA).

[0066] As used herein, a "detection antibody" is an antibody which carries a means for visualization or quantitation, which is typically a conjugated enzyme moiety that typically yields a colored or fluorescent reaction product following the addition of a suitable substrate. Conjugated enzymes commonly used with detection antibodies in the ELISA include horseradish peroxidase, urease, alkaline phosphatase, glucoamylase and β-galactosidase. In some embodiments, the detection antibody is directed against the antigen of interest, while in other embodiments, the detection antibody is not directed against the antigen of interest. In some embodiments, the detection antibody is an anti-species antibody. Alternatively, the detection antibody is prepared with a label such as biotin, a fluorescent marker, or a radioisotope, and is detected and/or quantitated using this label.

[0067] As used herein, the terms "reporter reagent," "reporter molecule," "detection substrate" and "detection reagent" are used in reference to reagents which permit the detection and/or quantitation of an antibody bound to an antigen. For example, in some embodiments, the reporter reagent is a colorimetric substrate for an enzyme that has been conjugated to an antibody. Addition of a suitable substrate to the antibody-enzyme conjugate results in the production of a colorimetric or fluorimetric signal (e.g., following the binding of the conjugated antibody to the antigen of interest). Other reporter reagents include, but are not limited to, radioactive compounds. This definition also encompasses the use of biotin and avidin-based compounds (e.g., including but not limited to neutravidin and streptavidin) as part of the detection system.

[0068] As used herein, the term "signal" is used generally in reference to any detectable process that indicates that a reaction has occurred, for example, binding of antibody to antigen. It is contemplated that signals in the form of radioactivity, fluorimetric or colorimetric products/reagents will all find use with the present invention. In various embodiments of the present invention, the signal is assessed qualitatively, while in alternative embodiments, the signal is assessed quantitatively.

[0069] As used herein, the term "amplifier" is used in reference to a system which enhances the signal in a detection method, such as an ELISA (e.g., an alkaline phosphatase amplifier system used in an ELISA).

[0070] Polypeptides of SEQ ID Nos: 1 to 56

[0071] Polypeptide Having Sequence Set Forth in SEQ ID NO: 1

[0072] This polypeptide, known as aggrecan 1, is encoded by the gene AGC1 which has been localized to 15q26. Aggrecan is an integral part of the extracellular matrix (ECM) in cartilaginous tissue and is released into bodily fluids when cleaved by aggrecanase or the like. Release of fragments of aggrecan enables measurement in synovial fluid, serum and urine. Peptides derived from aggrecan 1 are set forth as SEQ ID NOs: 57-59.

[0073] Polypeptide Having Sequence Set Forth in SEQ ID NO: 2

[0074] This polypeptide, known as asporin (ASPN), is a member of the leucine-rich repeat family of proteins associated with the cartilage matrix. Asporin contains a putative propeptide, four amino-terminal cysteines, 10 leucine-rich repeats and two carboxy-terminal cysteines.

[0075] Polypeptide Having Sequence Set Forth in SEQ ID NO: 3

[0076] This polypeptide, known as butyrylcholinesterase (BCHE) (or serum cholinesterase), is similar to the neuronal acetylcholinesterase. Mutant alleles at the BCHE locus are responsible for suxamethonium sensitivity manifested by persistent apnea following administration of the muscle relaxant during surgical anesthesia. Peptides derived from BCHE are set forth as SEQ ID NOs: 159 and 160.

[0077] Polypeptide Having Sequence Set Forth in SEQ ID NO: 4

[0078] This polypeptide, known as bone gamma-carboxyglutamate protein (BGLAP) or osteocalcin, is secreted by osteoblasts and thought to play a role in mineralization and calcium ion homeostasis.

[0079] Polypeptide Having Sequence Set Forth in SEQ ID NO: 5.

[0080] This polypeptide, known as BGN or biglycan, is a small leucine-rich repeat proteoglycan found in ECM tissues such as bone and cartilage. Biglycan consists of a core containing leucine-rich repeat regions and two glycosaminoglycan chains consisting of either chondroitin sulfate or dermatan sulfate. Biglycan appears to play a role in the mineralization of bone. Biglycan is thought to be involved in regulation of matrix assembly growth factor activity due to its ability to bind to TGFβ1. Peptides derived from BGN are set forth as SEQ ID NOs: 184-191.

[0081] Polypeptide Having Sequence Set Forth in SEQ ID NO: 6

[0082] This polypeptide, known as BMX, is a non-receptor tyrosine kinase. The BMX gene is a member of the BTK/ITK/TEC/TXK family located in chromosome Xp22.2.

[0083] Polypeptide Having Sequence Set Forth in SEQ ID NO: 7

[0084] This polypeptide, termed Ucma (unique cartilage matrix-associated protein), is a secreted cartilage-specific protein, highly conserved across species, but with no homology to other known proteins. Ucma is encoded by chrosome 10 open reading frame 49 (c10orf49).

[0085] Polypeptide Having Sequence Set Forth in SEQ ID NO: 8

[0086] This polypeptide, termed CALU or calumenin, is a calcium-binding protein located in the endo/sarcoplasmic reticulum of mammalian heart and other tissues. It is an endoplasmic reticulum chaperone protein, involved in protein folding and sorting. Calumenin is a member of the CERC EF-hand superfamily. The human and mouse CALU proteins are 98% identical. CALU and RCN3 are co-regulated; accordingly, a level of expression detected for CALU provides a measure of the level of expression of CALU or a peptide derived therefrom.

[0087] Polypeptide Having Sequence Set Forth in SEQ ID NO: 9

[0088] This polypeptide, termed cartilage paired-class homeoprotein 1 (CART1), also known as ALX1, is a member of tumor necrosis factor receptor-associated protein family. CART1 is selectively expressed in chondrocytes during embryonic development. The function of CART1 is humans has not yet been determined; however, in rodents, mutations in CART1 lead to neural tube defects.

[0089] Polypeptide Having the Sequence Set Forth in SEQ ID NO: 10

[0090] This polypeptide, termed chondroadherin (or CHAD), is a cartilage matrix protein thought to mediate adhesion of isolated chondrocytes. Chondroadherin contains 11 leucine-rich repeats flanked by cysteine-rich regions. CHAD is co-regulated with OGN and EPYC. Accordingly, a level of expression detected for CHAD provides a measure of the level of expression of OGN and/or EPYC.

[0091] Polypeptide Having the Sequence Set Forth in SEQ ID NO: 11

[0092] This polypeptide, termed chitinase 3-like 1 (CHI3L1), also known as cartilage glycoprotein-39, is a major secreted protein of ex vivo cultured articular chondrocytes and synovial cells. Chitinase 3-like 1 is a chitin-binding lectin which most likely functions in remodeling or degradation of ECM. Peptides derived from CHI3L1 are set forth as SEQ ID NOs: 161-168.

[0093] Polypeptide Having Sequence Set Forth in SEQ ID NO: 12

[0094] This polypeptide, termed cartilage intermediate layer protein (CILP) was identified and purified from human articular cartilage. The C-terminal 460 amino acids of the protein show 90% similarity to the pig ectonucleotide pyrophosphohydrolase NTPPHase. Peptides derived from CILP are set forth as SEQ ID NOs: 60-72.

[0095] Polypeptide Having Sequence Set Forth in SEQ ID NO: 13

[0096] This polypeptide, termed CILP2, is an isoform of CILP which is 50.6% identical. Peptides derived from CILP2 are set forth as SEQ ID NOs: 73-87.

[0097] Polypeptide Having Sequence Set Forth in SEQ ID NO: 14

[0098] This polypeptide, termed C-type lectin domain family 3 member A (CLEC3A), is an ECM structural constituent.

[0099] Polypeptide Having Sequence Set Forth in SEQ ID NO: 15

[0100] This polypeptide, termed Collection sub-family member 12 (COLEC12), is a member of the C-lectin family, the members of which possess collagen-like sequences and carbohydrate recognition domains. COLEC12 is a cell surface glycoprotein which can bind to carbohydrate antigens on microorganisms facilitating recognition/removal. COLEC12 may be involved in selective clearance of specific desialylated glycoproteins from circulation. Peptides derived from COLEC12 are set forth as SEQ ID NOs: 90-99.

[0101] Polypeptide Having Sequence Set Forth in SEQ ID NO: 16

[0102] This polypeptide, termed cartilage acidic protein 1 (CRTAC1), is a glycosylated ECM molecule of human articular cartilage secreted by chondrocytes. CRTAC1 is predicted to have four FG-GAP repeat domains, one RGD integrin binding motif and an EGF-like calcium binding domain.

[0103] Polypeptide Having Sequence Set Forth in SEQ ID NO: 17

[0104] This polypeptide, termed cytokine-like 1 (CYTL1) is a cytokine-like protein specifically expressed in bone marrow and cord blood mononuclear cells that bear the CD34 marker. CYTL appears to regulate the chondrogenesis of mesenchymal cells.

[0105] Polypeptide Having Sequence Set Forth in SEQ ID NO: 18

[0106] This polypeptide, termed endoglin (or ENG), is a homodimeric transmembrane RGD-containing glycoprotein highly expressed by endothelial cells. Endoglin is a component of the TGFβ receptor complex. Mutations in endoglin produce hereditary hemorrhagic telangiectasia. There are two isoforms of endoglin—SEQ ID NO: 18 is the longer of the two.

[0107] Polypeptide Having Sequence Set Forth in SEQ ID NO: 19

[0108] This polypeptide, termed epiphycan (EPYC), or dermatan sulfate proteoglycan 3, is a member of the small leucine-rich repeat proteoglycan family. Epiphycan regulates fibrillogenesis by interacting with collagen fibrils and other ECM proteins. EPYC is co-regulated with OGN and CHAD. Accordingly, a level of expression detected for EPYC provides a measure of the level of expression of OGN and/or CHAD.

[0109] Polypeptide Having Sequence Set Forth in SEQ ID NO: 20

[0110] This polypeptide, termed ethanolamine kinase 1 (ETNK1), functions in the first committed step of the phosphatidylethanolamine synthesis pathway. ETNK1 may be associated with prostatic neoplasms and seminoma. There are two distinct isoforms of ETNK—SEQ ID NO: 20 is the longer of the two.

[0111] Polypeptide Having Sequence Set Forth in SEQ ID NO: 21

[0112] This polypeptide, termed fibronectin leucine-rich transmembrane protein (FLRT) 2, may function in cell adhesion and/or receptor signaling. Peptides derived from FLRT2 are set forth as SEQ ID NOs: 100-106.

[0113] Polypeptide Having Sequence Set Forth in SEQ ID NO: 22

[0114] This polypeptide, termed FLRT3, is a member of the fibronectin leucine-rich transmembrane protein family. FLRT3 shares 44% amino acid sequence identity with FLRT2. Peptides derived from FLTR3 are set forth as SEQ ID NOs: 107-108.

[0115] Polypeptide Having Sequence Set Forth in SEQ ID NO: 23

[0116] This polypeptide, termed hyaluronan and proteoglycan link protein (HAPLN1), may function as a stabilizer of the interaction between aggrecan and hyaluronan in cartilage.

[0117] Polypeptide Having Sequence Set Forth in SEQ ID NO: 24

[0118] This polypeptide, termed IGF-like family member 3 (IGFL3), plays critical roles in cellular energy metabolism and growth and development.

[0119] Polypeptide Having Sequence Set Forth in SEQ ID NO: 25

[0120] This polypeptide, termed KIAA0999, also known as serine/threonine-protein kinase QSK, is a human cAMP-dependent protein kinase beta-catalytic subunit. QSK catalyzes the transfer of a phosphate from ATP to a protein. QSK belongs to the CAMK Ser/Thr protein kinase family.

[0121] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 26

[0122] This polypeptide, termed LOC283951, is expected to localize to the cell membrane. Little is known about this polypeptide. A peptide derived from LOC283951 is set forth as SEQ ID NO: 127.

[0123] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 27

[0124] This polypeptide, termed LOC284998, is a hypothetical protein encoded by a gene mapping to position 2q12.1 on chromosome 2.

[0125] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 28

[0126] This polypeptide, termed LOC646627, is a phospholipase inhibitor encoded by a gene mapping to position 1q44 on chromosome 1.

[0127] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 29

[0128] This polypeptide, termed lysyl oxidase-like 3 (LOXL3), is essential to the biogenesis and repair of connective tissue. LOXL3 is an extracellular copper-dependent amine oxidase that catalyzes the first step in the formation of crosslinks in collagens and elastin. LOXL3 is a susceptibility gene for intracranial aneurysms.

[0129] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 30

[0130] This polyeptide, termed lysyl oxidase-like 4 (LOXL4), like LOXL3, is a member of the lysyl oxidase gene family. LOXL3 and LOXL4 are described in WO/2001/083702.

[0131] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 31

[0132] This polypeptide, known as latent transforming growth factor beta (TGFβ) binding protein 1 (LTBP1), belongs to the LTBP family, members of which regulate the secretion and activation of TGFβ. LTBP1 targets latent complexes of TGFP to the ECM where TGFP is activated. There are two isoforms of LTBP1, the longer of which is represented by SEQ ID NO: 31. Peptides derived from LTBP1 are set forth as SEQ ID NOs: 109-114.

[0133] Polypeptide Having a Sequence Set Forth in SEQ ID NO: 32

[0134] This polypeptide, known as matrilin 1 (or MATN1), is a cartilage matrix protein and a member of the von Willebrand factor A domain containing family. Matrilin 1 is thought to be involved in the formation of filamentous networks in the ECM. The MATN1 gene is localized at 1p35 and is mainly expressed in cartilage. Along with MATN3 (see below), MATN1 is among the most up-regulated ECM proteins during chondrogenesis.

[0135] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 33

[0136] This polypeptide is known as MATN3, is a member of the von Willebrand factor A domain containing family having two von Willebrand factor A domains. It is present in the cartilage extracellular matrix.

[0137] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 34

[0138] This polypeptide, known as matrix, extracellular phosphoglycoprotein with ASARM motif (or MEPE), is an ECM phosphoglycoprotein and a member of the small integrin binding ligand N-linked glycoprotein (SIBLING) family. MEPE is predominantly expressed by osteocytes and is involved in phosphate and bone metabolism. MEPE promotes renal phosphate excretion and inhibits bone mineralization. A peptide derived from MEPE is set forth as SEQ ID NO: 134.

[0139] The Polypeptide Having Sequence Set Forth in SEQ ID NO: 35

[0140] This polypeptide, termed matrix Gla protein (or MGP), associates with the organic matrix of bone and cartilage and is thought to act as an inhibitor of bone formation.

[0141] The Polypeptide Having Sequence Set Forth in SEQ ID NO: 36

[0142] This polypeptide, known as matrix-remodeling associated 5 (MXRA5), also called adlican, contains leucine-rich repeat and immunoglobulin domains. MXRA5 is described in U.S. Pat. No. 7,094,890, the contents of which are incorporated herein by reference. Peptides derived from MXRA5 are set forth as SEQ ID Nos: 169-180.

[0143] The Polypeptide Having Sequence Set Forth in SEQ ID NO: 37

[0144] This polypeptide, known as matrix-remodeling-associated protein 8 (MXRA8) or limitrin, may play a role in the maturation and maintenance of blood-brain barrier, as the murine ortholog has been demonstrated to localize selectively to glia limitans in the mouse brain. Peptides derived from MXRA8 are set forth as SEQ ID Nos: 135-154.

[0145] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 38

[0146] This polypeptide, known as nidogen 2 (NID2) or osteonidogen, is a component of the basement membrane. Lack of nidogen 1 and nidogen 2 prevents basement membrane assembly in vitro. Nidogen 2 exhibits aberrant methylation in several human cancers. A peptide derived from NID2 is set forth as SEQ ID No: 88.

[0147] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 39

[0148] This polypeptide, known as NLRP5 or NALP5, is a member of the NALP protein family, originally identified as an oocyte specific antigen in mice. Members of this family typically contain a NACHT domain, a NACHT-associated domain (NAD), a C-terminal leucine-rich repeat (LRR) region, and an N-terminal pyrin domain (PYD). NALP5 appears to be a tissue-specific autoantigen involved in hypoparathyroidism in patients with APS-1. U.S. Patent Publication No. 20040248775 discloses that NALP5 expression is elevated after transient cerebral artery occlusion.

[0149] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 40

[0150] This polypeptide, known as nephronectin (or NPNT) is a human epidermal growth factor-like ECM protein expressed in a number of embryonic and adult tissues, including kidney, and lung. The gene encoding NPNT is located at chromosomal position 4q25. Peptides derived from NPNT are set forth as SEQ ID Nos: 115-126.

[0151] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 41

[0152] This polypeptide, known as osteoglycin (OGN), is a small proteoglycan which contains tandem leucine-rich repeats. Osteoglycin induces ectopic bone formation in conjunction with TGFβ. Altered expression of osteoglycin has been correlated with enlarged hearts, epecially left ventricular hypertrophy. Peptides derived from OGN are set forth as SEQ ID Nos: 130-133. OGN is co-regulated with CHAD and EPYC; accordingly, a level of expression detected for OGN or a peptide derived therefrom provides a measure of the level of expression of CHAD and/or EPYC.

[0153] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 42

[0154] This polypeptide, known as osteomodulin/osteoadherin (OMD) is a cell-binding keratin sulfate proteoglycan belonging to the leucine-rich proteoglycan family. OMD contains 12 leucine-rich repeats and may be implicated in biomineralization. OMD has been shown to bind $\alpha_5\beta_3$ integrin. Peptides derived from OMD are set forth as SEQ ID Nos: 192 and 193.

[0155] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 43

[0156] This polypeptide, known as oncostatin M receptor (OSMR), is part of a heterodimeric receptor complex (along with gp130) that mediates signal transduction of the cytokine oncostatin M, a member of the IL6 cytokine family. Mutations in OSM are associated with a form of amyloidosis. Mice deficient in OSMR exhibit a reduced number of peripheral erythrocytes and platelets relative to wild type mice.

[0157] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 44

[0158] This polyeptpide, termed osteocrin (OSTN) or musclin, is a vitamin-D regulated bone-specific protein. Osteocrin is highly expressed in osteoblasts and may function as a negative regulator of osteoblast differentiation and may also be involved in ossification. Peptides derived from OSTN are set forth as SEQ ID Nos: 128 and 129.

[0159] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 45

[0160] This polypeptide, termed periostin (POSTN) is an osteoblast specific factor which may modulate new bone formation and cell adhesion. POSTN has also been implicated as essential for cardiac healing after infarction.

[0161] The Polypeptide Having a Sequence Set Forth in SEQ ID NO: 46

[0162] This polypeptide, termed proteoglycan 4 (PRG4) is a large proteoglycan specifically synthesized by chondrocytes located at the surface of articular cartilage. PRG4 functions as a lubricant at the cartilage surface and contributes to the elastic absorption and energy dissipation of synovial fluid. PRG4 exists as multiple isoforms—SEQ ID NO 46 represents the longest of these isoforms. Peptides derived from PRG4 are set forth as SEQ ID Nos: 181-183.

[0163] The Polypeptide Having Sequence Set Forth in SEQ ID NO: 47

[0164] This polypeptide, termed pleiotrophin (PTN), also known as heparin binding growth factor 8 and neurite growth promoting factor 1, is a proangiogenic cytokine that potentiates cardiomyocyte apoptosis. PTN may participate in nervous system development, in bone mineralization and in learning. PTN may be associated with astrocytomas and brain neoplasms.

[0165] The Polypeptide Having Sequence Set Forth in SEQ ID NO: 48

[0166] This polypeptide, known as reticulocalbin 3 (RCN3), contains an EF-hand calcium binding domain. RCN3 is a member of the Cab45/reticulocalbin/ERC45/calumenin) (CREC) family of multiple EF-hand calcium-binding proteins localized to the secretory pathway. A peptide derived from RCN3 is set forth as SEQ ID NO: 89. RCN3 and CALU are co-regulated; accordingly, a level of expression detected for RCN3 or a peptide derived therefrom provides a measure of the level of expression of CALU.

[0167] The Polypeptide Having Sequence Set Forth in SEQ ID NO: 49

[0168] This polypeptide, known as sema domain, transmembrane and cytoplasmic domain (semaphorin) 6D (SEMA6D), is a member of the semaphorin family, a large protein family implicated as inhibitors or chemorepellents in axon pathfinding, branching and target selection. The SEMA6D gene encodes six identified transcripts; SEQ ID NO: 49 represents the longest of the encoded polypeptides.

[0169] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 50

[0170] This polypeptide, known as serine peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1) member 2 (SERPINE 2), is an extracellular serine proteinase inhibitor activity toward trypsin, thrombin, plasmin and other serine proteinases. SERPINE2 has been implicated as a chronic obstructive pulmonary disease (COPD) susceptibility gene. A peptide derived from SERPINE2 is set forth as SEQ ID NO: 155.

[0171] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 51

[0172] This polypeptide, termed solute carrier family 15, member 3 (SLC15A3), is a transporter protein likely involved in oligopeptide transport.

[0173] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 52

[0174] This polypeptide, termed solute carrier family 28 (sodium-coupled nucleoside transporter) member 3 (SLC28A3), is a member of the nucleoside transporter family, the members of which regulate multiple cellular processes including neurotransmission, vascular tone, and the transport and metabolism of nucleoside drugs.

[0175] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 53

[0176] This polypeptide, known as tubulin folding cofactor A (TBCA), is one of four proteins (cofactors A, D, E, C) involved in the pathway leading to correctly folded β-tubulin from intermediates. Peptides derived from TBCA are set forth as SEQ ID Nos: 156-158.

[0177] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 54

[0178] This polypeptide, known as twist homolog 2 (TWIST2), is a basic helix-loop-helix transcription factors which have been implicated in cell lineage determination and differneation. It is thought that during osteoblast development, TWIST2 may inhibit osteoblast maturation and maintain cells in preosteoblast phenotype. Reduced expression of TWIST2 may suppress the multistep process of peritoneal dissemination.

[0179] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 55

[0180] This polypeptide, known as LOC339316, is hypothetical protein encoded by a gene mapping to position 19q12 on chromosome 19.

[0181] The Polypeptide Having Sequence as Set Forth in SEQ ID NO: 56

[0182] This polypeptide, known as LRC15, or human leucine-rich repeat-containing protein 15 [precursor], is encoded by the LRRC15 gene mapping to position 3q29 on chromosome 3. LRC15 is a potential single-pass type 1 membrane protein of 581 amino acids.

[0183] It is to be understood that homologs of a polypeptide of SEQ ID NOs 1 to 56 may also be useful in the invention.

[0184] Antibodies

[0185] Polyclonal

[0186] In one embodiment, the present invention provides antibodies which bind to a polypeptide selected from SEQ ID Nos: 1-56 and/or a peptide selected from SEQ ID Nos: 57-193, and which may find use herein as diagnostic agents. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies

[0187] Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (especially when synthetic peptides are used) to a protein that is immunogenic in the species to be immunized. For example, the antigen can be conjugated to keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, e.g., maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, or $SOCl_2$.

[0188] Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

[0189] Monoclonal

[0190] Monoclonal antibodies may be made using the hybridoma method or may be made by recombinant DNA methods.

[0191] In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell.

[0192] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

[0193] Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, Calif. USA, and SP-2 and derivatives e.g., X63-Ag8-653 cells available from the American Type Culture Collection, Manassas, Va., USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies.

[0194] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA). The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis.

[0195] Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal e.g., by i.p. injection of the cells into mice.

[0196] The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (e.g., using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, or the like.

[0197] DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells.

[0198] In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries as a viable alternative to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

[0199] The DNA that encodes the antibody may be modified to produce chimeric or fusion antibody polypeptides, for example, by substituting human heavy chain and light chain constant domain (C_H and C_L) sequences for the homologous murine sequences or by fusing the immunoglobulin coding sequence with all or part of the coding sequence for a non-immunoglobulin polypeptide (heterologous polypeptide). The non-immunoglobulin polypeptide sequences can substitute for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

[0200] Human and Humanized Antibodies

[0201] The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')$_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[0202] Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies, wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

[0203] The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity and HAMA response (human anti-mouse antibody). According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody. Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies.

[0204] It is further important that antibodies be humanized with retention of high binding affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

[0205] As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge.

[0206] Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 [1990]) can be used to produce human antibodies and antibody fragments in vitro, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Several sources of V-gene segments can be used for phage display. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described.

[0207] Antibody Fragments

[0208] In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to antigen(s).

[0209] Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies. However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli,* thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form $F(ab')_2$ fragments. According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Fab and $F(ab')_2$ fragment with increased in vivo half-life comprising a salvage receptor binding epitope residues are known. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during in vivo use. sFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. The antibody fragment may also be a "linear antibody." Such linear antibody fragments may be monospecific or bispecific.

[0210] Bispecific Antibodies

[0211] Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193, as described herein. Other such antibodies may combine an epitope of a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 with a binding site for another protein. Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., $F(ab')_2$) bispecific antibodies.

[0212] Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities.

[0213] A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of the present invention can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (e.g. tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or more antigen binding sites. The preferred dimerization domain comprises (or consists of) an Fc region or a hinge region.

[0214] Epitope Mapping

[0215] Mapping of epitopes recognized by antibodies binding, preferably specifically, to a polypeptide selected from SEQ ID Nos: 1-56 and/or a peptide selected from SEQ ID Nos: 57-193 can be performed as described in detail in "Epitope Mapping Protocols (Methods in Molecular Biology) by Glenn E. Morris ISBN-089603-375-9 and in "Epitope Mapping: A Practical Approach" Practical Approach Series, 248 by Olwyn M. R. Westwood, Frank C. Hay. In a preferred embodiment, epitope scanning is used to identify epitopes recognized by antibodies specifically binding to a polypeptide selected from SEQ ID Nos: 1-56 and/or a peptide selected from SEQ ID Nos.: 57-193. Briefly, overlapping peptides encompassing the selected polypeptide sequence are synthesized on individual plastic pins. Recognition of these peptides by antibodies against the selected polypeptide is measured, preferably by ELISA.

[0216] Oligopeptides

[0217] Oligopeptides of the present invention are oligopeptides that bind, preferably specifically, to a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 as described herein. The oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. The oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 as described herein. The oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Pat. Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 81:3998-4002 (1984); Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 82:178-182 (1985); Geysen et al., in Synthetic Peptides as Antigens, 130-149 (1986); Geysen et al., J. Immunol. Meth., 102:259-274 (1987); Schoofs et al., J. Immunol., 140:611-616 (1988), Cwirla, S. E. et al. (1990) Proc. Natl. Acad. Sci. USA, 87:6378; Lowman, H. B. et al. (1991) Biochemistry, 30:10832; Clackson, T. et al. (1991) Nature, 352: 624; Marks, J. D. et al. (1991), J. Mol. Biol., 222:581; Kang, A. S. et al. (1991) Proc. Natl. Acad. Sci. USA, 88:8363, and Smith, G. P. (1991) Current Opin. Biotechnol., 2:668).

[0218] In this regard, bacteriophage (phage) display is one well known technique which allows one to screen large oligopeptide libraries to identify member(s) of those libraries which are capable of specifically binding to a polypeptide target. Phage display is a technique by which variant polypeptides are displayed as fusion proteins to the coat protein on the surface of bacteriophage particles. The utility of phage display lies in the fact that large libraries of selectively randomized protein variants (or randomly cloned cDNAs) can be rapidly and efficiently sorted for those sequences that bind to a target molecule with high affinity. Display of peptide or protein libraries on phage have been used for screening millions of polypeptides or oligopeptides for ones with specific binding properties (Smith, G. P. (1991) Current Opin. Biotechnol., 2:668). Sorting phage libraries of random mutants requires a strategy for constructing and propagating a large number of variants, a procedure for affinity purification using the target receptor, and a means of evaluating the results of binding enrichments. U.S. Pat. Nos. 5,223,409, 5,403,484, 5,571,689, and 5,663,143.

[0219] Organic Molecules that Bind a Polypeptide Selected from SEQ ID Nos: 1 to 56 and/or a Peptide Selected from SEQ ID Nos: 57-193.

[0220] Organic molecules of the invention are organic molecules other than oligopeptides or antibodies as defined herein that bind, preferably specifically, to a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 as described herein. The organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). The organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules that are capable of binding, preferably specifically, to a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). Organic molecules of the invention may be, for example, aldehydes, ketones, oximes, hydrazones, semicarbazones, carbazides, primary amines, secondary amines, tertiary amines, N-substituted hydrazines, hydrazides, alcohols, ethers, thiols, thioethers, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioketals, acetals, thioacetals, aryl halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, acid chlorides, or the like.

[0221] Kits

[0222] Kits are provided that are useful for various purposes, e.g., for the diagnosis of a bone and/or cartilage disorder or for purification or immunoprecipitation of a polypeptide selected SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 from cells, tissues and/or body fluids. For isolation and purification of such polypeptides, the kit can contain a specific binding agent (i.e. an antibody, oligopeptide, or organic molecule) coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of such polypeptide in vitro, e.g., in an ELISA or a Western blot. The kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising at least one antibody, oligopeptide or organic molecule of the invention. Additional containers may be included that contain, e.g., diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended in vitro or diagnostic use.

[0223] The present invention also provides ELISA kits for the detection of a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193. In addition, in some embodiments, the kits are customized for various applications. However, it is not intended that the kits of the present invention be limited to any particular format or design. In some embodiments, the kits of the present invention include, but are not limited to, materials for sample collection (e.g., spinal and/or venipuncture needles), tubes (e.g., sample collection tubes and reagent tubes), holders, trays, racks, dishes, plates (e.g., 96-well microtiter plates), instructions to the kit user, solutions or other chemical reagents, and samples to be used for standardization, and/or normalization, as well as positive and negative controls. In particularly preferred embodiments, reagents included in ELISA kits specifically intended for the detection of a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 include a control polypeptide or peptide selected from SEQ ID Nos: 1 to 193, antibody against said polypeptide or peptide, antibody against said polypeptide or peptide conjugated to an enzyme, 96-well microtiter plates precoated with said polypeptide or peptide, suitable capture antibody, 96-well microtiter plates precoated with a suitable capture antibody against said polypeptide or peptide, buffers (e.g., coating buffer, blocking buffer, and distilled water), enzyme reaction substrate and premixed enzyme substrate solutions.

[0224] The present invention also relates to a kit comprising an ordered array of antibodies that specifically bind to polypeptides of SEQ ID Nos: 1 to 56 and/or peptides of SEQ ID Nos: 57-193 for detecting the expression of a polypeptide selected from SEQ ID Nos: 1 to 56 and/or a peptide selected from SEQ ID Nos: 57-193 in a sample, comprising one or more antibodies associated with a solid support, wherein each antibody is specific for a polypeptide of SEQ ID Nos: 1 to 56 and/or a peptide of SEQ ID Nos: 57-193.

[0225] The phrase "ordered array" indicates that the probes are arranged in an identifiable or position-addressable pattern, e.g. such as the arrays disclosed in U.S. Pat. Nos. 6,156,501 and 6,077,673. The probes or antibodies are associated with the solid support in any effective way. For example, the probes can be bound to the solid support either by polymerizing the probes on the substrate or by attaching a probe to the substrate. Association can be covalent, noncovalent, electrostatic, hydrophobic, hydrophilic, adsorbed, absorbed, polar, etc.

[0226] Methods

[0227] Methods of Detecting Polypeptides

[0228] Polypeptides of SEQ ID Nos: 1 to 56 and/or peptides of SEQ ID Nos: 57-193 can be detected, visualized, determined, quantitated, etc. according to any effective method. Useful methods include, but are not limited to, immunoassays, radioimmunoassay (RIA), ELISA, immunofluorescence, flow cytometry, histology, electron microscopy, light microscopy, in situ assays, immunoprecipitation, Western blot and the like.

[0229] Immunoassays may be carried out in liquid or on a support. For instance, a sample (e.g. blood, urine, tissue, body fluids, etc.) can be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose or other solid support capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with detectably labeled antibody specifically recognizing a polypeptide of SEQ ID Nos: 1 to 56 and/or a peptide of SEQ ID Nos: 57-193. The solid phase support can then be washed with a buffer a second time to remove unbound antibody. The amount of bound label on the solid support may then be detected by conventional means.

[0230] Diagnosis of a Bone and/or Cartilage Disorder

[0231] Yet another embodiment of the present invention is directed to a method of diagnosing a bone and/or cartilage disorder, or a susceptibility to a bone and/or cartilage disorder, in a mammal, which is based on the altered expression of a polypeptide selected from SEQ ID Nos: 1 to 56, or a peptide selected from SEQ ID Nos: 57-193 derived therefrom, will provide a valuable clinical marker correlated with such a disorder.

[0232] Such methods comprise determining if a polypeptide selected from SEQ ID Nos: 1 to 56, or a peptide of SEQ ID Nos: 57-193 derived therefrom, is overexpressed or underexpressed in a test sample as compared to a normal sample. Polypeptides of SEQ ID Nos: 1 to 56 are selectively expressed in human bone and cartilage tissue, as shown in the examples of this application. Peptides of SEQ ID Nos: 57-193 are derived from polypeptides of SEQ ID Nos: 1 to 56. An increased or decreased presence of a polypeptide selected from SEQ ID Nos: 1 to 56, or a peptide selected from SEQ ID Nos: 57-193 derived therefrom, in a patient-derived sample is carried out using any standard methodology that measures levels (as compared to known normal controls) of a certain protein, e.g., by Western blot assays or a quantitative assay such as ELISA. For example, a standard competitive ELISA format using an antibody specific for a polypeptide selected from SEQ ID Nos: 1 to 56, or a peptide selected from SEQ ID Nos: 57-193, is used to quantify levels of the polypeptide. Alternatively, a sandwich ELISA using a first antibody as the capture antibody and a second antibody specific for a polypeptide or peptide selected from SEQ ID Nos: 1 to 193 as a detection antibody is used.

[0233] In one embodiment, the method comprises (a) obtaining a test sample from a patient suspected of having a bone and/or cartilage disorder (b) detecting an expression level of a polypeptide selected from the group consisting of SEQ ID NOs 19 (EPYC), 27 (LOC284998), 38 (NID2), 39 (NLRP5), 41 (OGN) and 55 (LOC339316), by assaying for a polypeptide selected from the group consisting of SEQ ID NOs: 19, 27, 38, 39, 41 and 55; and (c) comparing said level to that of a healthy control, whereby an alteration in the expression level of a polypeptide selected from the group consisting of SEQ ID NOs: 19, 27, 38, 39, 41 and 55 relative to the level of expression of a polypeptide selected from the group consisting of SEQ ID NOs: 19, 27, 38, 39, 41 and 55 in the control, indicates a positive result for a bone and/or a cartilage disorder.

[0234] In another embodiment, the method comprises (a) obtaining a test sample from a patient suspected of having a bone and/or cartilage disorder (b) detecting an expression level of a peptide selected from the group consisting of SEQ ID NOs: 88, 89, 130, 131, 132, 133, 127, 107 and 108, by assaying for said peptide; and (c) comparing said level to that of a healthy control, whereby an alteration in the expression level of a peptide selected from the group consisting of SEQ ID NOs: 88, 89, 130, 131, 132, 133, 127, 107 and 108 relative to the level of expression of the same peptide in the control, indicates a positive result for a bone and/or cartilage disorder.

[0235] For diagnostic purposes, the specific binding agents (i.e. antibodies, oligopeptides or small organic molecules) of the present invention may be detectably labeled, attached to a solid support, or the like. The nature of the solid surface may vary depending on the assay format. For assays carried out in microtiter wells, the solid surface is the wall of the well or cup. For assays using beads, the solid surface is the surface of the bead. Examples of useful solid supports include nitrocellulose (e.g. in membrane or microtiter well form), polyvinyl chloride (e.g. in sheets or microtiter wells), polystyrene latex (e.g. in beads or microtiter plates), polyvinylidine fluoride, diazotized paper, nylon membranes, activated beads and Protein A beads. The solid support containing the specific binding agent is typically washed after contacting it with the test sample, and prior to detection of bound complexes. Incubation of the specific binding agent with the test sample is followed by detection of complexes by a detectable label. For example, the label is enzymatic, fluorescent, chemiluminescent, radioactive or a dye. Assays which amplify the signals from the complex are also known in the art, e.g. assays which utilize biotin and avidin.

[0236] In preferred embodiments of the present invention, ELISA methods for quantitation of a polypeptide selected from SEQ ID Nos: 1 to 56 or a peptide selected from SEQ ID Nos: 57-193 (the antigen) in a test sample are provided. In some of these methods, the antigen is first immobilized on a solid support (e.g. in a microtiter plate well). Detection and quantitation of the immobilized antigen is accomplished by use of an antibody-enzyme conjugate capable of binding to the immombilized antigen and producing a quantifiable signal. In some embodiments, the amount of antigen present is directly proportional to the amount of enzyme reaction product produced after the addition of an appropriate enzyme substrate.

[0237] The end product of an ELISA is a signal typically observed as the development of color or fluorescence. Typically, this signal is read (i.e., quantitated) using a suitable spectrocolorimeter (i.e. a spectrophotometer) or spectrofluorometer. The amount of color or fluorescence is directly proportional to the amount of immobilized antigen. In some embodiments of the present invention, the amount of antigen in a sample (e.g. the amount of a polypeptide or peptide selected from SEQ ID Nos: 1 to 193 in a synovial fluid or blood sample) is quantitated by comparing results obtained for the sample with a series of control wells containing known concentrations of the antigen (i.e. a standard concentration curve). A negative control is also included in the assay system.

[0238] The present invention provides various ELISA protocols for the detection and/or quantitation of a polypeptide or peptide selected from SEQ ID Nos: 1 to 193 in a sample. In one embodiment, the present invention provides a "direct ELISA" for the detection of a polypeptide or peptide selected from SEQ ID Nos: 1 to 193 in a sample. In some embodiments, the antigen of interest in a sample (i.e. a polypeptide or peptide selected from SEQ ID Nos: 1 to 193) is bound (along with unrelated antigens) to the solid support. The immobilized antigen is then directly detected by an antigen-specific enzyme-conjugated antibody. Addition of an appropriate detection substrate results in color development or fluorescence that is proportional to the amount of antigen present in the well.

[0239] In another embodiment, the present invention provides an indirect ELISA for the detection of antigen in a sample. In this embodiment, antigen of interest in a sample is immobilized (along with unrelated antigens) to a solid support as in the direct ELISA but is detected indirectly by first adding an antigen-specific antibody, then followed by the addition of a detection antibody specific for the antibody that specifically binds the antigen, also known as "species-specific" antibodies (e.g. a goat anti-rabbit antibody).

[0240] In some embodiments, the concentration of sample added to each well is titrated so as to produce an antigen concentration curve. In other embodiments, the concentration of conjugated antibody is titrated. Indeed, such titrations are typically performed during the initial development of ELISA systems.

[0241] In another embodiment, the present invention provides "sandwich ELISA" methods, in which the antigen in a sample is immobilized on the solid support by a "capture antibody" that has been previously bound to the solid support. In general, the sandwich ELISA method is more sensitive than other configurations, and is capable of detecting 0.1-1.0 ng/ml protein antigen. As indicated above, the sandwich ELISA method involves pre-binding the "capture antibody" which recognizes the antigen of interest (i.e., a polypeptide or peptide selected from SEQ ID Nos: 1 to 193) to the solid support (e.g., wells of the microtiter plate). In some embodiments, a biotinylated capture antibody is used in conjunction with avidin-coated wells. Test samples and controls are then added to the wells containing the capture antibody. If antigen is present in the samples and/or controls, it is bound by the capture antibody.

[0242] In some embodiments, after a washing step, detection of antigen that has been immobilized by the capture antibody is detected directly (i.e., a direct sandwich ELISA). In other embodiments detection of antigen that has been immobilized by the capture antibody is detected indirectly (i.e., an indirect sandwich ELISA). In the direct sandwich ELISA, the captured antigen is detected using an antigen-specific enzyme-conjugated antibody. In the indirect sandwich ELISA, the captured antigen is detected by using an antibody directed against the antigen, which is then detected by another enzyme-conjugated antibody which binds the antigen-specific antibody, thus forming an antibody-antigen-antibody-antibody complex. In both the direct and indirect sandwich ELISAs, addition of a suitable detection substrate results in color development or fluorescence that is proportional to the amount of antigen that is present in the well.

[0243] It is not intended that the present invention be limited to the direct ELISA and sandwich ELISA protocols particularly described herein, as the art knows well numerous alternative ELISA protocols that also find use in the present invention (See, e.g., Crowther, "Enzyme-Linked Immunosorbent Assay (ELISA)," in *Molecular Biomethods Handbook,* Rapley et al. [eds.], pp. 595-617, Humana Press, Inc., Totowa, N.J. [1998]; and Ausubel et al. (eds.), *Current Protocols in Molecular Biology,* Ch. 11, John Wiley & Sons, Inc., New York [1994]). Thus, any suitable ELISA method including, but not limited to, competitive ELISAs also find use with the present invention. Similarly, it is not intended that detection methods be limited to ELISA methods, and the art knows well numerous alternative detection methods that also find use in the present invention including, but not limited to, immunofluorescence, flow cytometry, histology, electron microscopy, light microscopy, in situ assays, immunoprecipitation and Western blot.

[0244] All of the references discussed herein are incorporated by reference in their entirety.

[0245] The following Examples are meant to be illustrative of the invention and are not intended to limit the scope of the invention as set out is the appended claims.

EXAMPLE 1

Identification of Polypeptides Set Forth as SEQ ID Nos: 1 to 56 as Selectively Expressed in Bone and/or Cartilage Tissue

[0246] Procedures for the mining of databases containing information about gene expression in human tissues were developed. Genes selectively expressed in cartilage or bone tissue were identified by analyzing transcriptomes. The sources of the transcriptomes were public databases, in particular the UniGene and GEO databases.

[0247] The first three tasks were: (1) updating transcriptomes of human tissues for use in the MPW Analyzer, a bioinformatics mining tool that uses gene symbols to connect entries in databases (genes, transcripts, proteins and peptides) with gene transcripts (2) importing animal genomics resources into the data warehouse and (3) assessing the suitability of the transcriptomes for identification of tissue-specific proteins. Transcriptomes of tissues represented in databases were deemed to be of sufficient quality for analysis of tissue-selective expression of genes if enzymes and protein iso forms are well represented in twenty metabolic domains (e.g. amino acid metabolism; aromatic compound metabolism; one-carbon metabolism; carbhohydrate metabolism; coenzymes and vitamins; electron transport; enzyme metabolism; exogenous compounds; lipid metabolism; membrane transport; nucleic acid metabolism; oxygen metabolism; phosphorus metabolism; protein metabolism; purine metabolism; pyrimidine metabolism; signal transduction; and sulfur metabolism).

[0248] Transcriptomes of human tissues of sufficient quality for a systematic investigation of tissue-selective transcription were identified. That is, transcript levels could be assigned a number for selective expression in one tissue relative to forty-one other tissues, while correcting for false positives in the tissue samples. This number, the RD value, is RD=(1-(TPMb/TPMa)), wherein TPM is the number of transcripts per million transcripts. In this formula, TPMa is the TPM for the gene of interest in the tissue having the highest expression level (here bone or cartilage tissue), and TPMb is the TPM for the same gene in the tissue with the next highest expression level for that gene. Thus, RD provides a measure of the selectivity of expression of the gene of interest in cartilage or bone tissue. RD has a value between 0 and 1, with 1 being the highest possible RD value (corresponding to the highest selectivity of expression). Preferred polypeptides for use in the methods of the present invention are polypeptides encoded by genes with RD values$\geqq$0.8.

[0249] Over one hundred mammalian genes in the first instance were found to be expressed with high selectivity in cartilage, bone or the vasiculature, or combinations thereof. Of these, half are human genes. From these some human proteins were selected with priority. Criteria such as tissue-specificity of expression, occurrence of a gene product in body fluids, occurrence of veterinary homologues, low number of interactions with extracellular matrix (ECM) proteins, and undesired structural properties of the proteins were used in the selection procedure. Of these selected proteins, some represent hypothetical proteins ("unknowns"), some are highly selective for bone, some for cartilage and only a few for the vasculature. Of the selected proteins, only a few are expressed intracellularly; the remainder are secreted and are minor components of the ECM. Most selected proteins have congeners in veterinary animals. The amino acid sequences of the selected protein are set forth as SEQ ID Nos: 1 to 56 SEQ ID Nos: 1 to 56 include a set of proteins (CHAD, OMD, OGN, ASPN, CALU and RCN3) that is presumably co-regulated via TGF-β and Runx2. These proteins may be assayed for singly or in combinations, for example by antibodies against peptide(s) derived from one of the members.

[0250] The RD values for polypeptides of SEQ ID Nos: 1 to 56 are provided in Table 1. Body fluid peptides derived from polypeptides of SEQ ID NOs: 1 to 56 are also listed in Table 1.

TABLE 1

POLYPEPTIDE	SEQ ID #	RD VALUE (RANGE)	BODY FLUID PEPTIDES
AGC1	1	0.9-1.0	SEQ ID Nos: 57-59
ASPN	2	0.8-0.9	
BCHE	3	0.8-0.9	SEQ ID Nos: 159-160
BGN	5	0.6-0.7	SEQ ID Nos: 184-191
BMX	6	0.9-1.0	
C10orf49	7	0.9-1.0	
CALU	8	0.7-0.8	
CHAD	10	0.8-0.9	
CHI3L1	11	0.7-0.8	SEQ ID Nos: 161-168
CILP	12	0.8-0.9	SEQ ID Nos: 60-72
CILP2	13	0.8-0.9	SEQ ID Nos: 73-87
CLEC3A	14	0.6-0.7	
COLEC12	15	0.7-0.8	SEQ ID Nos: 90-99
CRTAC1	16	0.8-0.9	
CYTL1	17	0.9-1.0	
EPYC	19	0.8-0.9	
ETNK1	20	0.8-0.9	
FLRT2	21	0.7-0.8	SEQ ID Nos: 100-106
FLRT3	22	0.7-0.8	SEQ ID Nos: 107-108
HAPLN1	23	0.7-0.8	
IGFL3	24	0.6-0.7	
KIAA0999	25	0.6-0.7	
LOC283951	26	0.6-0.7	SEQ ID NO: 127
LOC284998	27	0.9-1.0	
LOC339316	55	0.7-0.8	
LOC646627	28	0.8-0.9	
LOXL4	30	0.6-0.7	
LTBP1	31	0.7-0.8	SEQ ID NOs: 109-114
MATN1	32	0.9-1.0	
MATN3	33	0.7-0.8	
MEPE	34	0.8-0.9	SEQ ID NO: 134
MXRA5	36	0.5-0.6	SEQ ID NOs: 169-180
MXRA8	37	0.7-0.8	SEQ ID NOs: 135-154
NID2	38	0.8-0.9	SEQ ID NO: 88
NLRP5	39	0.9-1.0	
NPNT	40	0.7-0.8	SEQ ID NOs: 115-126
OGN	41	0.9-1.0	SEQ ID NOs: 130-133
OMD	42	0.6-0.7	SEQ ID NOs: 192-193
OSMR	43	0.6-0.7	
OSTN	44	>0.8	SEQ ID NOs: 128-129
POSTN	45	0.7-0.8	
PRG4	46	0.8-0.9	SEQ ID NOs: 181-183
PTN	47	0.8-0.9	
RCN3	48	0.7-0.8	SEQ ID NO: 89
SEMA6D	49	0.6-0.7	
SERPINE2	50	0.7-0.8	SEQ ID NO: 155
SLC28A3	51	0.7-0.8	
TBCA	53	0.6-0.7	SEQ ID NOs: 156-158
TWIST2	54	0.5-0.6	
LRC15	56	0.9-1.0	

EXAMPLE 2

Testing for Altered Expression of a Polypeptide Selected From SEQ ID NOs: 1 to 56 or a Peptide Selected From SEQ ID NOs: 57 to 193 in a Bone and/or Cartilage Disease

[0251] Antibodies may be utilized in accordance with the present invention to detect altered expression of a polypeptide of SEQ ID NOs: 1 to 56 and/or a peptide of SEQ ID NOs: 57-193 in a bone and/or cartilage disorder. According to this procedure, an appropriate sample from a patient having a bone and/or cartilage disorder and a sample from a healthy age- and gender-matched control are collected. The samples are then added to an ELISA, as described above, containing antibodies which specifically bind one or more polypeptides and/or peptides of SEQ ID NOs: 1 to 193. The amount of binding is then quantified and compared.

[0252] It is to be understood that other techniques known in the art for measuring the expression level of proteins, including but not limited to, protein array, mass spectroscopy, gel electrophoresis and microarray immunoassay, may also be used to determine altered expression of a polypeptide or peptide selected from the group consisting of SEQ ID NOs: 1 to 193.

EXAMPLE 3

Correlation of Marker Concentration with Clinical Status of Patients Suffering from a Bone or Cartilage Disorder

[0253] In order to examine whether each of the polypeptides of SEQ ID NOs: 1-56 (i.e., the "targets") is a suitable biomarker of a bone or cartilage disorder, the concentration of each target was correlated with clinical status of patients suffering from a bone (e.g. osteoporosis) or cartilage (e.g. rheumatoid arthritis) disorder. To this end, the concentration of each target under investigation was aligned with clinical data or scores defined by the doctors treating those patients or other established biomarkers. For example, the "Larson Score" is a radiological defined value estimating the extent of cartilage degradation caused by arthritis. The proof of clinical concept for a given target in this case is the correlation with the Larson Score, i.e., that elevated or lowered levels of the target predict cartilage degradation.

[0254] The research consisted of (1) amino acid/epitope analysis of the targets for defining immunogens to be used to generate antibodies (2) immunizations with the synthetic peptides defined by epitope anaylsis in order to generate antibodies and characterization of the obtained antisera and (3) clinical evaluation of the targets in which suitable immunological screening assays using the generated antisera were developed and well defined clinical serum samples from osteoporotic or arthritic patients were tested using the assays. Each polypeptide or peptide of SEQ ID NOs: 1-56 was investigated.

[0255] Epitopes were determined by calculation with ProtScale (www.expasy.org/tools/protscale.html) according to the algorithm of Fraga S., "Theoretical prediction of protein antigenic determinants from amino acid sequences," Can. J. Chem., 60:2606-2610 (1982). The peptide fragments were chosen from those regions of the amino acid sequence of the respective targets, in which a maximum of the epitope recognition factors, accessibility and polarity (corresponding to the results of the ProtScale program) was obtained, since these epitopes proved to be particularly immunogenic and readily accessible for antibodies. The data for the targets: (1) epiphycan (EPYC) (SEQ ID NO: 19) (2) Asporin (ASPN) (SEQ ID NO: 2) (3) LOC 646627 (SEQ ID NO: 28) (4) LOXL3 (SEQ ID NO: 29) (5) TWIST2 (SEQ ID NO: 54) (6) CRTAC1 (SEQ ID NO: 16) and (7) CHAD (SEQ ID NO: 10) are presented below. Recognition factor, accessibility and polarity profiles for each of the aforementioned polypeptides are illustrated in FIGS. **1-7**.

[0256] Based on the epitope analysis, sequences (epitopes) corresponding to peak maxima of recognition factors, accessibility and polarity were chosen as immunogens for generating anbodies. 2-3 peptide/epitopes were chosen for each of SEQ ID NOs: 1 to 56. Selected epitopes for targets are presented at Table 1:

TABLE 1

	Epitope 1	Epitope 2	Epitope 3
EPYC	RLIDGSSPQEPEFTGVLGPH (SEQ ID NO: 194) (residues 91-110 of SEQ ID NO: 19)	INKNDFASLSDLKRI (SEQ ID NO: 195) (residues 158-172 of SEQ ID NO: 19)	FIDISNNRLGRKGIKQEA (SEQ ID NO: 196) (residues 215-232 of SEQ ID NO: 19)
ASPN	ENKVKKIQKDT (SEQ ID NO: 197) (residues 180-190 of SEQ ID NO: 2)	LKKIPSGLPE (SEQ ID NO: 198) (residues 301-310 of SEQ ID NO: 2)	KKSLYSAISLF (SEQ ID NO: 199) (residues 340-350 of SEQ ID NO: 2)
LOC646627	ISSSASSSLET (SEQ ID NO: 200) (residues 49-59 of SEQ ID NO: 28)	NDIESKSLVL (SEQ ID NO: 201) (residues 158-167 of SEQ ID NO: 28)	
LOXL3	PVYAASSGQKKQQQSK (SEQ ID NO: 202) (residues 285-300 of SEQ ID NO: 29)	AAEENCLASSARSANW (SEQ ID NO: 203) (residues 555-570 of SEQ ID NO: 29)	ILTPNGTKVAEGHKA (SEQ ID NO: 204) (residues 621-635 of SEQ ID NO: 29
TWIST2	ELERQPKRFGRKRRY SKKSSEDGSPTPGKR (SEQ ID NO: 205) (residues 21-50 of SEQ ID NO: 54)	KIIPTLPSDKLSKIQTLKLA (SEQ ID NO: 206) (residues 91-110 of SEQ ID NO: 54)	
CRTAC1	TGGRGVSVGPILSSSASDIF (SEQ ID NO: 207) (residues 238-257 of SEQ ID NO: 16)	VNTYGSYRCRTNKKCSRGYE (SEQ ID NO: 208) (residues 578-597 of SEQ ID NO: 16)	AQKRLVNIAVDERSSPYYAL (SEQ ID NO: 209) (residues 88-107 of SEQ ID NO: 16)
CHAD	DRNQLSSYPSAALSKLRVVE (SEQ ID NO: 210) (residues 203-222 of SEQ ID NO: 10)	FRSCKFPTKRSKKAGRH (SEQ ID NO: 211) (residues 343-359 of SEQ ID NO: 10)	

[0257] The selected peptides were chemically synthesized, conjugated to a suitable carrier protein (KLH, e.g.) and injected into 2 rabbits. For the first immunization, each rabbit received 0.5 mg of the corresponding antigen, mixed with Freund's Adjuvant (EUROGENTEC) and BCG (Baccillus Calmette-Guerin) and 0.25 mg of the immunogens to further increase the immune response. The immunization/bleeding pattern are presented in Table 2.

TABLE 2

Scheduled Immunizations		Scheduled Bleeds	
First immunization	Day 0	Preimmune Bleed	Day 0
Boost No. 1	Day 7	Medium Bleed	Day 21
Boost No. 2	Day 10		
Boost No. 3	Day 18		

[0258] No terminal bleeding was performed enabling additional boosts and bleeds depending on antibody yields and affinity. Titertests of the antiesera to determine the immune-response were set up as follows: 0.25 µg/ml of the different epitopes were coated on a microtiter plate. The plate was blocked to avoid nonspecific binding. Then the crude serum was diluted with phosphate buffer and 200 µl were incubated on the peptide plate. After the incubation for 3 hours at room temperature the plate was washed and incubated with 200 µl goat anti rabbit-HRP to detect the amount of antibody coated to the peptide of the plate. After this incubation, the plate was washed again and 200 µl TMB was incubated for 20 min. The reaction was stopped with acid and the signal was measured with a reader at 450 nm. Immune response to the target eptiopes was quantified by comparing the signal intensity of the test bleeds at various concentrations with the signal of serum from the same rabbit prior to immunization. Specificity was checked by testing background reaction of the antisera against plates without the epitope under investigation. Table 3 shows the relative signal at an antiserum dilution of 1:5000 of the test bleeds for all epitopes selected:

TABLE 3

	Rel Titer per Epitope		
Protein	Epitope 1	Epitope 2	Epitope 3
ASPN	1.62	x	1.80
EPYC	2.12	10.70	x
LOC646627	1.15	1.09	x
LOXL3	10.61	x	3.25
CHAD	7.50	3.93	x
CRTAC1	5.74	x	11.99
TWIST2	15.96	20.08	x

[0259] Non responding epitopes are marked "X." All responding antisera were selected for generation of antibody production intended to be used in setting up the screening assays. Antibody preparations from the crude antisera were obtained by affinity purification over standard protein G columns (Protein G-sepharose, 5 ml, GE-Healthcare) using an Akta-Explorer FPLC chromatography system and an internally evaluated standard protocol. The obtained antibody preparations were then used for setting the screening assays for clinical proof of concept.

[0260] Clinical evaluation of targets consisted of : (1) setting up a competitive screening assay (2) optimizing the assay sensitivity (3) testing sample pools from individuals with and without a bone/cartilage disease and (4) data analysis and establishing proof of clinical concept by data correlation to the clinical status of the patients and bone/cartilage serum markers.

[0261] A competitive assay with the antibody preparations was set up according to the following protocol: The peptide fragments corresponding to the selected epitopes were coated to microtiter plates and blocked to avoid nonspecific binding. Antibody and peptide concentrations were minimized to obtain maximum sensitivity of the assays. The test procedure was as follows: 200 μl of diluted antibody were incubated together with 50 μl of samples overnight. Plates were washed and incubated with 200 μl goat anti rabbit-HRP antibody to detect the amount of antibody on the peptide plate. After the incubation the plate was washed again and incubated with TMB for 20 minutes. The reaction was stopped with diluted sulfuric acid and the signal was measured at 450 nm/630nm with a plate reader.

[0262] Pools of samples from patients with osteoporosis and rheumatoid arthritis with a high degree bone (defined by high bone serum markers) or cartilage (defined by the Larson Score, a radiological measure for bone destruction in e.g. rheumatoid joints) degradation were tested. The usage of pool samples rather than of individual samples guarantees data consistency over the whole of the study due to the larger volume available.

[0263] Markers for bone and cartilage disease included (1) OPG (osteoprotegerin) and sRANKL (soluble RANK Ligand), markers for osteoclast (bone resorbing cells) regulation (2) DKK-1 (Dickkopf-1) and SOST (Sclerostin), markers for osteoblast (bone forming cells) regulation and (3) SPARC (secreted protein acidic and rich in cysteine), a glycoprotein associated with development, remodeling and tissue repair. The role of these markers in bone and cartilage disease is well documented by a vast number of publications. A correlation of a target to any of these markers, or a correlation to the Larson Score (only for Rheumatoid arthritis) is considered proof for the role of the target in the investigated disease.

[0264] The results of the screening tests are summarized in Table 4

TABLE 4

		Correlation Coefficient					
Target	Disease	Larson Score	OPG	DKK-1	sRANKL	SCST	SPARC
EPYC	Osteoporosis		0.536	0.278	<0.01	<0.01	n/a
	Rheumatoid Arthritis	0.615	0.760	<0.01	0.341	<0.01	0.148
ASPN	Osteoporosis		<0.01	0.526	0.838	0.306	n/a
	Rheumatoid Arthritis	0.726	<0.01	0.294	0.091	0.165	0.940
LOC646627	Osteoporosis		<0.01	<0.01	0.679	<0.01	n/a
	Rheumatoid Arthritis	0.783	0.835	<0.01	0.348	<0.01	<0.01
LOXL3	Osteoporosis		0.949	0.216	<0.01	<0.01	n/a
	Rheumatoid Arthritis	0.865	0.824	<0.01	0.327	<0.01	<0.01
CHAD	Osteoporosis		n/a	0.213	0.043	n/a	n/a
	Rheumatoid Arthritis	0.100	0.26	<0.01	0.706	n/a	n/a
CRTAC1	Osteoporosis		n/a	<0.01	0.222	n/a	n/a
	Rheumatoid Arthritis	0.627	0.438	0.403	0.039	n/a	n/a
TWIST2	Osteoporosis		n/a	0.108	0.286	n/a	n/a
	Rheumatoid Arthritis	0.319	<0.01	<0.01	n/a	n/a	n/a

[0265] Conclusions with respect to osteoporosis: Epiphycan concentrations showed a moderate (0.536) correlation with OPG. Asporin correlated well with DKK-1 and especially with sRANKL. LOC646627 correlated well with sRANKL. LOXL3 showed the best correlation of all parameters (0.949) to OPG. Based on this data the following targets should be useful markers for osteoporosis: Epiphycan, Asporin, LOC 646627 and LOXL3.

[0266] Preferably, a marker is used which shows a correlation coefficient of about 0.5 or higher, more preferably about 0.7 or higher, and most preferably about 0.8 or higher in at least one of the tests as described above.

[0267] Conclusions with respect to Rheumatoid Arthritis: Except Chondroadherin, all tested target markers showed a good, albeit broadly ranged (0.319-0.865) correlation to the Larson Score. Interestingly, CHAD did correlate well with sRANKL, which is a very good indicator for disease progression. There was also a surprisingly strong correlation of LOXL3, Epiphycan and LOC646627 with OPG further supporting the concept that these molecules are valuable markers for rheumatoid arthritis. Based on this data, all seven targets are suitable markers for rheumatoid arthritis.

[0268] This study is first to demonstrate the generation of antibodies suitable for detecting the markers, the first to demonstrate that the markers circulate in human plasma/serum in detectable amounts and the first to demonstrate that these markers provide useful clinical information about disease status in these patient groups.

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                                 SEQUENCE LISTING


<160> NUMBER OF SEQ ID NOS: 211

<210> SEQ ID NO 1
<211> LENGTH: 2416
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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1               5                   10                  15

Ala Val Thr Val Glu Thr Ser Asp His Asp Asn Ser Leu Ser Val Ser
            20                  25                  30

Ile Pro Gln Pro Ser Pro Leu Arg Val Leu Leu Gly Thr Ser Leu Thr
        35                  40                  45

Ile Pro Cys Tyr Phe Ile Asp Pro Met His Pro Val Thr Thr Ala Pro
    50                  55                  60

Ser Thr Ala Pro Leu Ala Pro Arg Ile Lys Trp Ser Arg Val Ser Lys
65                  70                  75                  80

Glu Lys Glu Val Val Leu Leu Val Ala Thr Glu Gly Arg Val Arg Val
                85                  90                  95

Asn Ser Ala Tyr Gln Asp Lys Val Ser Leu Pro Asn Tyr Pro Ala Ile
            100                 105                 110

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

Gly Val Tyr Arg Cys Glu Val Met His Gly Ile Glu Asp Ser Glu Ala
    130                 135                 140

Thr Leu Glu Val Val Val Lys Gly Ile Val Phe His Tyr Arg Ala Ile
145                 150                 155                 160

Ser Thr Arg Tyr Thr Leu Asp Phe Asp Arg Ala Gln Arg Ala Cys Leu
                165                 170                 175

Gln Asn Ser Ala Ile Ile Ala Thr Pro Glu Gln Leu Gln Ala Ala Tyr
            180                 185                 190

Glu Asp Gly Phe His Gln Cys Asp Ala Gly Trp Leu Ala Asp Gln Thr
        195                 200                 205

Val Arg Tyr Pro Ile His Thr Pro Arg Glu Gly Cys Tyr Gly Asp Lys
    210                 215                 220

Asp Glu Phe Pro Gly Val Arg Thr Tyr Gly Ile Arg Asp Thr Asn Glu
225                 230                 235                 240

Thr Tyr Asp Val Tyr Cys Phe Ala Glu Glu Met Glu Gly Glu Val Phe
                245                 250                 255

Tyr Ala Thr Ser Pro Glu Lys Phe Thr Phe Gln Glu Ala Ala Asn Glu
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            260                 265                 270

Cys Arg Arg Leu Gly Ala Arg Leu Ala Thr Thr Gly Gln Leu Tyr Leu
        275                 280                 285

Ala Trp Gln Ala Gly Met Asp Met Cys Ser Ala Gly Trp Leu Ala Asp
    290                 295                 300

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

Asn Leu Leu Gly Val Arg Thr Val Tyr Val His Ala Asn Gln Thr Gly
                325                 330                 335

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

Asp Phe Val Asp Ile Pro Glu Asn Phe Phe Gly Val Gly Gly Glu Glu
        355                 360                 365

Asp Ile Thr Val Gln Thr Val Thr Trp Pro Asp Met Glu Leu Pro Leu
    370                 375                 380

Pro Arg Asn Ile Thr Glu Gly Glu Ala Arg Gly Ser Val Ile Leu Thr
385                 390                 395                 400

Val Lys Pro Ile Phe Glu Val Ser Pro Ser Pro Leu Glu Pro Glu Glu
                405                 410                 415

Pro Phe Thr Phe Ala Pro Glu Ile Gly Ala Thr Ala Phe Ala Glu Val
            420                 425                 430

Glu Asn Glu Thr Gly Glu Ala Thr Arg Pro Trp Gly Phe Pro Thr Pro
        435                 440                 445

Gly Leu Gly Pro Ala Thr Ala Phe Thr Ser Glu Asp Leu Val Val Gln
    450                 455                 460

Val Thr Ala Val Pro Gly Gln Pro His Leu Pro Gly Gly Val Val Phe
465                 470                 475                 480

His Tyr Arg Pro Gly Pro Thr Arg Tyr Ser Leu Thr Phe Glu Glu Ala
                485                 490                 495

Gln Gln Ala Cys Leu Arg Thr Gly Ala Val Ile Ala Ser Pro Glu Gln
            500                 505                 510

Leu Gln Ala Ala Tyr Glu Ala Gly Tyr Glu Gln Cys Asp Ala Gly Trp
        515                 520                 525

Leu Arg Asp Gln Thr Val Arg Tyr Pro Ile Val Ser Pro Arg Thr Pro
    530                 535                 540

Cys Val Gly Asp Lys Asp Ser Ser Pro Gly Val Arg Thr Tyr Gly Val
545                 550                 555                 560

Arg Pro Ser Thr Glu Thr Tyr Asp Val Tyr Cys Phe Val Asp Arg Leu
                565                 570                 575

Glu Gly Glu Val Phe Phe Ala Thr Arg Leu Glu Gln Phe Thr Phe Gln
            580                 585                 590

Glu Ala Leu Glu Phe Cys Glu Ser His Asn Ala Thr Leu Ala Thr Thr
        595                 600                 605

Gly Gln Leu Tyr Ala Ala Trp Ser Arg Gly Leu Asp Lys Cys Tyr Ala
    610                 615                 620

Gly Trp Leu Ala Asp Gly Ser Leu Arg Tyr Pro Ile Val Thr Pro Arg
625                 630                 635                 640

Pro Ala Cys Gly Gly Asp Lys Pro Gly Val Arg Thr Val Tyr Leu Tyr
                645                 650                 655

Pro Asn Gln Thr Gly Leu Pro Asp Pro Leu Ser Arg His His Ala Phe
            660                 665                 670
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Cys Phe Arg Gly Ile Ser Ala Val Pro Ser Pro Gly Glu Glu Glu Gly
        675                 680                 685

Gly Thr Pro Thr Ser Pro Ser Gly Val Glu Glu Trp Ile Val Thr Gln
    690                 695                 700

Val Val Pro Gly Val Ala Ala Val Pro Val Glu Glu Glu Thr Thr Ala
705                 710                 715                 720

Val Pro Ser Gly Glu Thr Thr Ala Ile Leu Glu Phe Thr Thr Glu Pro
                725                 730                 735

Glu Asn Gln Thr Glu Trp Glu Pro Ala Tyr Thr Pro Val Gly Thr Ser
            740                 745                 750

Pro Leu Pro Gly Ile Leu Pro Thr Trp Pro Pro Thr Gly Ala Ala Thr
        755                 760                 765

Glu Glu Ser Thr Glu Gly Pro Ser Ala Thr Glu Val Pro Ser Ala Ser
    770                 775                 780

Glu Glu Pro Ser Pro Ser Glu Val Pro Phe Pro Ser Glu Glu Pro Ser
785                 790                 795                 800

Pro Ser Glu Glu Pro Phe Pro Ser Val Arg Pro Phe Pro Ser Val Glu
                805                 810                 815

Leu Phe Pro Ser Glu Glu Pro Phe Pro Ser Lys Glu Pro Ser Pro Ser
            820                 825                 830

Glu Glu Pro Ser Ala Ser Glu Glu Pro Tyr Thr Pro Ser Pro Pro Val
        835                 840                 845

Pro Ser Trp Thr Glu Leu Pro Ser Ser Gly Glu Glu Ser Gly Ala Pro
    850                 855                 860

Asp Val Ser Gly Asp Phe Thr Gly Ser Gly Asp Val Ser Gly His Leu
865                 870                 875                 880

Asp Phe Ser Gly Gln Leu Ser Gly Asp Arg Ala Ser Gly Leu Pro Ser
                885                 890                 895

Gly Asp Leu Asp Ser Ser Gly Leu Thr Ser Thr Val Gly Ser Gly Leu
            900                 905                 910

Pro Val Glu Ser Gly Leu Pro Ser Gly Asp Glu Glu Arg Ile Glu Trp
        915                 920                 925

Pro Ser Thr Pro Thr Val Gly Glu Leu Pro Ser Gly Ala Glu Ile Leu
    930                 935                 940

Glu Gly Ser Ala Ser Gly Val Gly Asp Leu Ser Gly Leu Pro Ser Gly
945                 950                 955                 960

Glu Val Leu Glu Thr Ser Ala Ser Gly Val Gly Asp Leu Ser Gly Leu
                965                 970                 975

Pro Ser Gly Glu Val Leu Glu Thr Thr Ala Pro Gly Val Glu Asp Ile
            980                 985                 990

Ser Gly Leu Pro Ser Gly Glu Val  Leu Glu Thr Thr Ala  Pro Gly Val
        995                 1000                 1005

Glu Asp  Ile Ser Gly Leu Pro  Ser Gly Glu Val Leu  Glu Thr Thr
    1010                 1015                 1020

Ala Pro  Gly Val Glu Asp Ile  Ser Gly Leu Pro Ser  Gly Glu Val
    1025                 1030                 1035

Leu Glu  Thr Thr Ala Pro Gly  Val Glu Asp Ile Ser  Gly Leu Pro
    1040                 1045                 1050

Ser Gly  Glu Val Leu Glu Thr  Thr Ala Pro Gly Val  Glu Asp Ile
    1055                 1060                 1065
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Ser Gly  Leu Pro Ser Gly Glu  Val Leu Glu Thr Thr  Ala Pro Gly
    1070                 1075                 1080

Val Glu  Asp Ile Ser Gly Leu  Pro Ser Gly Glu Val  Leu Glu Thr
    1085                 1090                 1095

Ala Ala  Pro Gly Val Glu Asp  Ile Ser Gly Leu Pro  Ser Gly Glu
    1100                 1105                 1110

Val Leu  Glu Thr Ala Ala Pro  Gly Val Glu Asp Ile  Ser Gly Leu
    1115                 1120                 1125

Pro Ser  Gly Glu Val Leu Glu  Thr Ala Ala Pro Gly  Val Glu Asp
    1130                 1135                 1140

Ile Ser  Gly Leu Pro Ser Gly  Glu Val Leu Glu Thr  Ala Ala Pro
    1145                 1150                 1155

Gly Val  Glu Asp Ile Ser Gly  Leu Pro Ser Gly Glu  Val Leu Glu
    1160                 1165                 1170

Thr Ala  Ala Pro Gly Val Glu  Asp Ile Ser Gly Leu  Pro Ser Gly
    1175                 1180                 1185

Glu Val  Leu Glu Thr Ala Ala  Pro Gly Val Glu Asp  Ile Ser Gly
    1190                 1195                 1200

Leu Pro  Ser Gly Glu Val Leu  Glu Thr Ala Ala Pro  Gly Val Glu
    1205                 1210                 1215

Asp Ile  Ser Gly Leu Pro Ser  Gly Glu Val Leu Glu  Thr Ala Ala
    1220                 1225                 1230

Pro Gly  Val Glu Asp Ile Ser  Gly Leu Pro Ser Gly  Glu Val Leu
    1235                 1240                 1245

Glu Thr  Ala Ala Pro Gly Val  Glu Asp Ile Ser Gly  Leu Pro Ser
    1250                 1255                 1260

Gly Glu  Val Leu Glu Thr Ala  Ala Pro Gly Val Glu  Asp Ile Ser
    1265                 1270                 1275

Gly Leu  Pro Ser Gly Glu Val  Leu Glu Thr Thr Ala  Pro Gly Val
    1280                 1285                 1290

Glu Glu  Ile Ser Gly Leu Pro  Ser Gly Glu Val Leu  Glu Thr Thr
    1295                 1300                 1305

Ala Pro  Gly Val Asp Glu Ile  Ser Gly Leu Pro Ser  Gly Glu Val
    1310                 1315                 1320

Leu Glu  Thr Thr Ala Pro Gly  Val Glu Glu Ile Ser  Gly Leu Pro
    1325                 1330                 1335

Ser Gly  Glu Val Leu Glu Thr  Ser Thr Ser Ala Val  Gly Asp Leu
    1340                 1345                 1350

Ser Gly  Leu Pro Ser Gly Gly  Glu Val Leu Glu Ile  Ser Val Ser
    1355                 1360                 1365

Gly Val  Glu Asp Ile Ser Gly  Leu Pro Ser Gly Glu  Val Val Glu
    1370                 1375                 1380

Thr Ser  Ala Ser Gly Ile Glu  Asp Val Ser Glu Leu  Pro Ser Gly
    1385                 1390                 1395

Glu Gly  Leu Glu Thr Ser Ala  Ser Gly Val Glu Asp  Leu Ser Arg
    1400                 1405                 1410

Leu Pro  Ser Gly Glu Glu Val  Leu Glu Ile Ser Ala  Ser Gly Phe
    1415                 1420                 1425

Gly Asp  Leu Ser Gly Leu Pro  Ser Gly Gly Glu Gly  Leu Glu Thr
    1430                 1435                 1440

Ser Ala  Ser Glu Val Gly Thr  Asp Leu Ser Gly Leu  Pro Ser Gly
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1445 1450 1455

Arg Glu Gly Leu Glu Thr Ser Ala Ser Gly Ala Glu Asp Leu Ser
1460 1465 1470

Gly Leu Pro Ser Gly Lys Glu Asp Leu Val Gly Ser Ala Ser Gly
1475 1480 1485

Asp Leu Asp Leu Gly Lys Leu Pro Ser Gly Thr Leu Gly Ser Gly
1490 1495 1500

Gln Ala Pro Glu Thr Ser Gly Leu Pro Ser Gly Phe Ser Gly Glu
1505 1510 1515

Tyr Ser Gly Val Asp Leu Gly Ser Gly Pro Pro Ser Gly Leu Pro
1520 1525 1530

Asp Phe Ser Gly Leu Pro Ser Gly Phe Pro Thr Val Ser Leu Val
1535 1540 1545

Asp Ser Thr Leu Val Glu Val Val Thr Ala Ser Thr Ala Ser Glu
1550 1555 1560

Leu Glu Gly Arg Gly Thr Ile Gly Ile Ser Gly Ala Gly Glu Ile
1565 1570 1575

Ser Gly Leu Pro Ser Ser Glu Leu Asp Ile Ser Gly Arg Ala Ser
1580 1585 1590

Gly Leu Pro Ser Gly Thr Glu Leu Ser Gly Gln Ala Ser Gly Ser
1595 1600 1605

Pro Asp Val Ser Gly Glu Ile Pro Gly Leu Phe Gly Val Ser Gly
1610 1615 1620

Gln Pro Ser Gly Phe Pro Asp Thr Ser Gly Glu Thr Ser Gly Val
1625 1630 1635

Thr Glu Leu Ser Gly Leu Ser Ser Gly Gln Pro Gly Ile Ser Gly
1640 1645 1650

Glu Ala Ser Gly Val Leu Tyr Gly Thr Ser Gln Pro Phe Gly Ile
1655 1660 1665

Thr Asp Leu Ser Gly Glu Thr Ser Gly Val Pro Asp Leu Ser Gly
1670 1675 1680

Gln Pro Ser Gly Leu Pro Gly Phe Ser Gly Ala Thr Ser Gly Val
1685 1690 1695

Pro Asp Leu Val Ser Gly Thr Thr Ser Gly Ser Gly Glu Ser Ser
1700 1705 1710

Gly Ile Thr Phe Val Asp Thr Ser Leu Val Glu Val Ala Pro Thr
1715 1720 1725

Thr Phe Lys Glu Glu Glu Gly Leu Gly Ser Val Glu Leu Ser Gly
1730 1735 1740

Leu Pro Ser Gly Glu Ala Asp Leu Ser Gly Lys Ser Gly Met Val
1745 1750 1755

Asp Val Ser Gly Gln Phe Ser Gly Thr Val Asp Ser Ser Gly Phe
1760 1765 1770

Thr Ser Gln Thr Pro Glu Phe Ser Gly Leu Pro Ser Gly Ile Ala
1775 1780 1785

Glu Val Ser Gly Glu Ser Ser Arg Ala Glu Ile Gly Ser Ser Leu
1790 1795 1800

Pro Ser Gly Ala Tyr Tyr Gly Ser Gly Thr Pro Ser Ser Phe Pro
1805 1810 1815

Thr Val Ser Leu Val Asp Arg Thr Leu Val Glu Ser Val Thr Gln
1820 1825 1830

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Ala Pro  Thr Ala Gln Glu Ala  Gly Glu Gly Pro Ser  Gly Ile Leu
    1835                 1840                 1845

Glu Leu  Ser Gly Ala His Ser  Gly Ala Pro Asp Met  Ser Gly Glu
    1850                 1855                 1860

His Ser  Gly Phe Leu Asp Leu  Ser Gly Leu Gln Ser  Gly Leu Ile
    1865                 1870                 1875

Glu Pro  Ser Gly Glu Pro Pro  Gly Thr Pro Tyr Phe  Ser Gly Asp
    1880                 1885                 1890

Phe Ala  Ser Thr Thr Asn Val  Ser Gly Glu Ser Ser  Val Ala Met
    1895                 1900                 1905

Gly Thr  Ser Gly Glu Ala Ser  Gly Leu Pro Glu Val  Thr Leu Ile
    1910                 1915                 1920

Thr Ser  Glu Phe Val Glu Gly  Val Thr Glu Pro Thr  Ile Ser Gln
    1925                 1930                 1935

Glu Leu  Gly Gln Arg Pro Pro  Val Thr His Thr Pro  Gln Leu Phe
    1940                 1945                 1950

Glu Ser  Ser Gly Lys Val Ser  Thr Ala Gly Asp Ile  Ser Gly Ala
    1955                 1960                 1965

Thr Pro  Val Leu Pro Gly Ser  Gly Val Glu Val Ser  Ser Val Pro
    1970                 1975                 1980

Glu Ser  Ser Ser Glu Thr Ser  Ala Tyr Pro Glu Ala  Gly Phe Gly
    1985                 1990                 1995

Ala Ser  Ala Ala Pro Glu Ala  Ser Arg Glu Asp Ser  Gly Ser Pro
    2000                 2005                 2010

Asp Leu  Ser Glu Thr Thr Ser  Ala Phe His Glu Ala  Asn Leu Glu
    2015                 2020                 2025

Arg Ser  Ser Gly Leu Gly Val  Ser Gly Ser Thr Leu  Thr Phe Gln
    2030                 2035                 2040

Glu Gly  Glu Ala Ser Ala Ala  Pro Glu Val Ser Gly  Glu Ser Thr
    2045                 2050                 2055

Thr Thr  Ser Asp Val Gly Thr  Glu Ala Pro Gly Leu  Pro Ser Ala
    2060                 2065                 2070

Thr Pro  Thr Ala Ser Gly Asp  Arg Thr Glu Ile Ser  Gly Asp Leu
    2075                 2080                 2085

Ser Gly  His Thr Ser Gln Leu  Gly Val Val Ile Ser  Thr Ser Ile
    2090                 2095                 2100

Pro Glu  Ser Glu Trp Thr Gln  Gln Thr Gln Arg Pro  Ala Glu Thr
    2105                 2110                 2115

His Leu  Glu Ile Glu Ser Ser  Ser Leu Leu Tyr Ser  Gly Glu Glu
    2120                 2125                 2130

Thr His  Thr Val Glu Thr Ala  Thr Ser Pro Thr Asp  Ala Ser Ile
    2135                 2140                 2145

Pro Ala  Ser Pro Glu Trp Lys  Arg Glu Ser Glu Ser  Thr Ala Ala
    2150                 2155                 2160

Ala Pro  Ala Arg Ser Cys Ala  Glu Glu Pro Cys Gly  Ala Gly Thr
    2165                 2170                 2175

Cys Lys  Glu Thr Glu Gly His  Val Ile Cys Leu Cys  Pro Pro Gly
    2180                 2185                 2190

Tyr Thr  Gly Glu His Cys Asn  Ile Asp Gln Glu Val  Cys Glu Glu
    2195                 2200                 2205
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Gly Trp  Asn Lys Tyr Gln Gly  His Cys Tyr Arg His  Phe Pro Asp
    2210                 2215                 2220

Arg Glu  Thr Trp Val Asp Ala  Glu Arg Arg Cys Arg  Glu Gln Gln
    2225                 2230                 2235

Ser His  Leu Ser Ser Ile Val  Thr Pro Glu Glu Gln  Glu Phe Val
    2240                 2245                 2250

Asn Asn  Asn Ala Gln Asp Tyr  Gln Trp Ile Gly Leu  Asn Asp Arg
    2255                 2260                 2265

Thr Ile  Glu Gly Asp Phe Arg  Trp Ser Asp Gly His  Pro Met Gln
    2270                 2275                 2280

Phe Glu  Asn Trp Arg Pro Asn  Gln Pro Asp Asn Phe  Phe Ala Ala
    2285                 2290                 2295

Gly Glu  Asp Cys Val Val Met  Ile Trp His Glu Lys  Gly Glu Trp
    2300                 2305                 2310

Asn Asp  Val Pro Cys Asn Tyr  His Leu Pro Phe Thr  Cys Lys Lys
    2315                 2320                 2325

Gly Thr  Val Ala Cys Gly Glu  Pro Pro Val Val Glu  His Ala Arg
    2330                 2335                 2340

Thr Phe  Gly Gln Lys Lys Asp  Arg Tyr Glu Ile Asn  Ser Leu Val
    2345                 2350                 2355

Arg Tyr  Gln Cys Thr Glu Gly  Phe Val Gln Arg His  Met Pro Thr
    2360                 2365                 2370

Ile Arg  Cys Gln Pro Ser Gly  His Trp Glu Glu Pro  Gln Ile Thr
    2375                 2380                 2385

Cys Thr  Asp Pro Thr Thr Tyr  Lys Arg Arg Leu Gln  Lys Arg Ser
    2390                 2395                 2400

Ser Arg  His Pro Arg Arg Ser  Arg Pro Ser Thr Ala  His
    2405                 2410                 2415


<210> SEQ ID NO 2
<211> LENGTH: 380
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Lys Glu Tyr Val Leu Leu Leu Phe Leu Ala Leu Cys Ser Ala Lys
1               5                   10                  15

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

Asp Met Glu Asp Thr Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
        35                  40                  45

Asp Asp Asp Glu Asp Asn Ser Leu Phe Pro Thr Arg Glu Pro Arg Ser
    50                  55                  60

His Phe Phe Pro Phe Asp Leu Phe Pro Met Cys Pro Phe Gly Cys Gln
65                  70                  75                  80

Cys Tyr Ser Arg Val Val His Cys Ser Asp Leu Gly Leu Thr Ser Val
                85                  90                  95

Pro Thr Asn Ile Pro Phe Asp Thr Arg Met Leu Asp Leu Gln Asn Asn
            100                 105                 110

Lys Ile Lys Glu Ile Lys Glu Asn Asp Phe Lys Gly Leu Thr Ser Leu
        115                 120                 125

Tyr Gly Leu Ile Leu Asn Asn Asn Lys Leu Thr Lys Ile His Pro Lys
    130                 135                 140
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Ala Phe Leu Thr Thr Lys Lys Leu Arg Arg Leu Tyr Leu Ser His Asn
145                 150                 155                 160

Gln Leu Ser Glu Ile Pro Leu Asn Leu Pro Lys Ser Leu Ala Glu Leu
                165                 170                 175

Arg Ile His Glu Asn Lys Val Lys Lys Ile Gln Lys Asp Thr Phe Lys
            180                 185                 190

Gly Met Asn Ala Leu His Val Leu Glu Met Ser Ala Asn Pro Leu Asp
        195                 200                 205

Asn Asn Gly Ile Glu Pro Gly Ala Phe Glu Gly Val Thr Val Phe His
    210                 215                 220

Ile Arg Ile Ala Glu Ala Lys Leu Thr Ser Val Pro Lys Gly Leu Pro
225                 230                 235                 240

Pro Thr Leu Leu Glu Leu His Leu Asp Tyr Asn Lys Ile Ser Thr Val
                245                 250                 255

Glu Leu Glu Asp Phe Lys Arg Tyr Lys Glu Leu Gln Arg Leu Gly Leu
            260                 265                 270

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

Pro Arg Val Arg Glu Ile His Leu Glu Asn Asn Lys Leu Lys Lys Ile
    290                 295                 300

Pro Ser Gly Leu Pro Glu Leu Lys Tyr Leu Gln Ile Ile Phe Leu His
305                 310                 315                 320

Ser Asn Ser Ile Ala Arg Val Gly Val Asn Asp Phe Cys Pro Thr Val
                325                 330                 335

Pro Lys Met Lys Lys Ser Leu Tyr Ser Ala Ile Ser Leu Phe Asn Asn
            340                 345                 350

Pro Val Lys Tyr Trp Glu Met Gln Pro Ala Thr Phe Arg Cys Val Leu
        355                 360                 365

Ser Arg Met Ser Val Gln Leu Gly Asn Phe Gly Met
    370                 375                 380


<210> SEQ ID NO 3
<211> LENGTH: 602
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met His Ser Lys Val Thr Ile Ile Cys Ile Arg Phe Leu Phe Trp Phe
1               5                   10                  15

Leu Leu Leu Cys Met Leu Ile Gly Lys Ser His Thr Glu Asp Asp Ile
            20                  25                  30

Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met Asn Leu Thr Val
        35                  40                  45

Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro Tyr Ala Gln Pro
    50                  55                  60

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

Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser Cys Cys Gln Asn
                85                  90                  95

Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu Met Trp Asn Pro
            100                 105                 110

Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn Val Trp Ile Pro
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        115                 120                 125

Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp Ile Tyr Gly Gly
    130                 135                 140

Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr Asp Gly Lys Phe
145                 150                 155                 160

Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met Asn Tyr Arg Val
                165                 170                 175

Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro Glu Ala Pro Gly
            180                 185                 190

Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln Trp Val Gln Lys
        195                 200                 205

Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val Thr Leu Phe Gly
    210                 215                 220

Glu Ser Ala Gly Ala Ala Ser Val Ser Leu His Leu Leu Ser Pro Gly
225                 230                 235                 240

Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser Gly Ser Phe Asn
                245                 250                 255

Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg Asn Arg Thr Leu
            260                 265                 270

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

Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile Leu Leu Asn Glu
    290                 295                 300

Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Ser Val Asn Phe Gly Pro
305                 310                 315                 320

Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp Ile Leu Leu Glu
                325                 330                 335

Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly Val Asn Lys Asp
            340                 345                 350

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

Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu Gly Leu Lys Ile
    370                 375                 380

Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser Ile Leu Phe His
385                 390                 395                 400

Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn Tyr Arg Glu Ala
                405                 410                 415

Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys Pro Ala Leu Glu
            420                 425                 430

Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala Phe Phe Tyr Tyr
        435                 440                 445

Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu Trp Met Gly Val
    450                 455                 460

Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu Pro Leu Glu Arg
465                 470                 475                 480

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

Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro Asn Glu Thr Gln
            500                 505                 510

Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr Glu Gln Lys Tyr
        515                 520                 525
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Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr Lys Leu Arg Ala
    530                 535                 540

Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys Val Leu Glu Met
545                 550                 555                 560

Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys Ala Gly Phe His
                565                 570                 575

Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln Phe Asn Asp Tyr
            580                 585                 590

Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
        595                 600


<210> SEQ ID NO 4
<211> LENGTH: 100
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Arg Ala Leu Thr Leu Leu Ala Leu Leu Ala Leu Ala Ala Leu Cys
1               5                   10                  15

Ile Ala Gly Gln Ala Gly Ala Lys Pro Ser Gly Ala Glu Ser Ser Lys
            20                  25                  30

Gly Ala Ala Phe Val Ser Lys Gln Glu Gly Ser Glu Val Val Lys Arg
        35                  40                  45

Pro Arg Arg Tyr Leu Tyr Gln Trp Leu Gly Ala Pro Val Pro Tyr Pro
    50                  55                  60

Asp Pro Leu Glu Pro Arg Arg Glu Val Cys Glu Leu Asn Pro Asp Cys
65                  70                  75                  80

Asp Glu Leu Ala Asp His Ile Gly Phe Gln Glu Ala Tyr Arg Arg Phe
                85                  90                  95

Tyr Gly Pro Val
            100


<210> SEQ ID NO 5
<211> LENGTH: 369
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Leu Ser Val Cys Val Ala Phe Leu Phe Leu Cys Thr Ala His Leu
1               5                   10                  15

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

Phe Gly Lys Asp Ile Asp Val Lys Glu Leu Met Met Met Met Asp Gln
        35                  40                  45

Glu Glu Gly Ser Ala Val Glu Pro Tyr Lys Pro Glu His Pro Thr Cys
    50                  55                  60

Pro Phe Gly Cys Arg Cys Glu Leu Arg Val Val Gln Cys Ser Asp Leu
65                  70                  75                  80

Gly Leu Gly Tyr Val Pro Tyr Asp Ile Pro Ala Asp Thr Leu Leu Leu
                85                  90                  95

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

Gly Leu Ser Asn Leu Tyr Ala Leu Val Leu Arg Tyr Asn Gln Ile Ser
        115                 120                 125
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Lys Ile His Pro Lys Ala Phe Leu Pro Leu Lys Arg Leu Gln Lys Leu
    130                 135                 140

Tyr Ile Ser His Asn Leu Leu Thr Ser Met Pro Lys Asn Leu Pro Ser
145                 150                 155                 160

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

Ala Phe Ser Phe Ser Gly Leu His Asn Met His Val Ile Glu Met Gly
            180                 185                 190

Arg Asn Pro Leu Gln Asn Ser Gly Phe Glu Pro Gly Ala Phe Met Gly
        195                 200                 205

Leu Lys Leu Asn Tyr Leu Arg Ile Ser Glu Ala Lys Leu Thr Gly Val
    210                 215                 220

Pro Lys Asp Leu Pro Gly Ser Leu His Glu Leu His Leu Asp Asn Asn
225                 230                 235                 240

Gln Ile Gln Ala Ile Glu Leu Val Asp Leu Ser Gln Tyr Thr Gln Leu
                245                 250                 255

Gln Arg Leu Gly Leu Gly Ser Asn Gln Ile Arg His Ile Glu His Gly
            260                 265                 270

Ala Leu Ser Tyr Leu Thr Asn Leu Arg Glu Leu His Leu Asp Asn Asn
        275                 280                 285

Arg Leu Pro Ser Val Pro Ser Gly Leu Ser His Met Lys Tyr Leu Gln
    290                 295                 300

Val Val Tyr Leu His Ser Asn Asn Ile Thr Asn Val Gly Glu Asp Asp
305                 310                 315                 320

Phe Cys Pro Thr Gly Phe Gly Leu Lys Lys Val Phe Tyr Asn Gly Ile
                325                 330                 335

Ser Leu Phe Asp Asn Pro Ile Arg Tyr Trp Glu Val Gln Pro Ser Thr
            340                 345                 350

Phe Arg Cys Val Ser Asp Gln Met Ala Val Gln Phe Gly Asn His Lys
        355                 360                 365

Lys


<210> SEQ ID NO 6
<211> LENGTH: 675
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Asp Thr Lys Ser Ile Leu Glu Glu Leu Leu Leu Lys Arg Ser Gln
1               5                   10                  15

Gln Lys Lys Lys Met Ser Pro Asn Asn Tyr Lys Glu Arg Leu Phe Val
            20                  25                  30

Leu Thr Lys Thr Asn Leu Ser Tyr Tyr Glu Tyr Asp Lys Met Lys Arg
        35                  40                  45

Gly Ser Arg Lys Gly Ser Ile Glu Ile Lys Lys Ile Arg Cys Val Glu
    50                  55                  60

Lys Val Asn Leu Glu Glu Gln Thr Pro Val Glu Arg Gln Tyr Pro Phe
65                  70                  75                  80

Gln Ile Val Tyr Lys Asp Gly Leu Leu Tyr Val Tyr Ala Ser Asn Glu
                85                  90                  95

Glu Ser Arg Ser Gln Trp Leu Lys Ala Leu Gln Lys Glu Ile Arg Gly
            100                 105                 110
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Asn Pro His Leu Leu Val Lys Tyr His Ser Gly Phe Phe Val Asp Gly
        115                 120                 125

Lys Phe Leu Cys Cys Gln Gln Ser Cys Lys Ala Ala Pro Gly Cys Thr
    130                 135                 140

Leu Trp Glu Ala Tyr Ala Asn Leu His Thr Ala Val Asn Glu Glu Lys
145                 150                 155                 160

His Arg Val Pro Thr Phe Pro Asp Arg Val Leu Lys Ile Pro Arg Ala
                165                 170                 175

Val Pro Val Leu Lys Met Asp Ala Pro Ser Ser Ser Thr Thr Leu Ala
            180                 185                 190

Gln Tyr Asp Asn Glu Ser Lys Lys Asn Tyr Gly Ser Gln Pro Pro Ser
        195                 200                 205

Ser Ser Thr Ser Leu Ala Gln Tyr Asp Ser Asn Ser Lys Lys Ile Tyr
    210                 215                 220

Gly Ser Gln Pro Asn Phe Asn Met Gln Tyr Ile Pro Arg Glu Asp Phe
225                 230                 235                 240

Pro Asp Trp Trp Gln Val Arg Lys Leu Lys Ser Ser Ser Ser Ser Glu
                245                 250                 255

Asp Val Ala Ser Ser Asn Gln Lys Glu Arg Asn Val Asn His Thr Thr
            260                 265                 270

Ser Lys Ile Ser Trp Glu Phe Pro Glu Ser Ser Ser Ser Glu Glu Glu
        275                 280                 285

Glu Asn Leu Asp Asp Tyr Asp Trp Phe Ala Gly Asn Ile Ser Arg Ser
    290                 295                 300

Gln Ser Glu Gln Leu Leu Arg Gln Lys Gly Lys Glu Gly Ala Phe Met
305                 310                 315                 320

Val Arg Asn Ser Ser Gln Val Gly Met Tyr Thr Val Ser Leu Phe Ser
                325                 330                 335

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

Thr Asn Ala Glu Asn Lys Leu Tyr Leu Ala Glu Asn Tyr Cys Phe Asp
        355                 360                 365

Ser Ile Pro Lys Leu Ile His Tyr His Gln His Asn Ser Ala Gly Met
    370                 375                 380

Ile Thr Arg Leu Arg His Pro Val Ser Thr Lys Ala Asn Lys Val Pro
385                 390                 395                 400

Asp Ser Val Ser Leu Gly Asn Gly Ile Trp Glu Leu Lys Arg Glu Glu
                405                 410                 415

Ile Thr Leu Leu Lys Glu Leu Gly Ser Gly Gln Phe Gly Val Val Gln
            420                 425                 430

Leu Gly Lys Trp Lys Gly Gln Tyr Asp Val Ala Val Lys Met Ile Lys
        435                 440                 445

Glu Gly Ser Met Ser Glu Asp Glu Phe Phe Gln Glu Ala Gln Thr Met
    450                 455                 460

Met Lys Leu Ser His Pro Lys Leu Val Lys Phe Tyr Gly Val Cys Ser
465                 470                 475                 480

Lys Glu Tyr Pro Ile Tyr Ile Val Thr Glu Tyr Ile Ser Asn Gly Cys
                485                 490                 495

Leu Leu Asn Tyr Leu Arg Ser His Gly Lys Gly Leu Glu Pro Ser Gln
            500                 505                 510
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Leu Leu Glu Met Cys Tyr Asp Val Cys Glu Gly Met Ala Phe Leu Glu
        515                 520                 525

Ser His Gln Phe Ile His Arg Asp Leu Ala Ala Arg Asn Cys Leu Val
    530                 535                 540

Asp Arg Asp Leu Cys Val Lys Val Ser Asp Phe Gly Met Thr Arg Tyr
545                 550                 555                 560

Val Leu Asp Asp Gln Tyr Val Ser Ser Val Gly Thr Lys Phe Pro Val
                565                 570                 575

Lys Trp Ser Ala Pro Glu Val Phe His Tyr Phe Lys Tyr Ser Ser Lys
            580                 585                 590

Ser Asp Val Trp Ala Phe Gly Ile Leu Met Trp Glu Val Phe Ser Leu
        595                 600                 605

Gly Lys Gln Pro Tyr Asp Leu Tyr Asp Asn Ser Gln Val Val Leu Lys
    610                 615                 620

Val Ser Gln Gly His Arg Leu Tyr Arg Pro His Leu Ala Ser Asp Thr
625                 630                 635                 640

Ile Tyr Gln Ile Met Tyr Ser Cys Trp His Glu Leu Pro Glu Lys Arg
                645                 650                 655

Pro Thr Phe Gln Gln Leu Leu Ser Ser Ile Glu Pro Leu Arg Glu Lys
            660                 665                 670

Asp Lys His
        675


<210> SEQ ID NO 7
<211> LENGTH: 138
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Thr Trp Arg Gln Ala Val Leu Leu Ser Cys Phe Ser Ala Val Val
1               5                   10                  15

Leu Leu Ser Met Leu Arg Glu Gly Thr Ser Val Ser Val Gly Thr Met
            20                  25                  30

Gln Met Ala Gly Glu Glu Ala Ser Glu Asp Ala Lys Gln Lys Ile Phe
        35                  40                  45

Met Gln Glu Ser Asp Ala Ser Asn Phe Leu Lys Arg Arg Gly Lys Arg
    50                  55                  60

Ser Pro Lys Ser Arg Asp Glu Val Asn Val Glu Asn Arg Gln Lys Leu
65                  70                  75                  80

Arg Val Asp Glu Leu Arg Arg Glu Tyr Tyr Glu Glu Gln Arg Asn Glu
                85                  90                  95

Phe Glu Asn Phe Val Glu Glu Gln Asn Asp Glu Gln Glu Glu Arg Ser
            100                 105                 110

Arg Glu Ala Val Glu Gln Trp Arg Gln Trp His Tyr Asp Gly Leu His
        115                 120                 125

Pro Ser Tyr Leu Tyr Asn Arg His His Thr
    130                 135


<210> SEQ ID NO 8
<211> LENGTH: 315
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8
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Met Asp Leu Arg Gln Phe Leu Met Cys Leu Ser Leu Cys Thr Ala Phe
1               5                   10                  15

Ala Leu Ser Lys Pro Thr Glu Lys Lys Asp Arg Val His His Glu Pro
            20                  25                  30

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

His Asp Ala Phe Leu Gly Ala Glu Glu Ala Lys Thr Phe Asp Gln Leu
    50                  55                  60

Thr Pro Glu Glu Ser Lys Glu Arg Leu Gly Lys Ile Val Ser Lys Ile
65                  70                  75                  80

Asp Gly Asp Lys Asp Gly Phe Val Thr Val Asp Glu Leu Lys Asp Trp
                85                  90                  95

Ile Lys Phe Ala Gln Lys Arg Trp Ile Tyr Glu Asp Val Glu Arg Gln
            100                 105                 110

Trp Lys Gly His Asp Leu Asn Glu Asp Gly Leu Val Ser Trp Glu Glu
        115                 120                 125

Tyr Lys Asn Ala Thr Tyr Gly Tyr Val Leu Asp Asp Pro Asp Pro Asp
    130                 135                 140

Asp Gly Phe Asn Tyr Lys Gln Met Met Val Arg Asp Glu Arg Arg Phe
145                 150                 155                 160

Lys Met Ala Asp Lys Asp Gly Asp Leu Ile Ala Thr Lys Glu Glu Phe
                165                 170                 175

Thr Ala Phe Leu His Pro Glu Glu Tyr Asp Tyr Met Lys Asp Ile Val
            180                 185                 190

Val Gln Glu Thr Met Glu Asp Ile Asp Lys Asn Ala Asp Gly Phe Ile
        195                 200                 205

Asp Leu Glu Glu Tyr Ile Gly Asp Met Tyr Ser His Asp Gly Asn Thr
    210                 215                 220

Asp Glu Pro Glu Trp Val Lys Thr Glu Arg Glu Gln Phe Val Glu Phe
225                 230                 235                 240

Arg Asp Lys Asn Arg Asp Gly Lys Met Asp Lys Glu Glu Thr Lys Asp
                245                 250                 255

Trp Ile Leu Pro Ser Asp Tyr Asp His Ala Glu Ala Glu Ala Arg His
            260                 265                 270

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

Glu Ile Val Asp Lys Tyr Asp Leu Phe Val Gly Ser Gln Ala Thr Asp
    290                 295                 300

Phe Gly Glu Ala Leu Val Arg His Asp Glu Phe
305                 310                 315


<210> SEQ ID NO 9
<211> LENGTH: 326
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Glu Phe Leu Ser Glu Lys Phe Ala Leu Lys Ser Pro Pro Ser Lys
1               5                   10                  15

Asn Ser Asp Phe Tyr Met Gly Ala Gly Gly Pro Leu Glu His Val Met
            20                  25                  30

Glu Thr Leu Asp Asn Glu Ser Phe Tyr Ser Lys Ala Ser Ala Gly Lys
        35                  40                  45
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Cys Val Gln Ala Phe Gly Pro Leu Pro Arg Ala Glu His His Val Arg
    50                  55                  60

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

Thr Lys Val Glu Gly Gln Pro Leu His Thr Glu Leu Asn Arg Ala Met
                85                  90                  95

Asp Asn Cys Asn Ser Leu Arg Met Ser Pro Val Lys Gly Met Gln Glu
            100                 105                 110

Lys Gly Glu Leu Asp Glu Leu Gly Asp Lys Cys Asp Ser Asn Val Ser
        115                 120                 125

Ser Ser Lys Lys Arg Arg His Arg Thr Thr Phe Thr Ser Leu Gln Leu
    130                 135                 140

Glu Glu Leu Glu Lys Val Phe Gln Lys Thr His Tyr Pro Asp Val Tyr
145                 150                 155                 160

Val Arg Glu Gln Leu Ala Leu Arg Thr Glu Leu Thr Glu Ala Arg Val
                165                 170                 175

Gln Val Trp Phe Gln Asn Arg Arg Ala Lys Trp Arg Lys Arg Glu Arg
            180                 185                 190

Tyr Gly Gln Ile Gln Gln Ala Lys Ser His Phe Ala Ala Thr Tyr Asp
        195                 200                 205

Ile Ser Val Leu Pro Arg Thr Asp Ser Tyr Pro Gln Ile Gln Asn Asn
    210                 215                 220

Leu Trp Ala Gly Asn Ala Ser Gly Gly Ser Val Val Thr Ser Cys Met
225                 230                 235                 240

Leu Pro Arg Asp Thr Ser Ser Cys Met Thr Pro Tyr Ser His Ser Pro
                245                 250                 255

Arg Thr Asp Ser Ser Tyr Thr Gly Phe Ser Asn His Gln Asn Gln Phe
            260                 265                 270

Ser His Val Pro Leu Asn Asn Phe Phe Thr Asp Ser Leu Leu Thr Gly
        275                 280                 285

Ala Thr Asn Gly His Ala Phe Glu Thr Lys Pro Glu Phe Glu Arg Arg
    290                 295                 300

Ser Ser Ser Ile Ala Val Leu Arg Met Lys Ala Lys Glu His Thr Ala
305                 310                 315                 320

Asn Ile Ser Trp Ala Met
                325


<210> SEQ ID NO 10
<211> LENGTH: 359
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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

Leu Pro Ala Leu Ala Ala Cys Pro Gln Asn Cys His Cys His Ser Asp
            20                  25                  30

Leu Gln His Val Ile Cys Asp Lys Val Gly Leu Gln Lys Ile Pro Lys
        35                  40                  45

Val Ser Glu Lys Thr Lys Leu Leu Asn Leu Gln Arg Asn Asn Phe Pro
    50                  55                  60

Val Leu Ala Ala Asn Ser Phe Arg Ala Met Pro Asn Leu Val Ser Leu
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65                  70                  75                  80

His Leu Gln His Cys Gln Ile Arg Glu Val Ala Ala Gly Ala Phe Arg
                85                  90                  95

Gly Leu Lys Gln Leu Ile Tyr Leu Tyr Leu Ser His Asn Asp Ile Arg
            100                 105                 110

Val Leu Arg Ala Gly Ala Phe Asp Asp Leu Thr Glu Leu Thr Tyr Leu
        115                 120                 125

Tyr Leu Asp His Asn Lys Val Thr Glu Leu Pro Arg Gly Leu Leu Ser
    130                 135                 140

Pro Leu Val Asn Leu Phe Ile Leu Gln Leu Asn Asn Asn Lys Ile Arg
145                 150                 155                 160

Glu Leu Arg Ala Gly Ala Phe Gln Gly Ala Lys Asp Leu Arg Trp Leu
                165                 170                 175

Tyr Leu Ser Glu Asn Ala Leu Ser Ser Leu Gln Pro Gly Ala Leu Asp
            180                 185                 190

Asp Val Glu Asn Leu Ala Lys Phe His Val Asp Arg Asn Gln Leu Ser
        195                 200                 205

Ser Tyr Pro Ser Ala Ala Leu Ser Lys Leu Arg Val Val Glu Glu Leu
    210                 215                 220

Lys Leu Ser His Asn Pro Leu Lys Ser Ile Pro Asp Asn Ala Phe Gln
225                 230                 235                 240

Ser Phe Gly Arg Tyr Leu Glu Thr Leu Trp Leu Asp Asn Thr Asn Leu
                245                 250                 255

Glu Lys Phe Ser Asp Gly Ala Phe Leu Gly Val Thr Thr Leu Lys His
            260                 265                 270

Val His Leu Glu Asn Asn Arg Leu Asn Gln Leu Pro Ser Asn Phe Pro
        275                 280                 285

Phe Asp Ser Leu Glu Thr Leu Ala Leu Thr Asn Asn Pro Trp Lys Cys
    290                 295                 300

Thr Cys Gln Leu Arg Gly Leu Arg Arg Trp Leu Glu Ala Lys Ala Ser
305                 310                 315                 320

Arg Pro Asp Ala Thr Cys Ala Ser Pro Ala Lys Phe Lys Gly Gln His
                325                 330                 335

Ile Arg Asp Thr Asp Ala Phe Arg Ser Cys Lys Phe Pro Thr Lys Arg
            340                 345                 350

Ser Lys Lys Ala Gly Arg His
        355


<210> SEQ ID NO 11
<211> LENGTH: 383
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Gly Val Lys Ala Ser Gln Thr Gly Phe Val Val Leu Val Leu Leu
1               5                   10                  15

Gln Cys Cys Ser Ala Tyr Lys Leu Val Cys Tyr Tyr Thr Ser Trp Ser
            20                  25                  30

Gln Tyr Arg Glu Gly Asp Gly Ser Cys Phe Pro Asp Ala Leu Asp Arg
        35                  40                  45

Phe Leu Cys Thr His Ile Ile Tyr Ser Phe Ala Asn Ile Ser Asn Asp
    50                  55                  60
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His Ile Asp Thr Trp Glu Trp Asn Asp Val Thr Leu Tyr Gly Met Leu
65                  70                  75                  80

Asn Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys Thr Leu Leu Ser Val
                85                  90                  95

Gly Gly Trp Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile Ala Ser Asn
            100                 105                 110

Thr Gln Ser Arg Arg Thr Phe Ile Lys Ser Val Pro Pro Phe Leu Arg
        115                 120                 125

Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg
    130                 135                 140

Arg Asp Lys Gln His Phe Thr Thr Leu Ile Lys Glu Met Lys Ala Glu
145                 150                 155                 160

Phe Ile Lys Glu Ala Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser Ala
                165                 170                 175

Ala Leu Ser Ala Gly Lys Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala
            180                 185                 190

Lys Ile Ser Gln His Leu Asp Phe Ile Ser Ile Met Thr Tyr Asp Phe
        195                 200                 205

His Gly Ala Trp Arg Gly Thr Thr Gly His His Ser Pro Leu Phe Arg
    210                 215                 220

Gly Gln Glu Asp Ala Ser Pro Asp Arg Phe Ser Asn Thr Asp Tyr Ala
225                 230                 235                 240

Val Gly Tyr Met Leu Arg Leu Gly Ala Pro Ala Ser Lys Leu Val Met
                245                 250                 255

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

Gly Val Gly Ala Pro Ile Ser Gly Pro Gly Ile Pro Gly Arg Phe Thr
        275                 280                 285

Lys Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg
    290                 295                 300

Gly Ala Thr Val His Arg Ile Leu Gly Gln Gln Val Pro Tyr Ala Thr
305                 310                 315                 320

Lys Gly Asn Gln Trp Val Gly Tyr Asp Asp Gln Glu Ser Val Lys Ser
                325                 330                 335

Lys Val Gln Tyr Leu Lys Asp Arg Gln Leu Ala Gly Ala Met Val Trp
            340                 345                 350

Ala Leu Asp Leu Asp Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp Leu
        355                 360                 365

Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala Leu Ala Ala Thr
    370                 375                 380


<210> SEQ ID NO 12
<211> LENGTH: 1184
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Met Val Gly Thr Lys Ala Trp Val Phe Ser Phe Leu Val Leu Glu Val
1               5                   10                  15

Thr Ser Val Leu Gly Arg Gln Thr Met Leu Thr Gln Ser Val Arg Arg
            20                  25                  30

Val Gln Pro Gly Lys Lys Asn Pro Ser Ile Phe Ala Lys Pro Ala Asp
        35                  40                  45
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Thr Leu Glu Ser Pro Gly Glu Trp Thr Thr Trp Phe Asn Ile Asp Tyr
    50                  55                  60

Pro Gly Gly Lys Gly Asp Tyr Glu Arg Leu Asp Ala Ile Arg Phe Tyr
65                  70                  75                  80

Tyr Gly Asp Arg Val Cys Ala Arg Pro Leu Arg Leu Glu Ala Arg Thr
                85                  90                  95

Thr Asp Trp Thr Pro Ala Gly Ser Thr Gly Gln Val Val His Gly Ser
            100                 105                 110

Pro Arg Glu Gly Phe Trp Cys Leu Asn Arg Glu Gln Arg Pro Gly Gln
        115                 120                 125

Asn Cys Ser Asn Tyr Thr Val Arg Phe Leu Cys Pro Pro Gly Ser Leu
    130                 135                 140

Arg Arg Asp Thr Glu Arg Ile Trp Ser Pro Trp Ser Pro Trp Ser Lys
145                 150                 155                 160

Cys Ser Ala Ala Cys Gly Gln Thr Gly Val Gln Thr Arg Thr Arg Ile
                165                 170                 175

Cys Leu Ala Glu Met Val Ser Leu Cys Ser Glu Ala Ser Glu Glu Gly
            180                 185                 190

Gln His Cys Met Gly Gln Asp Cys Thr Ala Cys Asp Leu Thr Cys Pro
        195                 200                 205

Met Gly Gln Val Asn Ala Asp Cys Asp Ala Cys Met Cys Gln Asp Phe
    210                 215                 220

Met Leu His Gly Ala Val Ser Leu Pro Gly Gly Ala Pro Ala Ser Gly
225                 230                 235                 240

Ala Ala Ile Tyr Leu Leu Thr Lys Thr Pro Lys Leu Leu Thr Gln Thr
                245                 250                 255

Asp Ser Asp Gly Arg Phe Arg Ile Pro Gly Leu Cys Pro Asp Gly Lys
            260                 265                 270

Ser Ile Leu Lys Ile Thr Lys Val Lys Phe Ala Pro Ile Val Leu Thr
        275                 280                 285

Met Pro Lys Thr Ser Leu Lys Ala Ala Thr Ile Lys Ala Glu Phe Val
    290                 295                 300

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

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

Arg Pro Asp Lys Tyr Phe Trp Tyr His Asn Asp Thr Leu Leu Asp Pro
            340                 345                 350

Ser Leu Tyr Lys His Glu Ser Lys Leu Val Leu Arg Lys Leu Gln Gln
        355                 360                 365

His Gln Ala Gly Glu Tyr Phe Cys Lys Ala Gln Ser Asp Ala Gly Ala
    370                 375                 380

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

Pro Cys Asn Pro Val Pro Glu Ser Tyr Leu Ile Arg Leu Pro His Asp
                405                 410                 415

Cys Phe Gln Asn Ala Thr Asn Ser Phe Tyr Tyr Asp Val Gly Arg Cys
            420                 425                 430

Pro Val Lys Thr Cys Ala Gly Gln Gln Asp Asn Gly Ile Arg Cys Arg
        435                 440                 445
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Asp Ala Val Gln Asn Cys Cys Gly Ile Ser Lys Thr Glu Glu Arg Glu
    450                 455                 460

Ile Gln Cys Ser Gly Tyr Thr Leu Pro Thr Lys Val Ala Lys Glu Cys
465                 470                 475                 480

Ser Cys Gln Arg Cys Thr Glu Thr Arg Ser Ile Val Arg Gly Arg Val
                485                 490                 495

Ser Ala Ala Asp Asn Gly Glu Pro Met Arg Phe Gly His Val Tyr Met
            500                 505                 510

Gly Asn Ser Arg Val Ser Met Thr Gly Tyr Lys Gly Thr Phe Thr Leu
        515                 520                 525

His Val Pro Gln Asp Thr Glu Arg Leu Val Leu Thr Phe Val Asp Arg
    530                 535                 540

Leu Gln Lys Phe Val Asn Thr Thr Lys Val Leu Pro Phe Asn Lys Lys
545                 550                 555                 560

Gly Ser Ala Val Phe His Glu Ile Lys Met Leu Arg Arg Lys Glu Pro
                565                 570                 575

Ile Thr Leu Glu Ala Met Glu Thr Asn Ile Ile Pro Leu Gly Glu Val
            580                 585                 590

Val Gly Glu Asp Pro Met Ala Glu Leu Glu Ile Pro Ser Arg Ser Phe
        595                 600                 605

Tyr Arg Gln Asn Gly Glu Pro Tyr Ile Gly Lys Val Lys Ala Ser Val
    610                 615                 620

Thr Phe Leu Asp Pro Arg Asn Ile Ser Thr Ala Thr Ala Ala Gln Thr
625                 630                 635                 640

Asp Leu Asn Phe Ile Asn Asp Glu Gly Asp Thr Phe Pro Leu Arg Thr
                645                 650                 655

Tyr Gly Met Phe Ser Val Asp Phe Arg Asp Glu Val Thr Ser Glu Pro
            660                 665                 670

Leu Asn Ala Gly Lys Val Lys Val His Leu Asp Ser Thr Gln Val Lys
        675                 680                 685

Met Pro Glu His Ile Ser Thr Val Lys Leu Trp Ser Leu Asn Pro Asp
    690                 695                 700

Thr Gly Leu Trp Glu Glu Glu Gly Asp Phe Lys Phe Glu Asn Gln Arg
705                 710                 715                 720

Arg Asn Lys Arg Glu Asp Arg Thr Phe Leu Val Gly Asn Leu Glu Ile
                725                 730                 735

Arg Glu Arg Arg Leu Phe Asn Leu Asp Val Pro Glu Ser Arg Arg Cys
            740                 745                 750

Phe Val Lys Val Arg Ala Tyr Arg Ser Glu Arg Phe Leu Pro Ser Glu
        755                 760                 765

Gln Ile Gln Gly Val Val Ile Ser Val Ile Asn Leu Glu Pro Arg Thr
    770                 775                 780

Gly Phe Leu Ser Asn Pro Arg Ala Trp Gly Arg Phe Asp Ser Val Ile
785                 790                 795                 800

Thr Gly Pro Asn Gly Ala Cys Val Pro Ala Phe Cys Asp Asp Gln Ser
                805                 810                 815

Pro Asp Ala Tyr Ser Ala Tyr Val Leu Ala Ser Leu Ala Gly Glu Glu
            820                 825                 830

Leu Gln Ala Val Glu Ser Ser Pro Lys Phe Asn Pro Asn Ala Ile Gly
        835                 840                 845

Val Pro Gln Pro Tyr Leu Asn Lys Leu Asn Tyr Arg Arg Thr Asp His
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    850                 855                 860

Glu Asp Pro Arg Val Lys Lys Thr Ala Phe Gln Ile Ser Met Ala Lys
865                 870                 875                 880

Pro Arg Pro Asn Ser Ala Glu Glu Ser Asn Gly Pro Ile Tyr Ala Phe
                885                 890                 895

Glu Asn Leu Arg Ala Cys Glu Glu Ala Pro Pro Ser Ala Ala His Phe
            900                 905                 910

Arg Phe Tyr Gln Ile Glu Gly Asp Arg Tyr Asp Tyr Asn Thr Val Pro
        915                 920                 925

Phe Asn Glu Asp Asp Pro Met Ser Trp Thr Glu Asp Tyr Leu Ala Trp
    930                 935                 940

Trp Pro Lys Pro Met Glu Phe Arg Ala Cys Tyr Ile Lys Val Lys Ile
945                 950                 955                 960

Val Gly Pro Leu Glu Val Asn Val Arg Ser Arg Asn Met Gly Gly Thr
                965                 970                 975

His Arg Arg Thr Val Gly Lys Leu Tyr Gly Ile Arg Asp Val Arg Ser
            980                 985                 990

Thr Arg Asp Arg Asp Gln Pro Asn  Val Ser Ala Ala Cys  Leu Glu Phe
        995                 1000                 1005

Lys Cys  Ser Gly Met Leu Tyr  Asp Gln Asp Arg Val  Asp Arg Thr
    1010                 1015                 1020

Leu Val  Lys Val Ile Pro Gln  Gly Ser Cys Arg Arg  Ala Ser Val
    1025                 1030                 1035

Asn Pro  Met Leu His Glu Tyr  Leu Val Asn His Leu  Pro Leu Ala
    1040                 1045                 1050

Val Asn  Asn Asp Thr Ser Glu  Tyr Thr Met Leu Ala  Pro Leu Asp
    1055                 1060                 1065

Pro Leu  Gly His Asn Tyr Gly  Ile Tyr Thr Val Thr  Asp Gln Asp
    1070                 1075                 1080

Pro Arg  Thr Ala Lys Glu Ile  Ala Leu Gly Arg Cys  Phe Asp Gly
    1085                 1090                 1095

Thr Ser  Asp Gly Ser Ser Arg  Ile Met Lys Ser Asn  Val Gly Val
    1100                 1105                 1110

Ala Leu  Thr Phe Asn Cys Val  Glu Arg Gln Val Gly  Arg Gln Ser
    1115                 1120                 1125

Ala Phe  Gln Tyr Leu Gln Ser  Thr Pro Ala Gln Ser  Pro Ala Ala
    1130                 1135                 1140

Gly Thr  Val Gln Gly Arg Val  Pro Ser Arg Arg Gln  Gln Arg Ala
    1145                 1150                 1155

Ser Arg  Gly Gly Gln Arg Gln  Gly Gly Val Val Ala  Ser Leu Arg
    1160                 1165                 1170

Phe Pro  Arg Val Ala Gln Gln  Pro Leu Ile Asn
    1175                 1180


<210> SEQ ID NO 13
<211> LENGTH: 1156
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Met Ala Ser Leu Leu Pro Leu Leu Cys Leu Cys Val Val Ala Ala His
1               5                   10                  15
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Leu Ala Gly Ala Arg Asp Ala Thr Pro Thr Glu Glu Pro Met Ala Thr
            20                  25                  30

Ala Leu Gly Leu Glu Arg Arg Ser Val Tyr Thr Gly Gln Pro Ser Pro
        35                  40                  45

Ala Leu Glu Asp Trp Glu Glu Ala Ser Glu Trp Thr Ser Trp Phe Asn
    50                  55                  60

Val Asp His Pro Gly Gly Asp Gly Asp Phe Glu Ser Leu Ala Ala Ile
65                  70                  75                  80

Arg Phe Tyr Tyr Gly Pro Ala Arg Val Cys Pro Arg Pro Leu Ala Leu
                85                  90                  95

Glu Ala Arg Thr Thr Asp Trp Ala Leu Pro Ser Ala Val Gly Glu Arg
            100                 105                 110

Val His Leu Asn Pro Thr Arg Gly Phe Trp Cys Leu Asn Arg Glu Gln
        115                 120                 125

Pro Arg Gly Arg Arg Cys Ser Asn Tyr His Val Arg Phe Arg Cys Pro
    130                 135                 140

Leu Glu Ala Ser Trp Gly Ala Trp Gly Pro Trp Gly Pro Cys Ser Gly
145                 150                 155                 160

Ser Cys Gly Pro Gly Arg Arg Leu Arg Arg Arg His Cys Pro Ser Pro
                165                 170                 175

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

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

His Ile Leu Leu Gly Ser Val Val Thr Pro Ser Gly Gln Pro Leu Leu
    210                 215                 220

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

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

Ala Asn Ile Arg Ala Gln Met Asp Gly Phe Ser Ala Gly Glu Ala Gln
            260                 265                 270

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

Leu Glu Lys Pro Tyr Leu Val Lys His Pro Glu Ser Arg Val Arg Glu
    290                 295                 300

Ala Gly Gln Asn Val Thr Phe Cys Cys Lys Ala Ser Gly Thr Pro Met
305                 310                 315                 320

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

Ala His Gly Tyr Gly Ala His Leu Glu Leu Arg Gly Leu Arg Pro Asp
            340                 345                 350

Gln Ala Gly Ile Tyr His Cys Lys Ala Trp Asn Glu Ala Gly Ala Val
        355                 360                 365

Arg Ser Gly Thr Ala Arg Leu Thr Val Leu Ala Pro Gly Gln Pro Ala
    370                 375                 380

Cys Asp Pro Arg Pro Arg Glu Tyr Leu Ile Lys Leu Pro Glu Asp Cys
385                 390                 395                 400

Gly Gln Pro Gly Ser Gly Pro Ala Tyr Leu Asp Val Gly Leu Cys Pro
                405                 410                 415

Asp Thr Arg Cys Pro Ser Leu Ala Gly Ser Ser Pro Arg Cys Gly Asp
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            420                 425                 430

Ala Ser Ser Arg Cys Cys Ser Val Arg Arg Leu Glu Arg Arg Glu Ile
        435                 440                 445

His Cys Pro Gly Tyr Val Leu Pro Val Lys Val Val Ala Glu Cys Gly
    450                 455                 460

Cys Gln Lys Cys Leu Pro Pro Arg Gly Leu Val Arg Gly Arg Val Val
465                 470                 475                 480

Ala Ala Asp Ser Gly Glu Pro Leu Arg Phe Ala Arg Ile Leu Leu Gly
                485                 490                 495

Gln Glu Pro Ile Gly Phe Thr Ala Tyr Gln Gly Asp Phe Thr Ile Glu
            500                 505                 510

Val Pro Pro Ser Thr Gln Arg Leu Val Val Thr Phe Val Asp Pro Ser
        515                 520                 525

Gly Glu Phe Met Asp Ala Val Arg Val Leu Pro Phe Asp Pro Arg Gly
    530                 535                 540

Ala Gly Val Tyr His Glu Val Lys Ala Met Arg Lys Lys Ala Pro Val
545                 550                 555                 560

Ile Leu His Thr Ser Gln Ser Asn Thr Ile Pro Leu Gly Glu Leu Glu
                565                 570                 575

Asp Glu Ala Pro Leu Gly Glu Leu Val Leu Pro Ser Gly Ala Phe Arg
            580                 585                 590

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

Phe Val Asp Pro Arg Asp Leu Thr Ser Ala Ala Ser Ala Pro Ser Asp
    610                 615                 620

Leu Arg Phe Val Asp Ser Asp Gly Glu Leu Ala Pro Leu Arg Thr Tyr
625                 630                 635                 640

Gly Met Phe Ser Val Asp Leu Arg Ala Pro Gly Ser Ala Glu Gln Leu
                645                 650                 655

Gln Val Gly Pro Val Ala Val Arg Val Ala Ala Ser Gln Ile His Met
            660                 665                 670

Pro Gly His Val Glu Ala Leu Lys Leu Trp Ser Leu Asn Pro Glu Thr
        675                 680                 685

Gly Leu Trp Glu Glu Glu Ser Gly Phe Arg Arg Glu Gly Ser Ser Gly
    690                 695                 700

Pro Arg Val Arg Arg Glu Glu Arg Val Phe Leu Val Gly Asn Val Glu
705                 710                 715                 720

Ile Arg Glu Arg Arg Leu Phe Asn Leu Asp Val Pro Glu Arg Arg Arg
                725                 730                 735

Cys Phe Val Lys Val Arg Ala Tyr Ala Asn Asp Lys Phe Thr Pro Ser
            740                 745                 750

Glu Gln Val Glu Gly Val Val Val Thr Leu Val Asn Leu Glu Pro Ala
        755                 760                 765

Pro Gly Phe Ser Ala Asn Pro Arg Ala Trp Gly Arg Phe Asp Ser Ala
    770                 775                 780

Val Thr Gly Pro Asn Gly Ala Cys Leu Pro Ala Phe Cys Asp Ala Asp
785                 790                 795                 800

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

Glu Leu Glu Pro Ala Pro Ser Leu Pro Arg Pro Leu Pro Ala Thr Val
            820                 825                 830
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Gly Val Thr Gln Pro Tyr Leu Asp Arg Leu Gly Tyr Arg Arg Thr Asp
        835                 840                 845

His Asp Asp Pro Ala Phe Lys Arg Asn Gly Phe Arg Ile Asn Leu Ala
    850                 855                 860

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

Trp Arg Ser Leu Arg Glu Cys Gln Gly Ala Pro Val Thr Ala Ser His
                885                 890                 895

Phe Arg Phe Ala Arg Val Glu Ala Asp Lys Tyr Glu Tyr Asn Val Val
            900                 905                 910

Pro Phe Arg Glu Gly Thr Pro Ala Ser Trp Thr Gly Asp Leu Leu Ala
        915                 920                 925

Trp Trp Pro Asn Pro Gln Glu Phe Arg Ala Cys Phe Leu Lys Val Lys
    930                 935                 940

Ile Gln Gly Pro Gln Glu Tyr Met Val Arg Ser His Asn Ala Gly Gly
945                 950                 955                 960

Ser His Pro Arg Thr Arg Gly Gln Leu Tyr Gly Leu Arg Asp Ala Arg
                965                 970                 975

Ser Val Arg Asp Pro Glu Arg Pro Gly Thr Ser Ala Ala Cys Val Glu
            980                 985                 990

Phe Lys Cys Ser Gly Met Leu Phe  Asp Gln Arg Gln Val  Asp Arg Thr
        995                 1000                 1005

Leu Val  Thr Ile Met Pro Gln  Gly Ser Cys Arg Arg  Val Ala Val
    1010                 1015                 1020

Asn Gly  Leu Leu Arg Asp Tyr  Leu Thr Arg His Pro  Pro Pro Val
    1025                 1030                 1035

Pro Ala  Glu Asp Pro Ala Ala  Phe Ser Met Leu Ala  Pro Leu Asp
    1040                 1045                 1050

Pro Leu  Gly His Asn Tyr Gly  Val Tyr Thr Val Thr  Asp Gln Ser
    1055                 1060                 1065

Pro Arg  Leu Ala Lys Glu Ile  Ala Ile Gly Arg Cys  Phe Asp Gly
    1070                 1075                 1080

Ser Ser  Asp Gly Phe Ser Arg  Glu Met Lys Ala Asp  Ala Gly Thr
    1085                 1090                 1095

Ala Val  Thr Phe Gln Cys Arg  Glu Pro Pro Ala Gly  Arg Pro Ser
    1100                 1105                 1110

Leu Phe  Gln Arg Leu Leu Glu  Ser Pro Ala Thr Ala  Leu Gly Asp
    1115                 1120                 1125

Ile Arg  Arg Glu Met Ser Glu  Ala Ala Gln Ala Gln  Ala Arg Ala
    1130                 1135                 1140

Ser Gly  Pro Leu Arg Thr Arg  Arg Gly Arg Val Arg  Gln
    1145                 1150                 1155


<210> SEQ ID NO 14
<211> LENGTH: 197
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Ala Lys Asn Gly Leu Val Ile Cys Ile Leu Val Ile Thr Leu Leu
1               5                   10                  15

Leu Asp Gln Thr Thr Ser His Thr Ser Arg Leu Lys Ala Arg Lys His
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            20                  25                  30

Ser Lys Arg Arg Val Arg Asp Lys Asp Gly Asp Leu Lys Thr Gln Ile
        35                  40                  45

Glu Lys Leu Trp Thr Glu Val Asn Ala Leu Lys Glu Ile Gln Ala Leu
    50                  55                  60

Gln Thr Val Cys Leu Arg Gly Thr Lys Val His Lys Lys Cys Tyr Leu
65                  70                  75                  80

Ala Ser Glu Gly Leu Lys His Phe His Glu Ala Asn Glu Asp Cys Ile
                85                  90                  95

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

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

Trp Leu Gly Ile Asn Asp Met Val Thr Glu Gly Lys Phe Val Asp Val
    130                 135                 140

Asn Gly Ile Ala Ile Ser Phe Leu Asn Trp Asp Arg Ala Gln Pro Asn
145                 150                 155                 160

Gly Gly Lys Arg Glu Asn Cys Val Leu Phe Ser Gln Ser Ala Gln Gly
                165                 170                 175

Lys Trp Ser Asp Glu Ala Cys Arg Ser Ser Lys Arg Tyr Ile Cys Glu
            180                 185                 190

Phe Thr Ile Pro Gln
        195


<210> SEQ ID NO 15
<211> LENGTH: 742
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Lys Asp Asp Phe Ala Glu Glu Glu Glu Val Gln Ser Phe Gly Tyr
1               5                   10                  15

Lys Arg Phe Gly Ile Gln Glu Gly Thr Gln Cys Thr Lys Cys Lys Asn
            20                  25                  30

Asn Trp Ala Leu Lys Phe Ser Ile Ile Leu Leu Tyr Ile Leu Cys Ala
        35                  40                  45

Leu Leu Thr Ile Thr Val Ala Ile Leu Gly Tyr Lys Val Val Glu Lys
    50                  55                  60

Met Asp Asn Val Thr Gly Gly Met Glu Thr Ser Arg Gln Thr Tyr Asp
65                  70                  75                  80

Asp Lys Leu Thr Ala Val Glu Ser Asp Leu Lys Lys Leu Gly Asp Gln
                85                  90                  95

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

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

Thr Ser Lys Asn Lys Asp Thr Leu Glu Lys Leu Gln Ala Ser Gly Asp
    130                 135                 140

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

Ser Phe Leu Ile Thr Thr Val Asn Lys Thr Leu Gln Ala Tyr Asn Gly
                165                 170                 175
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Tyr Val Thr Asn Leu Gln Gln Asp Thr Ser Val Leu Gln Gly Asn Leu
            180                 185                 190

Gln Asn Gln Met Tyr Ser His Asn Val Val Ile Met Asn Leu Asn Asn
        195                 200                 205

Leu Asn Leu Thr Gln Val Gln Gln Arg Asn Leu Ile Thr Asn Leu Gln
    210                 215                 220

Arg Ser Val Asp Asp Thr Ser Gln Ala Ile Gln Arg Ile Lys Asn Asp
225                 230                 235                 240

Phe Gln Asn Leu Gln Gln Val Phe Leu Gln Ala Lys Lys Asp Thr Asp
                245                 250                 255

Trp Leu Lys Glu Lys Val Gln Ser Leu Gln Thr Leu Ala Ala Asn Asn
            260                 265                 270

Ser Ala Leu Ala Lys Ala Asn Asn Asp Thr Leu Glu Asp Met Asn Ser
        275                 280                 285

Gln Leu Asn Ser Phe Thr Gly Gln Met Glu Asn Ile Thr Thr Ile Ser
    290                 295                 300

Gln Ala Asn Glu Gln Asn Leu Lys Asp Leu Gln Asp Leu His Lys Asp
305                 310                 315                 320

Ala Glu Asn Arg Thr Ala Ile Lys Phe Asn Gln Leu Glu Glu Arg Phe
                325                 330                 335

Gln Leu Phe Glu Thr Asp Ile Val Asn Ile Ile Ser Asn Ile Ser Tyr
            340                 345                 350

Thr Ala His His Leu Arg Thr Leu Thr Ser Asn Leu Asn Glu Val Arg
        355                 360                 365

Thr Thr Cys Thr Asp Thr Leu Thr Lys His Thr Asp Asp Leu Thr Ser
    370                 375                 380

Leu Asn Asn Thr Leu Ala Asn Ile Arg Leu Asp Ser Val Ser Leu Arg
385                 390                 395                 400

Met Gln Gln Asp Leu Met Arg Ser Arg Leu Asp Thr Glu Val Ala Asn
                405                 410                 415

Leu Ser Val Ile Met Glu Glu Met Lys Leu Val Asp Ser Lys His Gly
            420                 425                 430

Gln Leu Ile Lys Asn Phe Thr Ile Leu Gln Gly Pro Pro Gly Pro Arg
        435                 440                 445

Gly Pro Arg Gly Asp Arg Gly Ser Gln Gly Pro Pro Gly Pro Thr Gly
    450                 455                 460

Asn Lys Gly Gln Lys Gly Glu Lys Gly Glu Pro Gly Pro Pro Gly Pro
465                 470                 475                 480

Ala Gly Glu Arg Gly Pro Ile Gly Pro Ala Gly Pro Pro Gly Glu Arg
                485                 490                 495

Gly Gly Lys Gly Ser Lys Gly Ser Gln Gly Pro Lys Gly Ser Arg Gly
            500                 505                 510

Ser Pro Gly Lys Pro Gly Pro Gln Gly Pro Ser Gly Asp Pro Gly Pro
        515                 520                 525

Pro Gly Pro Pro Gly Lys Glu Gly Leu Pro Gly Pro Gln Gly Pro Pro
    530                 535                 540

Gly Phe Gln Gly Leu Gln Gly Thr Val Gly Glu Pro Gly Val Pro Gly
545                 550                 555                 560

Pro Arg Gly Leu Pro Gly Leu Pro Gly Val Pro Gly Met Pro Gly Pro
                565                 570                 575

Lys Gly Pro Pro Gly Pro Pro Gly Pro Ser Gly Ala Val Val Pro Leu
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            580                 585                 590

Ala Leu Gln Asn Glu Pro Thr Pro Ala Pro Glu Asp Asn Gly Cys Pro
        595                 600                 605

Pro His Trp Lys Asn Phe Thr Asp Lys Cys Tyr Tyr Phe Ser Val Glu
    610                 615                 620

Lys Glu Ile Phe Glu Asp Ala Lys Leu Phe Cys Glu Asp Lys Ser Ser
625                 630                 635                 640

His Leu Val Phe Ile Asn Thr Arg Glu Glu Gln Gln Trp Ile Lys Lys
                645                 650                 655

Gln Met Val Gly Arg Glu Ser His Trp Ile Gly Leu Thr Asp Ser Glu
            660                 665                 670

Arg Glu Asn Glu Trp Lys Trp Leu Asp Gly Thr Ser Pro Asp Tyr Lys
        675                 680                 685

Asn Trp Lys Ala Gly Gln Pro Asp Asn Trp Gly His Gly His Gly Pro
    690                 695                 700

Gly Glu Asp Cys Ala Gly Leu Ile Tyr Ala Gly Gln Trp Asn Asp Phe
705                 710                 715                 720

Gln Cys Glu Asp Val Asn Asn Phe Ile Cys Glu Lys Asp Arg Glu Thr
                725                 730                 735

Val Leu Ser Ser Ala Leu
            740


<210> SEQ ID NO 16
<211> LENGTH: 661
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Ala Pro Ser Ala Asp Pro Gly Met Ser Arg Met Leu Pro Phe Leu
1               5                   10                  15

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

Pro Met Phe Thr Ala Val Thr Asn Ser Val Leu Pro Pro Asp Tyr Asp
        35                  40                  45

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

His Asp Gly Asp Phe Glu Ile Val Val Ala Gly Tyr Asn Gly Pro Asn
65                  70                  75                  80

Leu Val Leu Lys Tyr Asp Arg Ala Gln Lys Arg Leu Val Asn Ile Ala
                85                  90                  95

Val Asp Glu Arg Ser Ser Pro Tyr Tyr Ala Leu Arg Asp Arg Gln Gly
            100                 105                 110

Asn Ala Ile Gly Val Thr Ala Cys Asp Ile Asp Gly Asp Gly Arg Glu
        115                 120                 125

Glu Ile Tyr Phe Leu Asn Thr Asn Asn Ala Phe Ser Gly Val Ala Thr
    130                 135                 140

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

Leu Ser Asp Glu Val Asn Val Ala Arg Gly Val Ala Ser Leu Phe Ala
                165                 170                 175

Gly Arg Ser Val Ala Cys Val Asp Arg Lys Gly Ser Gly Arg Tyr Ser
            180                 185                 190
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Ile Tyr Ile Ala Asn Tyr Ala Tyr Gly Asn Val Gly Pro Asp Ala Leu
        195                 200                 205

Ile Glu Met Asp Pro Glu Ala Ser Asp Leu Ser Arg Gly Ile Leu Ala
    210                 215                 220

Leu Arg Asp Val Ala Ala Glu Ala Gly Val Ser Lys Tyr Thr Gly Gly
225                 230                 235                 240

Arg Gly Val Ser Val Gly Pro Ile Leu Ser Ser Ser Ala Ser Asp Ile
                245                 250                 255

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

Asp Gly Thr Phe Val Asp Ala Ala Ala Ser Ala Gly Val Asp Asp Pro
        275                 280                 285

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

Lys Val Asp Ile Val Tyr Gly Asn Trp Asn Gly Pro His Arg Leu Tyr
305                 310                 315                 320

Leu Gln Met Ser Thr His Gly Lys Val Arg Phe Arg Asp Ile Ala Ser
                325                 330                 335

Pro Lys Phe Ser Met Pro Ser Pro Val Arg Thr Val Ile Thr Ala Asp
            340                 345                 350

Phe Asp Asn Asp Gln Glu Leu Glu Ile Phe Phe Asn Asn Ile Ala Tyr
        355                 360                 365

Arg Ser Ser Ser Ala Asn Arg Leu Phe Arg Val Ile Arg Arg Glu His
    370                 375                 380

Gly Asp Pro Leu Ile Glu Glu Leu Asn Pro Gly Asp Ala Leu Glu Pro
385                 390                 395                 400

Glu Gly Arg Gly Thr Gly Gly Val Val Thr Asp Phe Asp Gly Asp Gly
                405                 410                 415

Met Leu Asp Leu Ile Leu Ser His Gly Glu Ser Met Ala Gln Pro Leu
            420                 425                 430

Ser Val Phe Arg Gly Asn Gln Gly Phe Asn Asn Asn Trp Leu Arg Val
        435                 440                 445

Val Pro Arg Thr Arg Phe Gly Ala Phe Ala Arg Gly Ala Lys Val Val
    450                 455                 460

Leu Tyr Thr Lys Lys Ser Gly Ala His Leu Arg Ile Ile Asp Gly Gly
465                 470                 475                 480

Ser Gly Tyr Leu Cys Glu Met Glu Pro Val Ala His Phe Gly Leu Gly
                485                 490                 495

Lys Asp Glu Ala Ser Ser Val Glu Val Thr Trp Pro Asp Gly Lys Met
            500                 505                 510

Val Ser Arg Asn Val Ala Ser Gly Glu Met Asn Ser Val Leu Glu Ile
        515                 520                 525

Leu Tyr Pro Arg Asp Glu Asp Thr Leu Gln Asp Pro Ala Pro Leu Glu
    530                 535                 540

Cys Gly Gln Gly Phe Ser Gln Gln Glu Asn Gly His Cys Met Asp Thr
545                 550                 555                 560

Asn Glu Cys Ile Gln Phe Pro Phe Val Cys Pro Arg Asp Lys Pro Val
                565                 570                 575

Cys Val Asn Thr Tyr Gly Ser Tyr Arg Cys Arg Thr Asn Lys Lys Cys
            580                 585                 590

Ser Arg Gly Tyr Glu Pro Asn Glu Asp Gly Thr Ala Cys Val Gly Thr
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        595                 600                 605

Leu Gly Gln Ser Pro Gly Pro Arg Pro Thr Thr Pro Thr Ala Ala Ala
    610                 615                 620

Ala Thr Ala Ala Ala Ala Ala Ala Ala Gly Ala Ala Thr Ala Ala Pro
625                 630                 635                 640

Val Leu Val Asp Gly Asp Leu Asn Leu Gly Ser Val Val Lys Glu Ser
                645                 650                 655

Cys Glu Pro Ser Cys
            660


<210> SEQ ID NO 17
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

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

Ala Pro Ala Ala Arg Pro Thr Pro Pro Thr Cys Tyr Ser Arg Met Arg
            20                  25                  30

Ala Leu Ser Gln Glu Ile Thr Arg Asp Phe Asn Leu Leu Gln Val Ser
        35                  40                  45

Glu Pro Ser Glu Pro Cys Val Arg Tyr Leu Pro Arg Leu Tyr Leu Asp
    50                  55                  60

Ile His Asn Tyr Cys Val Leu Asp Lys Leu Arg Asp Phe Val Ala Ser
65                  70                  75                  80

Pro Pro Cys Trp Lys Val Ala Gln Val Asp Ser Leu Lys Asp Lys Ala
                85                  90                  95

Arg Lys Leu Tyr Thr Ile Met Asn Ser Phe Cys Arg Arg Asp Leu Val
            100                 105                 110

Phe Leu Leu Asp Asp Cys Asn Ala Leu Glu Tyr Pro Ile Pro Val Thr
        115                 120                 125

Thr Val Leu Pro Asp Arg Gln Arg
    130                 135


<210> SEQ ID NO 18
<211> LENGTH: 658
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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

Cys Ser Leu Ser Pro Thr Ser Leu Ala Glu Thr Val His Cys Asp Leu
            20                  25                  30

Gln Pro Val Gly Pro Glu Arg Gly Glu Val Thr Tyr Thr Thr Ser Gln
        35                  40                  45

Val Ser Lys Gly Cys Val Ala Gln Ala Pro Asn Ala Ile Leu Glu Val
    50                  55                  60

His Val Leu Phe Leu Glu Phe Pro Thr Gly Pro Ser Gln Leu Glu Leu
65                  70                  75                  80

Thr Leu Gln Ala Ser Lys Gln Asn Gly Thr Trp Pro Arg Glu Val Leu
                85                  90                  95

Leu Val Leu Ser Val Asn Ser Ser Val Phe Leu His Leu Gln Ala Leu
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            100                 105                 110

Gly Ile Pro Leu His Leu Ala Tyr Asn Ser Ser Leu Val Thr Phe Gln
        115                 120                 125

Glu Pro Pro Gly Val Asn Thr Thr Glu Leu Pro Ser Phe Pro Lys Thr
    130                 135                 140

Gln Ile Leu Glu Trp Ala Ala Glu Arg Gly Pro Ile Thr Ser Ala Ala
145                 150                 155                 160

Glu Leu Asn Asp Pro Gln Ser Ile Leu Leu Arg Leu Gly Gln Ala Gln
                165                 170                 175

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

Thr Leu Glu Trp Arg Pro Arg Thr Pro Ala Leu Val Arg Gly Cys His
        195                 200                 205

Leu Glu Gly Val Ala Gly His Lys Glu Ala His Ile Leu Arg Val Leu
    210                 215                 220

Pro Gly His Ser Ala Gly Pro Arg Thr Val Thr Val Lys Val Glu Leu
225                 230                 235                 240

Ser Cys Ala Pro Gly Asp Leu Asp Ala Val Leu Ile Leu Gln Gly Pro
                245                 250                 255

Pro Tyr Val Ser Trp Leu Ile Asp Ala Asn His Asn Met Gln Ile Trp
            260                 265                 270

Thr Thr Gly Glu Tyr Ser Phe Lys Ile Phe Pro Glu Lys Asn Ile Arg
        275                 280                 285

Gly Phe Lys Leu Pro Asp Thr Pro Gln Gly Leu Leu Gly Glu Ala Arg
    290                 295                 300

Met Leu Asn Ala Ser Ile Val Ala Ser Phe Val Glu Leu Pro Leu Ala
305                 310                 315                 320

Ser Ile Val Ser Leu His Ala Ser Ser Cys Gly Gly Arg Leu Gln Thr
                325                 330                 335

Ser Pro Ala Pro Ile Gln Thr Thr Pro Pro Lys Asp Thr Cys Ser Pro
            340                 345                 350

Glu Leu Leu Met Ser Leu Ile Gln Thr Lys Cys Ala Asp Asp Ala Met
        355                 360                 365

Thr Leu Val Leu Lys Lys Glu Leu Val Ala His Leu Lys Cys Thr Ile
    370                 375                 380

Thr Gly Leu Thr Phe Trp Asp Pro Ser Cys Glu Ala Glu Asp Arg Gly
385                 390                 395                 400

Asp Lys Phe Val Leu Arg Ser Ala Tyr Ser Ser Cys Gly Met Gln Val
                405                 410                 415

Ser Ala Ser Met Ile Ser Asn Glu Ala Val Val Asn Ile Leu Ser Ser
            420                 425                 430

Ser Ser Pro Gln Arg Lys Lys Val His Cys Leu Asn Met Asp Ser Leu
        435                 440                 445

Ser Phe Gln Leu Gly Leu Tyr Leu Ser Pro His Phe Leu Gln Ala Ser
    450                 455                 460

Asn Thr Ile Glu Pro Gly Gln Gln Ser Phe Val Gln Val Arg Val Ser
465                 470                 475                 480

Pro Ser Val Ser Glu Phe Leu Leu Gln Leu Asp Ser Cys His Leu Asp
                485                 490                 495

Leu Gly Pro Glu Gly Gly Thr Val Glu Leu Ile Gln Gly Arg Ala Ala
            500                 505                 510
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Lys Gly Asn Cys Val Ser Leu Leu Ser Pro Ser Pro Glu Gly Asp Pro
        515                 520                 525

Arg Phe Ser Phe Leu Leu His Phe Tyr Thr Val Pro Ile Pro Lys Thr
    530                 535                 540

Gly Thr Leu Ser Cys Thr Val Ala Leu Arg Pro Lys Thr Gly Ser Gln
545                 550                 555                 560

Asp Gln Glu Val His Arg Thr Val Phe Met Arg Leu Asn Ile Ile Ser
                565                 570                 575

Pro Asp Leu Ser Gly Cys Thr Ser Lys Gly Leu Val Leu Pro Ala Val
            580                 585                 590

Leu Gly Ile Thr Phe Gly Ala Phe Leu Ile Gly Ala Leu Leu Thr Ala
        595                 600                 605

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

Pro Val Val Ala Val Ala Ala Pro Ala Ser Ser Glu Ser Ser Ser Thr
625                 630                 635                 640

Asn His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Thr Ser Ser
                645                 650                 655

Met Ala


<210> SEQ ID NO 19
<211> LENGTH: 322
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Lys Thr Leu Ala Gly Leu Val Leu Gly Leu Val Ile Phe Asp Ala
1               5                   10                  15

Ala Val Thr Ala Pro Thr Leu Glu Ser Ile Asn Tyr Asp Ser Glu Thr
            20                  25                  30

Tyr Asp Ala Thr Leu Glu Asp Leu Asp Asn Leu Tyr Asn Tyr Glu Asn
        35                  40                  45

Ile Pro Val Asp Lys Val Glu Ile Glu Ile Ala Thr Val Met Pro Ser
    50                  55                  60

Gly Asn Arg Glu Leu Leu Thr Pro Pro Pro Gln Pro Glu Lys Ala Gln
65                  70                  75                  80

Glu Glu Glu Glu Glu Glu Glu Ser Thr Pro Arg Leu Ile Asp Gly Ser
                85                  90                  95

Ser Pro Gln Glu Pro Glu Phe Thr Gly Val Leu Gly Pro His Thr Asn
            100                 105                 110

Glu Asp Phe Pro Thr Cys Leu Leu Cys Thr Cys Ile Ser Thr Thr Val
        115                 120                 125

Tyr Cys Asp Asp His Glu Leu Asp Ala Ile Pro Pro Leu Pro Lys Asn
    130                 135                 140

Thr Ala Tyr Phe Tyr Ser Arg Phe Asn Arg Ile Lys Lys Ile Asn Lys
145                 150                 155                 160

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

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

Leu Arg Glu Leu Val Leu Arg Asp Asn Lys Ile Arg Gln Leu Pro Glu
        195                 200                 205
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Leu Pro Thr Thr Leu Thr Phe Ile Asp Ile Ser Asn Asn Arg Leu Gly
    210                 215                 220

Arg Lys Gly Ile Lys Gln Glu Ala Phe Lys Asp Met Tyr Asp Leu His
225                 230                 235                 240

His Leu Tyr Leu Thr Asp Asn Asn Leu Asp His Ile Pro Leu Pro Leu
                245                 250                 255

Pro Glu Asn Leu Arg Ala Leu His Leu Gln Asn Asn Asn Ile Leu Glu
            260                 265                 270

Met His Glu Asp Thr Phe Cys Asn Val Lys Asn Leu Thr Tyr Ile Arg
        275                 280                 285

Lys Ala Leu Glu Asp Ile Arg Leu Asp Gly Asn Pro Ile Asn Leu Ser
    290                 295                 300

Lys Thr Pro Gln Ala Tyr Met Cys Leu Pro Arg Leu Pro Val Gly Ser
305                 310                 315                 320

Leu Val


<210> SEQ ID NO 20
<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Leu Cys Gly Arg Pro Arg Ser Ser Ser Asp Asn Arg Asn Phe Leu
1               5                   10                  15

Arg Glu Arg Ala Gly Leu Ser Ser Ala Ala Val Gln Thr Arg Ile Gly
            20                  25                  30

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

Ala Pro Pro Ala Leu Pro Arg Gly Arg Pro Gly Thr Glu Gly Ser Thr
    50                  55                  60

Ser Leu Ser Ala Pro Ala Val Leu Val Val Ala Val Ala Val Val Val
65                  70                  75                  80

Val Val Val Ser Ala Val Ala Trp Ala Met Ala Asn Tyr Ile His Val
                85                  90                  95

Pro Pro Gly Ser Pro Glu Val Pro Lys Leu Asn Val Thr Val Gln Asp
            100                 105                 110

Gln Glu Glu His Arg Cys Arg Glu Gly Ala Leu Ser Leu Leu Gln His
        115                 120                 125

Leu Arg Pro His Trp Asp Pro Gln Glu Val Thr Leu Gln Leu Phe Thr
    130                 135                 140

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

Glu Asp Val Val Leu Val Arg Ile Tyr Gly Asn Lys Thr Glu Leu Leu
                165                 170                 175

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

Gly Cys Ala Pro Gln Leu Tyr Cys Thr Phe Asn Asn Gly Leu Cys Tyr
        195                 200                 205

Glu Phe Ile Gln Gly Glu Ala Leu Asp Pro Lys His Val Cys Asn Pro
    210                 215                 220

Ala Ile Phe Arg Leu Ile Ala Arg Gln Leu Ala Lys Ile His Ala Ile
225                 230                 235                 240
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```
His Ala His Asn Gly Trp Ile Pro Lys Ser Asn Leu Trp Leu Lys Met
                245                 250                 255

Gly Lys Tyr Phe Ser Leu Ile Pro Thr Gly Phe Ala Asp Glu Asp Ile
            260                 265                 270

Asn Lys Arg Phe Leu Ser Asp Ile Pro Ser Ser Gln Ile Leu Gln Glu
        275                 280                 285

Glu Met Thr Trp Met Lys Glu Ile Leu Ser Asn Leu Gly Ser Pro Val
    290                 295                 300

Val Leu Cys His Asn Asp Leu Leu Cys Lys Asn Ile Ile Tyr Asn Glu
305                 310                 315                 320

Lys Gln Gly Asp Val Gln Phe Ile Asp Tyr Glu Tyr Ser Gly Tyr Asn
                325                 330                 335

Tyr Leu Ala Tyr Asp Ile Gly Asn His Phe Asn Glu Phe Ala Gly Val
            340                 345                 350

Ser Asp Val Asp Tyr Ser Leu Tyr Pro Asp Arg Glu Leu Gln Ser Gln
        355                 360                 365

Trp Leu Arg Ala Tyr Leu Glu Ala Tyr Lys Glu Phe Lys Gly Phe Gly
    370                 375                 380

Thr Glu Val Thr Glu Lys Glu Val Glu Ile Leu Phe Ile Gln Val Asn
385                 390                 395                 400

Gln Phe Ala Leu Ala Ser His Phe Phe Trp Gly Leu Trp Ala Leu Ile
                405                 410                 415

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

Val Arg Phe Asn Gln Tyr Phe Lys Met Lys Pro Glu Val Thr Ala Leu
        435                 440                 445

Lys Val Pro Glu
    450
```

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<210> SEQ ID NO 21
<211> LENGTH: 660
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Gly Leu Gln Thr Thr Lys Trp Pro Ser His Gly Ala Phe Phe Leu
1               5                   10                  15

Lys Ser Trp Leu Ile Ile Ser Leu Gly Leu Tyr Ser Gln Val Ser Lys
            20                  25                  30

Leu Leu Ala Cys Pro Ser Val Cys Arg Cys Asp Arg Asn Phe Val Tyr
        35                  40                  45

Cys Asn Glu Arg Ser Leu Thr Ser Val Pro Leu Gly Ile Pro Glu Gly
    50                  55                  60

Val Thr Val Leu Tyr Leu His Asn Asn Gln Ile Asn Asn Ala Gly Phe
65                  70                  75                  80

Pro Ala Glu Leu His Asn Val Gln Ser Val His Thr Val Tyr Leu Tyr
                85                  90                  95

Gly Asn Gln Leu Asp Glu Phe Pro Met Asn Leu Pro Lys Asn Val Arg
            100                 105                 110

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

Leu Ala Gln Leu Leu Lys Leu Glu Glu Leu His Leu Asp Asp Asn Ser
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    130                 135                 140

Ile Ser Thr Val Gly Val Glu Asp Gly Ala Phe Arg Glu Ala Ile Ser
145                 150                 155                 160

Leu Lys Leu Leu Phe Leu Ser Lys Asn His Leu Ser Ser Val Pro Val
                165                 170                 175

Gly Leu Pro Val Asp Leu Gln Glu Leu Arg Val Asp Glu Asn Arg Ile
            180                 185                 190

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

Leu Ile Val Asp Gly Asn Leu Leu Thr Asn Lys Gly Ile Ala Glu Gly
    210                 215                 220

Thr Phe Ser His Leu Thr Lys Leu Lys Glu Phe Ser Ile Val Arg Asn
225                 230                 235                 240

Ser Leu Ser His Pro Pro Pro Asp Leu Pro Gly Thr His Leu Ile Arg
                245                 250                 255

Leu Tyr Leu Gln Asp Asn Gln Ile Asn His Ile Pro Leu Thr Ala Phe
            260                 265                 270

Ser Asn Leu Arg Lys Leu Glu Arg Leu Asp Ile Ser Asn Asn Gln Leu
        275                 280                 285

Arg Met Leu Thr Gln Gly Val Phe Asp Asn Leu Ser Asn Leu Lys Gln
    290                 295                 300

Leu Thr Ala Arg Asn Asn Pro Trp Phe Cys Asp Cys Ser Ile Lys Trp
305                 310                 315                 320

Val Thr Glu Trp Leu Lys Tyr Ile Pro Ser Ser Leu Asn Val Arg Gly
                325                 330                 335

Phe Met Cys Gln Gly Pro Glu Gln Val Arg Gly Met Ala Val Arg Glu
            340                 345                 350

Leu Asn Met Asn Leu Leu Ser Cys Pro Thr Thr Thr Pro Gly Leu Pro
        355                 360                 365

Leu Phe Thr Pro Ala Pro Ser Thr Ala Ser Pro Thr Thr Gln Pro Pro
    370                 375                 380

Thr Leu Ser Ile Pro Asn Pro Ser Arg Ser Tyr Thr Pro Pro Thr Pro
385                 390                 395                 400

Thr Thr Ser Lys Leu Pro Thr Ile Pro Asp Trp Asp Gly Arg Glu Arg
                405                 410                 415

Val Thr Pro Pro Ile Ser Glu Arg Ile Gln Leu Ser Ile His Phe Val
            420                 425                 430

Asn Asp Thr Ser Ile Gln Val Ser Trp Leu Ser Leu Phe Thr Val Met
        435                 440                 445

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

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

Val Asn Leu Glu Pro Arg Ser Thr Tyr Arg Ile Cys Leu Val Pro Leu
                485                 490                 495

Asp Ala Phe Asn Tyr Arg Ala Val Glu Asp Thr Ile Cys Ser Glu Ala
            500                 505                 510

Thr Thr His Ala Ser Tyr Leu Asn Asn Gly Ser Asn Thr Ala Ser Ser
        515                 520                 525

His Glu Gln Thr Thr Ser His Ser Met Gly Ser Pro Phe Leu Leu Ala
    530                 535                 540
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Gly Leu Ile Gly Gly Ala Val Ile Phe Val Leu Val Val Leu Leu Ser
545                 550                 555                 560

Val Phe Cys Trp His Met His Lys Lys Gly Arg Tyr Thr Ser Gln Lys
                565                 570                 575

Trp Lys Tyr Asn Arg Gly Arg Arg Lys Asp Asp Tyr Cys Glu Ala Gly
            580                 585                 590

Thr Lys Lys Asp Asn Ser Ile Leu Glu Met Thr Glu Thr Ser Phe Gln
        595                 600                 605

Ile Val Ser Leu Asn Asn Asp Gln Leu Leu Lys Gly Asp Phe Arg Leu
    610                 615                 620

Gln Pro Ile Tyr Thr Pro Asn Gly Gly Ile Asn Tyr Thr Asp Cys His
625                 630                 635                 640

Ile Pro Asn Asn Met Arg Tyr Cys Asn Ser Ser Val Pro Asp Leu Glu
                645                 650                 655

His Cys His Thr
            660


<210> SEQ ID NO 22
<211> LENGTH: 649
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Ile Ser Ala Ala Trp Ser Ile Phe Leu Ile Gly Thr Lys Ile Gly
1               5                   10                  15

Leu Phe Leu Gln Val Ala Pro Leu Ser Val Met Ala Lys Ser Cys Pro
            20                  25                  30

Ser Val Cys Arg Cys Asp Ala Gly Phe Ile Tyr Cys Asn Asp Arg Phe
        35                  40                  45

Leu Thr Ser Ile Pro Thr Gly Ile Pro Glu Asp Ala Thr Thr Leu Tyr
    50                  55                  60

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

Asn Leu Leu Lys Val Glu Arg Ile Tyr Leu Tyr His Asn Ser Leu Asp
                85                  90                  95

Glu Phe Pro Thr Asn Leu Pro Lys Tyr Val Lys Glu Leu His Leu Gln
            100                 105                 110

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

Tyr Leu Glu Glu Leu His Leu Asp Asp Asn Ser Val Ser Ala Val Ser
    130                 135                 140

Ile Glu Glu Gly Ala Phe Arg Asp Ser Asn Tyr Leu Arg Leu Leu Phe
145                 150                 155                 160

Leu Ser Arg Asn His Leu Ser Thr Ile Pro Trp Gly Leu Pro Arg Thr
                165                 170                 175

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

Pro Ser Leu Gln Gly Leu Thr Ser Leu Lys Arg Leu Val Leu Asp Gly
        195                 200                 205

Asn Leu Leu Asn Asn His Gly Leu Gly Asp Lys Val Phe Phe Asn Leu
    210                 215                 220

Val Asn Leu Thr Glu Leu Ser Leu Val Arg Asn Ser Leu Thr Ala Ala
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225                 230                 235                 240

Pro Val Asn Leu Pro Gly Thr Asn Leu Arg Lys Leu Tyr Leu Gln Asp
                245                 250                 255

Asn His Ile Asn Arg Val Pro Pro Asn Ala Phe Ser Tyr Leu Arg Gln
            260                 265                 270

Leu Tyr Arg Leu Asp Met Ser Asn Asn Asn Leu Ser Asn Leu Pro Gln
        275                 280                 285

Gly Ile Phe Asp Asp Leu Asp Asn Ile Thr Gln Leu Ile Leu Arg Asn
    290                 295                 300

Asn Pro Trp Tyr Cys Gly Cys Lys Met Lys Trp Val Arg Asp Trp Leu
305                 310                 315                 320

Gln Ser Leu Pro Val Lys Val Asn Val Arg Gly Leu Met Cys Gln Ala
                325                 330                 335

Pro Glu Lys Val Arg Gly Met Ala Ile Lys Asp Leu Asn Ala Glu Leu
            340                 345                 350

Phe Asp Cys Lys Asp Ser Gly Ile Val Ser Thr Ile Gln Ile Thr Thr
        355                 360                 365

Ala Ile Pro Asn Thr Val Tyr Pro Ala Gln Gly Gln Trp Pro Ala Pro
    370                 375                 380

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

Gln Thr Thr Gly Ser Pro Ser Arg Lys Thr Ile Thr Ile Thr Val Lys
                405                 410                 415

Ser Val Thr Ser Asp Thr Ile His Ile Ser Trp Lys Leu Ala Leu Pro
            420                 425                 430

Met Thr Ala Leu Arg Leu Ser Trp Leu Lys Leu Gly His Ser Pro Ala
        435                 440                 445

Phe Gly Ser Ile Thr Glu Thr Ile Val Thr Gly Glu Arg Ser Glu Tyr
    450                 455                 460

Leu Val Thr Ala Leu Glu Pro Asp Ser Pro Tyr Lys Val Cys Met Val
465                 470                 475                 480

Pro Met Glu Thr Ser Asn Leu Tyr Leu Phe Asp Glu Thr Pro Val Cys
                485                 490                 495

Ile Glu Thr Glu Thr Ala Pro Leu Arg Met Tyr Asn Pro Thr Thr Thr
            500                 505                 510

Leu Asn Arg Glu Gln Glu Lys Glu Pro Tyr Lys Asn Pro Asn Leu Pro
        515                 520                 525

Leu Ala Ala Ile Ile Gly Gly Ala Val Ala Leu Val Thr Ile Ala Leu
    530                 535                 540

Leu Ala Leu Val Cys Trp Tyr Val His Arg Asn Gly Ser Leu Phe Ser
545                 550                 555                 560

Arg Asn Cys Ala Tyr Ser Lys Gly Arg Arg Arg Lys Asp Asp Tyr Ala
                565                 570                 575

Glu Ala Gly Thr Lys Lys Asp Asn Ser Ile Leu Glu Ile Arg Glu Thr
            580                 585                 590

Ser Phe Gln Met Leu Pro Ile Ser Asn Glu Pro Ile Ser Lys Glu Glu
        595                 600                 605

Phe Val Ile His Thr Ile Phe Pro Pro Asn Gly Met Asn Leu Tyr Lys
    610                 615                 620

Asn Asn His Ser Glu Ser Ser Ser Asn Arg Ser Tyr Arg Asp Ser Gly
625                 630                 635                 640
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Ile Pro Asp Ser Asp His Ser His Ser
                645


<210> SEQ ID NO 23
<211> LENGTH: 354
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

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

His Leu Ser Asp Asn Tyr Thr Leu Asp His Asp Arg Ala Ile His Ile
            20                  25                  30

Gln Ala Glu Asn Gly Pro His Leu Leu Val Glu Ala Glu Gln Ala Lys
        35                  40                  45

Val Phe Ser His Arg Gly Gly Asn Val Thr Leu Pro Cys Lys Phe Tyr
    50                  55                  60

Arg Asp Pro Thr Ala Phe Gly Ser Gly Ile His Lys Ile Arg Ile Lys
65                  70                  75                  80

Trp Thr Lys Leu Thr Ser Asp Tyr Leu Lys Glu Val Asp Val Phe Val
                85                  90                  95

Ser Met Gly Tyr His Lys Lys Thr Tyr Gly Gly Tyr Gln Gly Arg Val
            100                 105                 110

Phe Leu Lys Gly Gly Ser Asp Ser Asp Ala Ser Leu Val Ile Thr Asp
        115                 120                 125

Leu Thr Leu Glu Asp Tyr Gly Arg Tyr Lys Cys Glu Val Ile Glu Gly
    130                 135                 140

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

Phe Pro Tyr Phe Pro Arg Leu Gly Arg Tyr Asn Leu Asn Phe His Glu
                165                 170                 175

Ala Gln Gln Ala Cys Leu Asp Gln Asp Ala Val Ile Ala Ser Phe Asp
            180                 185                 190

Gln Leu Tyr Asp Ala Trp Arg Gly Gly Leu Asp Trp Cys Asn Ala Gly
        195                 200                 205

Trp Leu Ser Asp Gly Ser Val Gln Tyr Pro Ile Thr Lys Pro Arg Glu
    210                 215                 220

Pro Cys Gly Gly Gln Asn Thr Val Pro Gly Val Arg Asn Tyr Gly Phe
225                 230                 235                 240

Trp Asp Lys Asp Lys Ser Arg Tyr Asp Val Phe Cys Phe Thr Ser Asn
                245                 250                 255

Phe Asn Gly Arg Phe Tyr Tyr Leu Ile His Pro Thr Lys Leu Thr Tyr
            260                 265                 270

Asp Glu Ala Val Gln Ala Cys Leu Asn Asp Gly Ala Gln Ile Ala Lys
        275                 280                 285

Val Gly Gln Ile Phe Ala Ala Trp Lys Ile Leu Gly Tyr Asp Arg Cys
    290                 295                 300

Asp Ala Gly Trp Leu Ala Asp Gly Ser Val Arg Tyr Pro Ile Ser Arg
305                 310                 315                 320

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

Phe Pro Asp Lys Lys His Lys Leu Tyr Gly Val Tyr Cys Phe Arg Ala
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            340                 345                 350

Tyr Asn


<210> SEQ ID NO 24
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

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

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

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

Asn Pro Ser Glu Gln Cys Cys Tyr Asp Asp Ala Ile Leu Ser Leu Lys
    50                  55                  60

Glu Thr Arg Arg Cys Gly Ser Thr Cys Thr Phe Trp Pro Cys Phe Glu
65                  70                  75                  80

Leu Cys Cys Pro Glu Ser Phe Gly Pro Gln Gln Lys Phe Leu Val Lys
                85                  90                  95

Leu Arg Val Leu Gly Met Lys Ser Gln Cys His Leu Ser Pro Ile Ser
            100                 105                 110

Arg Ser Cys Thr Arg Asn Arg Arg His Val Leu Tyr Pro
        115                 120                 125


<210> SEQ ID NO 25
<211> LENGTH: 1263
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Met Pro Ala Arg Ile Gly Tyr Tyr Glu Ile Asp Arg Thr Ile Gly Lys
1               5                   10                  15

Gly Asn Phe Ala Val Val Lys Arg Ala Thr His Leu Val Thr Lys Ala
            20                  25                  30

Lys Val Ala Ile Lys Ile Ile Asp Lys Thr Gln Leu Asp Glu Glu Asn
        35                  40                  45

Leu Lys Lys Ile Phe Arg Glu Val Gln Ile Met Lys Met Leu Cys His
    50                  55                  60

Pro His Ile Ile Arg Leu Tyr Gln Val Met Glu Thr Glu Arg Met Ile
65                  70                  75                  80

Tyr Leu Val Thr Glu Tyr Ala Ser Gly Gly Glu Ile Phe Asp His Leu
                85                  90                  95

Val Ala His Gly Arg Met Ala Glu Lys Glu Ala Arg Arg Lys Phe Lys
            100                 105                 110

Gln Ile Val Thr Ala Val Tyr Phe Cys His Cys Arg Asn Ile Val His
        115                 120                 125

Arg Asp Leu Lys Ala Glu Asn Leu Leu Leu Asp Ala Asn Leu Asn Ile
    130                 135                 140

Lys Ile Ala Asp Phe Gly Phe Ser Asn Leu Phe Thr Pro Gly Gln Leu
145                 150                 155                 160

Leu Lys Thr Trp Cys Gly Ser Pro Pro Tyr Ala Ala Pro Glu Leu Phe
                165                 170                 175
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Glu Gly Lys Glu Tyr Asp Gly Pro Lys Val Asp Ile Trp Ser Leu Gly
            180                 185                 190

Val Val Leu Tyr Val Leu Val Cys Gly Ala Leu Pro Phe Asp Gly Ser
        195                 200                 205

Thr Leu Gln Asn Leu Arg Ala Arg Val Leu Ser Gly Lys Phe Arg Ile
    210                 215                 220

Pro Phe Phe Met Ser Thr Glu Cys Glu His Leu Ile Arg His Met Leu
225                 230                 235                 240

Val Leu Asp Pro Asn Lys Arg Leu Ser Met Glu Gln Ile Cys Lys His
                245                 250                 255

Lys Trp Met Lys Leu Gly Asp Ala Asp Pro Asn Phe Asp Arg Leu Ile
            260                 265                 270

Ala Glu Cys Gln Gln Leu Lys Glu Glu Arg Gln Val Asp Pro Leu Asn
        275                 280                 285

Glu Asp Val Leu Leu Ala Met Glu Asp Met Gly Leu Asp Lys Glu Gln
    290                 295                 300

Thr Leu Gln Ser Leu Arg Ser Asp Ala Tyr Asp His Tyr Ser Ala Ile
305                 310                 315                 320

Tyr Ser Leu Leu Cys Asp Arg His Lys Arg His Lys Thr Leu Arg Leu
                325                 330                 335

Gly Ala Leu Pro Ser Met Pro Arg Ala Leu Ala Phe Gln Ala Pro Val
            340                 345                 350

Asn Ile Gln Ala Glu Gln Ala Gly Thr Ala Met Asn Ile Ser Val Pro
        355                 360                 365

Gln Val Gln Leu Ile Asn Pro Glu Asn Gln Ile Val Glu Pro Asp Gly
    370                 375                 380

Thr Leu Asn Leu Asp Ser Asp Glu Gly Glu Glu Pro Ser Pro Glu Ala
385                 390                 395                 400

Leu Val Arg Tyr Leu Ser Met Arg Arg His Thr Val Gly Val Ala Asp
                405                 410                 415

Pro Arg Thr Glu Val Met Glu Asp Leu Gln Lys Leu Leu Pro Gly Phe
            420                 425                 430

Pro Gly Val Asn Pro Gln Ala Pro Phe Leu Gln Val Ala Pro Asn Val
        435                 440                 445

Asn Phe Met His Asn Leu Leu Pro Met Gln Asn Leu Gln Pro Thr Gly
    450                 455                 460

Gln Leu Glu Tyr Lys Glu Gln Ser Leu Leu Gln Pro Pro Thr Leu Gln
465                 470                 475                 480

Leu Leu Asn Gly Met Gly Pro Leu Gly Arg Arg Ala Ser Asp Gly Gly
                485                 490                 495

Ala Asn Ile Gln Leu His Ala Gln Gln Leu Leu Lys Arg Pro Arg Gly
            500                 505                 510

Pro Ser Pro Leu Val Thr Met Thr Pro Ala Val Pro Ala Val Thr Pro
        515                 520                 525

Val Asp Glu Glu Ser Ser Asp Gly Glu Pro Asp Gln Glu Ala Val Gln
    530                 535                 540

Ser Ser Thr Tyr Lys Asp Ser Asn Thr Leu His Leu Pro Thr Glu Arg
545                 550                 555                 560

Phe Ser Pro Val Arg Arg Phe Ser Asp Gly Ala Ala Ser Ile Gln Ala
                565                 570                 575
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Phe Lys Ala His Leu Glu Lys Met Gly Asn Asn Ser Ser Ile Lys Gln
            580                 585                 590

Leu Gln Gln Glu Cys Glu Gln Leu Gln Lys Met Tyr Gly Gly Gln Ile
        595                 600                 605

Asp Glu Arg Thr Leu Glu Lys Thr Gln Gln Gln His Met Leu Tyr Gln
    610                 615                 620

Gln Glu Gln His His Gln Ile Leu Gln Gln Gln Ile Gln Asp Ser Ile
625                 630                 635                 640

Cys Pro Pro Gln Pro Ser Pro Pro Leu Gln Ala Ala Cys Glu Asn Gln
                645                 650                 655

Pro Ala Leu Leu Thr His Gln Leu Gln Arg Leu Arg Ile Gln Pro Ser
            660                 665                 670

Ser Pro Pro Pro Asn His Pro Asn Asn His Leu Phe Arg Gln Pro Ser
        675                 680                 685

Asn Ser Pro Pro Pro Met Ser Ser Ala Met Ile Gln Pro His Gly Ala
    690                 695                 700

Ala Ser Ser Ser Gln Phe Gln Gly Leu Pro Ser Arg Ser Ala Ile Phe
705                 710                 715                 720

Gln Gln Gln Pro Glu Asn Cys Ser Ser Pro Pro Asn Val Ala Leu Thr
                725                 730                 735

Cys Leu Gly Met Gln Gln Pro Ala Gln Ser Gln Gln Val Thr Ile Gln
            740                 745                 750

Val Gln Glu Pro Val Asp Met Leu Ser Asn Met Pro Gly Thr Ala Ala
        755                 760                 765

Gly Ser Ser Gly Arg Gly Ile Ser Ile Ser Pro Ser Ala Gly Gln Met
    770                 775                 780

Gln Met Gln His Arg Thr Asn Leu Met Ala Thr Leu Ser Tyr Gly His
785                 790                 795                 800

Arg Pro Leu Ser Lys Gln Leu Ser Ala Asp Ser Ala Glu Ala His Ser
                805                 810                 815

Leu Asn Val Asn Arg Phe Ser Pro Ala Asn Tyr Asp Gln Ala His Leu
            820                 825                 830

His Pro His Leu Phe Ser Asp Gln Ser Arg Gly Ser Pro Ser Ser Tyr
        835                 840                 845

Ser Pro Ser Thr Gly Val Gly Phe Ser Pro Thr Gln Ala Leu Lys Val
    850                 855                 860

Pro Pro Leu Asp Gln Phe Pro Thr Phe Pro Pro Ser Ala His Gln Gln
865                 870                 875                 880

Pro Pro His Tyr Thr Thr Ser Ala Leu Gln Gln Ala Leu Leu Ser Pro
                885                 890                 895

Thr Pro Pro Asp Tyr Thr Arg His Gln Gln Val Pro His Ile Leu Gln
            900                 905                 910

Gly Leu Leu Ser Pro Arg His Ser Leu Thr Gly His Ser Asp Ile Arg
        915                 920                 925

Leu Pro Pro Thr Glu Phe Ala Gln Leu Ile Lys Arg Gln Gln Gln Gln
    930                 935                 940

Arg Gln Gln Gln Gln Gln Gln Gln Gln Gln Gln Glu Tyr Gln Glu Leu
945                 950                 955                 960

Phe Arg His Met Asn Gln Gly Asp Ala Gly Ser Leu Ala Pro Ser Leu
                965                 970                 975

Gly Gly Gln Ser Met Thr Glu Arg Gln Ala Leu Ser Tyr Gln Asn Ala
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            980                 985                 990

Asp Ser Tyr His His His Thr Ser  Pro Gln His Leu Leu  Gln Ile Arg
        995                 1000                1005

Ala Gln  Glu Cys Val Ser Gln  Ala Ser Ser Pro Thr  Pro Pro His
    1010                 1015                 1020

Gly Tyr  Ala His Gln Pro Ala  Leu Met His Ser Glu  Ser Met Glu
    1025                 1030                 1035

Glu Asp  Cys Ser Cys Glu Gly  Ala Lys Asp Gly Phe  Gln Asp Ser
    1040                 1045                 1050

Lys Ser  Ser Ser Thr Leu Thr  Lys Gly Cys His Asp  Ser Pro Leu
    1055                 1060                 1065

Leu Leu  Ser Thr Gly Gly Pro  Gly Asp Pro Glu Ser  Leu Leu Gly
    1070                 1075                 1080

Thr Val  Ser His Ala Gln Glu  Leu Gly Ile His Pro  Tyr Gly His
    1085                 1090                 1095

Gln Pro  Thr Ala Ala Phe Ser  Lys Asn Lys Val Pro  Ser Arg Glu
    1100                 1105                 1110

Pro Val  Ile Gly Asn Cys Met  Asp Arg Ser Ser Pro  Gly Gln Ala
    1115                 1120                 1125

Val Glu  Leu Pro Asp His Asn  Gly Leu Gly Tyr Pro  Ala Arg Pro
    1130                 1135                 1140

Ser Val  His Glu His His Arg  Pro Arg Ala Leu Gln  Arg His His
    1145                 1150                 1155

Thr Ile  Gln Asn Ser Asp Asp  Ala Tyr Val Gln Leu  Asp Asn Leu
    1160                 1165                 1170

Pro Gly  Met Ser Leu Val Ala  Gly Lys Ala Leu Ser  Ser Ala Arg
    1175                 1180                 1185

Met Ser  Asp Ala Val Leu Ser  Gln Ser Ser Leu Met  Gly Ser Gln
    1190                 1195                 1200

Gln Phe  Gln Asp Gly Glu Asn  Glu Glu Cys Gly Ala  Ser Leu Gly
    1205                 1210                 1215

Gly His  Glu His Pro Asp Leu  Ser Asp Gly Ser Gln  His Leu Asn
    1220                 1225                 1230

Ser Ser  Cys Tyr Pro Ser Thr  Cys Ile Thr Asp Ile  Leu Leu Ser
    1235                 1240                 1245

Tyr Lys  His Pro Glu Val Ser  Phe Ser Met Glu Gln  Ala Gly Val
    1250                 1255                 1260


<210> SEQ ID NO 26
<211> LENGTH: 356
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Met Gly Leu Met Val Arg Gly Gly Val Thr Cys Arg Ser Gln Glu Arg
1               5                   10                  15

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

Ala Ser Pro Tyr Cys Ser Phe Thr Gly Arg Ser Arg Ala Asp Ala Pro
        35                  40                  45

Ala Arg Ala Ala Gly Asn Gly Gln Pro Arg Leu Arg Ala Gln Val Asp
    50                  55                  60
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Leu Ser Ser Ala Ser Ser Val Leu Val Thr Val Leu Asp Ala Lys Ala
65                  70                  75                  80

Leu Pro Leu Thr Leu Leu Ser Trp Gly Ser Leu Cys Ala Thr Ala Gln
                85                  90                  95

Asn His Asn Asn Gln Glu Gly Ala Pro Ala Gln Pro Lys Gly Ser Met
            100                 105                 110

Ala Asn Gln Arg Ala Leu Arg Phe Pro Pro Pro Ser Gly Ser Pro Pro
        115                 120                 125

Gly Leu His Thr Arg Met Arg Leu Thr Ser Pro Pro Gln Pro His Phe
    130                 135                 140

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

Asp Trp Phe Gly Ser Asp Ser Arg Ala Val Arg Ala Leu Arg Leu Ile
                165                 170                 175

Gly Trp Ala Ser Arg Ser Leu His Pro Leu Pro Gly Ser Arg Asp Arg
            180                 185                 190

Ala His Pro Ala Ala Glu Glu Glu Asp Asp Pro Asp Arg Pro Ile Glu
        195                 200                 205

Phe Ser Ser Ser Lys Ala Asn Pro His Arg Trp Ser Val Gly His Thr
    210                 215                 220

Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser
225                 230                 235                 240

Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser
                245                 250                 255

Glu Ala Asp Gln Trp Leu Arg Gln Glu Gly Ser Arg Gln Pro Pro Phe
            260                 265                 270

Gly Phe Asp Val Thr Phe Ala Arg Asp Cys Pro Gly Tyr Ala Cys Val
        275                 280                 285

Leu Ser Thr Glu Gly Leu Gly Trp Trp Met Gly His Leu Ala Met Leu
    290                 295                 300

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

Arg Leu Ala Leu Asp Val Gln Gly Phe His Arg Gln Asp Phe Ser Asp
                325                 330                 335

Pro Trp Gly Arg Phe Gln Leu His Cys Met Leu Leu Asp Leu Pro Ser
            340                 345                 350

Leu Cys Ile Thr
        355


<210> SEQ ID NO 27
<211> LENGTH: 75
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Met Ser His Ile Gln Leu Leu Ser Ala Phe Glu Ser His Arg Thr Thr
1               5                   10                  15

Cys Arg Lys Asn Ser Arg Glu Phe Gly Lys Lys Gly Gly Glu Asp Arg
            20                  25                  30

Gln Lys Met His Phe Ser Phe Lys Lys Gln Glu Asn Val Arg Lys Ile
        35                  40                  45

Glu Gly Val Leu Lys Cys Val Cys Cys Cys Leu Thr Gln Val Asn Pro
    50                  55                  60
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Val Ala Gly His Ser Ala Leu Leu Ile Ala Ser
65                  70                  75


<210> SEQ ID NO 28
<211> LENGTH: 237
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Lys Gly Ile Leu Val Ala Gly Ile Thr Ala Val Leu Val Ala Ala
1               5                   10                  15

Val Glu Ser Leu Ser Cys Val Gln Cys Asn Ser Trp Glu Lys Ser Cys
            20                  25                  30

Val Asn Ser Ile Ala Ser Glu Cys Pro Ser His Ala Asn Thr Ser Cys
        35                  40                  45

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

Gln Asn Met Phe Cys Ser Ala Glu Asn Cys Ser Glu Glu Thr His Ile
65                  70                  75                  80

Thr Ala Phe Thr Val His Val Ser Ala Glu Glu His Phe His Phe Val
                85                  90                  95

Ser Gln Cys Cys Gln Gly Lys Glu Cys Ser Asn Thr Ser Asp Ala Leu
            100                 105                 110

Asp Pro Pro Leu Lys Asn Val Ser Ser Asn Ala Glu Cys Pro Ala Cys
        115                 120                 125

Tyr Glu Ser Asn Gly Thr Ser Cys Arg Gly Lys Pro Trp Lys Cys Tyr
    130                 135                 140

Glu Glu Glu Gln Cys Val Phe Leu Val Ala Glu Leu Lys Asn Asp Ile
145                 150                 155                 160

Glu Ser Lys Ser Leu Val Leu Lys Gly Cys Ser Asn Val Ser Asn Ala
                165                 170                 175

Thr Cys Gln Phe Leu Ser Gly Glu Asn Lys Thr Leu Gly Gly Val Ile
            180                 185                 190

Phe Arg Lys Phe Glu Cys Ala Asn Val Asn Ser Leu Thr Pro Thr Ser
        195                 200                 205

Ala Pro Thr Thr Ser His Asn Val Gly Ser Lys Ala Ser Leu Tyr Leu
    210                 215                 220

Leu Ala Leu Ala Ser Leu Leu Leu Arg Gly Leu Leu Pro
225                 230                 235


<210> SEQ ID NO 29
<211> LENGTH: 753
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Met Arg Pro Val Ser Val Trp Gln Trp Ser Pro Trp Gly Leu Leu Leu
1               5                   10                  15

Cys Leu Leu Cys Ser Ser Cys Leu Gly Ser Pro Ser Pro Ser Thr Gly
            20                  25                  30

Pro Glu Lys Lys Ala Gly Ser Gln Gly Leu Arg Phe Arg Leu Ala Gly
        35                  40                  45

Phe Pro Arg Lys Pro Tyr Glu Gly Arg Val Glu Ile Gln Arg Ala Gly
    50                  55                  60
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Glu Trp Gly Thr Ile Cys Asp Asp Asp Phe Thr Leu Gln Ala Ala His
65                  70                  75                  80

Ile Leu Cys Arg Glu Leu Gly Phe Thr Glu Ala Thr Gly Trp Thr His
                85                  90                  95

Ser Ala Lys Tyr Gly Pro Gly Thr Gly Arg Ile Trp Leu Asp Asn Leu
            100                 105                 110

Ser Cys Ser Gly Thr Glu Gln Ser Val Thr Glu Cys Ala Ser Arg Gly
        115                 120                 125

Trp Gly Asn Ser Asp Cys Thr His Asp Glu Asp Ala Gly Val Ile Cys
    130                 135                 140

Lys Asp Gln Arg Leu Pro Gly Phe Ser Asp Ser Asn Val Ile Glu Val
145                 150                 155                 160

Glu His His Leu Gln Val Glu Glu Val Arg Ile Arg Pro Ala Val Gly
                165                 170                 175

Trp Gly Arg Arg Pro Leu Pro Val Thr Glu Gly Leu Val Glu Val Arg
            180                 185                 190

Leu Pro Asp Gly Trp Ser Gln Val Cys Asp Lys Gly Trp Ser Ala His
        195                 200                 205

Asn Ser His Val Val Cys Gly Met Leu Gly Phe Pro Ser Glu Lys Arg
    210                 215                 220

Val Asn Ala Ala Phe Tyr Arg Leu Leu Ala Gln Arg Gln Gln His Ser
225                 230                 235                 240

Phe Gly Leu His Gly Val Ala Cys Val Gly Thr Glu Ala His Leu Ser
                245                 250                 255

Leu Cys Ser Leu Glu Phe Tyr Arg Ala Asn Asp Thr Ala Arg Cys Pro
            260                 265                 270

Gly Gly Gly Pro Ala Val Val Ser Cys Val Pro Gly Pro Val Tyr Ala
        275                 280                 285

Ala Ser Ser Gly Gln Lys Lys Gln Gln Gln Ser Lys Pro Gln Gly Glu
    290                 295                 300

Ala Arg Val Arg Leu Lys Gly Gly Ala His Pro Gly Glu Gly Arg Val
305                 310                 315                 320

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

Asp Leu His Ala Ala Ser Val Val Cys Arg Glu Leu Gly Phe Gly Ser
            340                 345                 350

Ala Arg Glu Ala Leu Ser Gly Ala Arg Met Gly Gln Gly Met Gly Ala
        355                 360                 365

Ile His Leu Ser Glu Val Arg Cys Ser Gly Gln Glu Leu Ser Leu Trp
    370                 375                 380

Lys Cys Pro His Lys Asn Ile Thr Ala Glu Asp Cys Ser His Ser Gln
385                 390                 395                 400

Asp Ala Gly Val Arg Cys Asn Leu Pro Tyr Thr Gly Ala Glu Thr Arg
                405                 410                 415

Ile Arg Leu Ser Gly Gly Arg Ser Gln His Glu Gly Arg Val Glu Val
            420                 425                 430

Gln Ile Gly Gly Pro Gly Pro Leu Arg Trp Gly Leu Ile Cys Gly Asp
        435                 440                 445

Asp Trp Gly Thr Leu Glu Ala Met Val Ala Cys Arg Gln Leu Gly Leu
    450                 455                 460
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Gly Tyr Ala Asn His Gly Leu Gln Glu Thr Trp Tyr Trp Asp Ser Gly
465   470   475   480

Asn Ile Thr Glu Val Val Met Ser Gly Val Arg Cys Thr Gly Thr Glu
                485   490   495

Leu Ser Leu Asp Gln Cys Ala His His Gly Thr His Ile Thr Cys Lys
            500   505   510

Arg Thr Gly Thr Arg Phe Thr Ala Gly Val Ile Cys Ser Glu Thr Ala
        515   520   525

Ser Asp Leu Leu Leu His Ser Ala Leu Val Gln Glu Thr Ala Tyr Ile
    530   535   540

Glu Asp Arg Pro Leu His Met Leu Tyr Cys Ala Ala Glu Glu Asn Cys
545   550   555   560

Leu Ala Ser Ser Ala Arg Ser Ala Asn Trp Pro Tyr Gly His Arg Arg
                565   570   575

Leu Leu Arg Phe Ser Ser Gln Ile His Asn Leu Gly Arg Ala Asp Phe
            580   585   590

Arg Pro Lys Ala Gly Arg His Ser Trp Val Trp His Glu Cys His Gly
        595   600   605

His Tyr His Ser Met Asp Ile Phe Thr His Tyr Asp Ile Leu Thr Pro
    610   615   620

Asn Gly Thr Lys Val Ala Glu Gly His Lys Ala Ser Phe Cys Leu Glu
625   630   635   640

Asp Thr Glu Cys Gln Glu Asp Val Ser Lys Arg Tyr Glu Cys Ala Asn
                645   650   655

Phe Gly Glu Gln Gly Ile Thr Val Gly Cys Trp Asp Leu Tyr Arg His
            660   665   670

Asp Ile Asp Cys Gln Trp Ile Asp Ile Thr Asp Val Lys Pro Gly Asn
        675   680   685

Tyr Ile Leu Gln Val Val Ile Asn Pro Asn Phe Glu Val Ala Glu Ser
    690   695   700

Asp Phe Thr Asn Asn Ala Met Lys Cys Asn Cys Lys Tyr Asp Gly His
705   710   715   720

Arg Ile Trp Val His Asn Cys His Ile Gly Asp Ala Phe Ser Glu Glu
                725   730   735

Ala Asn Arg Arg Phe Glu Arg Tyr Pro Gly Gln Thr Ser Asn Gln Ile
            740   745   750

Ile

<210> SEQ ID NO 30
<211> LENGTH: 756
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Met Ala Trp Ser Pro Pro Ala Thr Leu Phe Leu Phe Leu Leu Leu Leu
1   5   10   15

Gly Gln Pro Pro Pro Ser Arg Pro Gln Ser Leu Gly Thr Thr Lys Leu
            20   25   30

Arg Leu Val Gly Pro Glu Ser Lys Pro Glu Glu Gly Arg Leu Glu Val
        35   40   45

Leu His Gln Gly Gln Trp Gly Thr Val Cys Asp Asp Asn Phe Ala Ile
    50   55   60

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Gln Glu Ala Thr Val Ala Cys Arg Gln Leu Gly Phe Glu Ala Ala Leu
65                  70                  75                  80

Thr Trp Ala His Ser Ala Lys Tyr Gly Gln Gly Glu Gly Pro Ile Trp
                85                  90                  95

Leu Asp Asn Val Arg Cys Val Gly Thr Glu Ser Ser Leu Asp Gln Cys
            100                 105                 110

Gly Ser Asn Gly Trp Gly Val Ser Asp Cys Ser His Ser Glu Asp Val
        115                 120                 125

Gly Val Ile Cys His Pro Arg Arg His Arg Gly Tyr Leu Ser Glu Thr
    130                 135                 140

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

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

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

Gln Gly Trp Thr Met Asn Asn Ser Arg Val Val Cys Gly Met Leu Gly
        195                 200                 205

Phe Pro Ser Glu Val Pro Val Asp Ser His Tyr Tyr Arg Lys Val Trp
    210                 215                 220

Asp Leu Lys Met Arg Asp Pro Lys Ser Arg Leu Lys Ser Leu Thr Asn
225                 230                 235                 240

Lys Asn Ser Phe Trp Ile His Gln Val Thr Cys Leu Gly Thr Glu Pro
                245                 250                 255

His Met Ala Asn Cys Gln Val Gln Val Ala Pro Ala Arg Gly Lys Leu
            260                 265                 270

Arg Pro Ala Cys Pro Gly Gly Met His Ala Val Val Ser Cys Val Ala
        275                 280                 285

Gly Pro His Phe Arg Pro Pro Lys Thr Lys Pro Gln Arg Lys Gly Ser
    290                 295                 300

Trp Ala Glu Glu Pro Arg Val Arg Leu Arg Ser Gly Ala Gln Val Gly
305                 310                 315                 320

Glu Gly Arg Val Glu Val Leu Met Asn Arg Gln Trp Gly Thr Val Cys
                325                 330                 335

Asp His Arg Trp Asn Leu Ile Ser Ala Ser Val Val Cys Arg Gln Leu
            340                 345                 350

Gly Phe Gly Ser Ala Arg Glu Ala Leu Phe Gly Ala Arg Leu Gly Gln
        355                 360                 365

Gly Leu Gly Pro Ile His Leu Ser Glu Val Arg Cys Arg Gly Tyr Glu
    370                 375                 380

Arg Thr Leu Ser Asp Cys Pro Ala Leu Glu Gly Ser Gln Asn Gly Cys
385                 390                 395                 400

Gln His Glu Asn Asp Ala Ala Val Arg Cys Asn Val Pro Asn Met Gly
                405                 410                 415

Phe Gln Asn Gln Val Arg Leu Ala Gly Gly Arg Ile Pro Glu Glu Gly
            420                 425                 430

Leu Leu Glu Val Gln Val Glu Val Asn Gly Val Pro Arg Trp Gly Ser
        435                 440                 445

Val Cys Ser Glu Asn Trp Gly Leu Thr Glu Ala Met Val Ala Cys Arg
    450                 455                 460

Gln Leu Gly Leu Gly Phe Ala Ile His Ala Tyr Lys Glu Thr Trp Phe
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465                 470                 475                 480

Trp Ser Gly Thr Pro Arg Ala Gln Glu Val Val Met Ser Gly Val Arg
                485                 490                 495

Cys Ser Gly Thr Glu Leu Ala Leu Gln Gln Cys Gln Arg His Gly Pro
            500                 505                 510

Val His Cys Ser His Gly Gly Gly Arg Phe Leu Ala Gly Val Ser Cys
        515                 520                 525

Met Asp Ser Ala Pro Asp Leu Val Met Asn Ala Gln Leu Val Gln Glu
    530                 535                 540

Thr Ala Tyr Leu Glu Asp Arg Pro Leu Ser Gln Leu Tyr Cys Ala His
545                 550                 555                 560

Glu Glu Asn Cys Leu Ser Lys Ser Ala Asp His Met Asp Trp Pro Tyr
                565                 570                 575

Gly Tyr Arg Arg Leu Leu Arg Phe Ser Thr Gln Ile Tyr Asn Leu Gly
            580                 585                 590

Arg Thr Asp Phe Arg Pro Lys Thr Gly Arg Asp Ser Trp Val Trp His
        595                 600                 605

Gln Cys His Arg His Tyr His Ser Ile Glu Val Phe Thr His Tyr Asp
    610                 615                 620

Leu Leu Thr Leu Asn Gly Ser Lys Val Ala Glu Gly His Lys Ala Ser
625                 630                 635                 640

Phe Cys Leu Glu Asp Thr Asn Cys Pro Thr Gly Leu Gln Arg Arg Tyr
                645                 650                 655

Ala Cys Ala Asn Phe Gly Glu Gln Gly Val Thr Val Gly Cys Trp Asp
            660                 665                 670

Thr Tyr Arg His Asp Ile Asp Cys Gln Trp Val Asp Ile Thr Asp Val
        675                 680                 685

Gly Pro Gly Asn Tyr Ile Phe Gln Val Ile Val Asn Pro His Tyr Glu
    690                 695                 700

Val Ala Glu Ser Asp Phe Ser Asn Asn Met Leu Gln Cys Arg Cys Lys
705                 710                 715                 720

Tyr Asp Gly His Arg Val Trp Leu His Asn Cys His Thr Gly Asn Ser
                725                 730                 735

Tyr Pro Ala Asn Ala Glu Leu Ser Leu Glu Gln Glu Gln Arg Leu Arg
            740                 745                 750

Asn Asn Leu Ile
        755


<210> SEQ ID NO 31
<211> LENGTH: 1722
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

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

Leu Ala Ser Ser Ala His Gly Arg Leu Arg Arg Ile Thr Tyr Val Val
            20                  25                  30

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

Pro Arg Ser Arg Thr Phe Asn Val Ala Leu Asn Ala Arg Tyr Ser Arg
    50                  55                  60
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Ser Ser Ala Ala Ala Gly Ala Pro Ser Arg Ala Ser Pro Gly Val Pro
65                  70                  75                  80

Ser Glu Arg Thr Arg Arg Thr Ser Lys Pro Gly Gly Ala Ala Leu Gln
                85                  90                  95

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

Val Pro Gly Gly Gln Leu His Pro Asn Pro Gly Gly His Pro Ala Ala
        115                 120                 125

Ala Pro Phe Thr Lys Gln Gly Arg Gln Val Val Arg Ser Lys Val Pro
    130                 135                 140

Gln Glu Thr Gln Ser Gly Gly Ser Arg Leu Gln Val His Gln Lys
145                 150                 155                 160

Gln Gln Leu Gln Gly Val Asn Val Cys Gly Gly Arg Cys Cys His Gly
                165                 170                 175

Trp Ser Lys Ala Pro Gly Ser Gln Arg Cys Thr Lys Pro Ser Cys Val
            180                 185                 190

Pro Pro Cys Gln Asn Gly Gly Met Cys Leu Arg Pro Gln Leu Cys Val
        195                 200                 205

Cys Lys Pro Gly Thr Lys Gly Lys Ala Cys Glu Thr Ile Ala Ala Gln
    210                 215                 220

Asp Thr Ser Ser Pro Val Phe Gly Gly Gln Ser Pro Gly Ala Ala Ser
225                 230                 235                 240

Ser Trp Gly Pro Pro Glu Gln Ala Ala Lys His Thr Ser Ser Lys Lys
                245                 250                 255

Ala Asp Thr Leu Pro Arg Val Ser Pro Val Ala Gln Met Thr Leu Thr
            260                 265                 270

Leu Lys Pro Lys Pro Ser Val Gly Leu Pro Gln Gln Ile His Ser Gln
        275                 280                 285

Val Thr Pro Leu Ser Ser Gln Ser Val Val Ile His His Gly Gln Thr
    290                 295                 300

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

Ser Gly Glu Gln Ser Thr Glu Gly Ser Phe Pro Leu Arg Tyr Val Gln
                325                 330                 335

Asp Gln Val Ala Ala Pro Phe Gln Leu Ser Asn His Thr Gly Arg Ile
            340                 345                 350

Lys Val Val Phe Thr Pro Ser Ile Cys Lys Val Thr Cys Thr Lys Gly
        355                 360                 365

Ser Cys Gln Asn Ser Cys Glu Lys Gly Asn Thr Thr Thr Leu Ile Ser
    370                 375                 380

Glu Asn Gly His Ala Ala Asp Thr Leu Thr Ala Thr Asn Phe Arg Val
385                 390                 395                 400

Val Ile Cys His Leu Pro Cys Met Asn Gly Gly Gln Cys Ser Ser Arg
                405                 410                 415

Asp Lys Cys Gln Cys Pro Pro Asn Phe Thr Gly Lys Leu Cys Gln Ile
            420                 425                 430

Pro Val His Gly Ala Ser Val Pro Lys Leu Tyr Gln His Ser Gln Gln
        435                 440                 445

Pro Gly Lys Ala Leu Gly Thr His Val Ile His Ser Thr His Thr Leu
    450                 455                 460

Pro Leu Thr Val Thr Ser Gln Gln Gly Val Lys Val Lys Phe Pro Pro
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465                 470                 475                 480

Asn Ile Val Asn Ile His Val Lys His Pro Pro Glu Ala Ser Val Gln
                485                 490                 495

Ile His Gln Val Ser Arg Ile Asp Gly Pro Thr Gly Gln Lys Thr Lys
            500                 505                 510

Glu Ala Gln Pro Gly Gln Ser Gln Val Ser Tyr Gln Gly Leu Pro Val
        515                 520                 525

Gln Lys Thr Gln Thr Ile His Ser Thr Tyr Ser His Gln Gln Val Ile
    530                 535                 540

Pro His Val Tyr Pro Val Ala Ala Lys Thr Gln Leu Gly Arg Cys Phe
545                 550                 555                 560

Gln Glu Thr Ile Gly Ser Gln Cys Gly Lys Ala Leu Pro Gly Leu Ser
                565                 570                 575

Lys Gln Glu Asp Cys Cys Gly Thr Val Gly Thr Ser Trp Gly Phe Asn
            580                 585                 590

Lys Cys Gln Lys Cys Pro Lys Lys Pro Ser Tyr His Gly Tyr Asn Gln
        595                 600                 605

Met Met Glu Cys Leu Pro Gly Tyr Lys Arg Val Asn Asn Thr Phe Cys
    610                 615                 620

Gln Asp Ile Asn Glu Cys Gln Leu Gln Gly Val Cys Pro Asn Gly Glu
625                 630                 635                 640

Cys Leu Asn Thr Met Gly Ser Tyr Arg Cys Thr Cys Lys Ile Gly Phe
                645                 650                 655

Gly Pro Asp Pro Thr Phe Ser Ser Cys Val Pro Asp Pro Pro Val Ile
            660                 665                 670

Ser Glu Glu Lys Gly Pro Cys Tyr Arg Leu Val Ser Ser Gly Arg Gln
        675                 680                 685

Cys Met His Pro Leu Ser Val His Leu Thr Lys Gln Leu Cys Cys Cys
    690                 695                 700

Ser Val Gly Lys Ala Trp Gly Pro His Cys Glu Lys Cys Pro Leu Pro
705                 710                 715                 720

Gly Thr Ala Ala Phe Lys Glu Ile Cys Pro Gly Gly Met Gly Tyr Thr
                725                 730                 735

Val Ser Gly Val His Arg Arg Arg Pro Ile His His His Val Gly Lys
            740                 745                 750

Gly Pro Val Phe Val Lys Pro Lys Asn Thr Gln Pro Val Ala Lys Ser
        755                 760                 765

Thr His Pro Pro Pro Leu Pro Ala Lys Glu Glu Pro Val Glu Ala Leu
    770                 775                 780

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

Thr Ala Pro Pro Glu Lys Glu Ile Pro Ser Leu Asp Gln Glu Lys Thr
                805                 810                 815

Lys Leu Glu Pro Gly Gln Pro Gln Leu Ser Pro Gly Ile Ser Thr Ile
            820                 825                 830

His Leu His Pro Gln Phe Pro Gly Ile Val Ile Glu Lys Thr Ser Pro
        835                 840                 845

Pro Val Pro Val Glu Val Ala Pro Glu Ala Ser Thr Ser Ser Ala Ser
    850                 855                 860

Gln Val Ile Ala Pro Thr Gln Val Thr Glu Ile Asn Glu Cys Thr Val
865                 870                 875                 880
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Asn Pro Asp Ile Cys Gly Ala Gly His Cys Ile Asn Leu Pro Val Arg
                885                 890                 895

Tyr Thr Cys Ile Cys Tyr Glu Gly Tyr Arg Phe Ser Glu Gln Gln Arg
            900                 905                 910

Lys Cys Val Asp Ile Asp Glu Cys Thr Gln Val Gln His Leu Cys Ser
        915                 920                 925

Gln Gly Arg Cys Glu Asn Thr Glu Gly Ser Phe Leu Cys Ile Cys Pro
    930                 935                 940

Ala Gly Phe Met Ala Ser Glu Glu Gly Thr Asn Cys Ile Asp Val Asp
945                 950                 955                 960

Glu Cys Leu Arg Pro Asp Val Cys Gly Glu Gly His Cys Val Asn Thr
                965                 970                 975

Val Gly Ala Phe Arg Cys Glu Tyr Cys Asp Ser Gly Tyr Arg Met Thr
            980                 985                 990

Gln Arg Gly Arg Cys Glu Asp Ile  Asp Glu Cys Leu Asn  Pro Ser Thr
        995                 1000                1005

Cys Pro  Asp Glu Gln Cys Val  Asn Ser Pro Gly Ser  Tyr Gln Cys
    1010                 1015                 1020

Val Pro  Cys Thr Glu Gly Phe  Arg Gly Trp Asn Gly  Gln Cys Leu
    1025                 1030                 1035

Asp Val  Asp Glu Cys Leu Glu  Pro Asn Val Cys Ala  Asn Gly Asp
    1040                 1045                 1050

Cys Ser  Asn Leu Glu Gly Ser  Tyr Met Cys Ser Cys  His Lys Gly
    1055                 1060                 1065

Tyr Thr  Arg Thr Pro Asp His  Lys His Cys Arg Asp  Ile Asp Glu
    1070                 1075                 1080

Cys Gln  Gln Gly Asn Leu Cys  Val Asn Gly Gln Cys  Lys Asn Thr
    1085                 1090                 1095

Glu Gly  Ser Phe Arg Cys Thr  Cys Gly Gln Gly Tyr  Gln Leu Ser
    1100                 1105                 1110

Ala Ala  Lys Asp Gln Cys Glu  Asp Ile Asp Glu Cys  Gln His Arg
    1115                 1120                 1125

His Leu  Cys Ala His Gly Gln  Cys Arg Asn Thr Glu  Gly Ser Phe
    1130                 1135                 1140

Gln Cys  Val Cys Asp Gln Gly  Tyr Arg Ala Ser Gly  Leu Gly Asp
    1145                 1150                 1155

His Cys  Glu Asp Ile Asn Glu  Cys Leu Glu Asp Lys  Ser Val Cys
    1160                 1165                 1170

Gln Arg  Gly Asp Cys Ile Asn  Thr Ala Gly Ser Tyr  Asp Cys Thr
    1175                 1180                 1185

Cys Pro  Asp Gly Phe Gln Leu  Asp Asp Asn Lys Thr  Cys Gln Asp
    1190                 1195                 1200

Ile Asn  Glu Cys Glu His Pro  Gly Leu Cys Gly Pro  Gln Gly Glu
    1205                 1210                 1215

Cys Leu  Asn Thr Glu Gly Ser  Phe His Cys Val Cys  Gln Gln Gly
    1220                 1225                 1230

Phe Ser  Ile Ser Ala Asp Gly  Arg Thr Cys Glu Asp  Ile Asp Glu
    1235                 1240                 1245

Cys Val  Asn Asn Thr Val Cys  Asp Ser His Gly Phe  Cys Asp Asn
    1250                 1255                 1260
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Thr Ala  Gly Ser Phe Arg Cys  Leu Cys Tyr Gln Gly  Phe Gln Ala
    1265                 1270                 1275

Pro Gln  Asp Gly Gln Gly Cys  Val Asp Val Asn Glu  Cys Glu Leu
    1280                 1285                 1290

Leu Ser  Gly Val Cys Gly Glu  Ala Phe Cys Glu Asn  Val Glu Gly
    1295                 1300                 1305

Ser Phe  Leu Cys Val Cys Ala  Asp Glu Asn Gln Glu  Tyr Ser Pro
    1310                 1315                 1320

Met Thr  Gly Gln Cys Arg Ser  Arg Thr Ser Thr Asp  Leu Asp Val
    1325                 1330                 1335

Asp Val  Asp Gln Pro Lys Glu  Glu Lys Lys Glu Cys  Tyr Tyr Asn
    1340                 1345                 1350

Leu Asn  Asp Ala Ser Leu Cys  Asp Asn Val Leu Ala  Pro Asn Val
    1355                 1360                 1365

Thr Lys  Gln Glu Cys Cys Cys  Thr Ser Gly Ala Gly  Trp Gly Asp
    1370                 1375                 1380

Asn Cys  Glu Ile Phe Pro Cys  Pro Val Leu Gly Thr  Ala Glu Phe
    1385                 1390                 1395

Thr Glu  Met Cys Pro Lys Gly  Lys Gly Phe Val Pro  Ala Gly Glu
    1400                 1405                 1410

Ser Ser  Ser Glu Ala Gly Gly  Glu Asn Tyr Lys Asp  Ala Asp Glu
    1415                 1420                 1425

Cys Leu  Leu Phe Gly Gln Glu  Ile Cys Lys Asn Gly  Phe Cys Leu
    1430                 1435                 1440

Asn Thr  Arg Pro Gly Tyr Glu  Cys Tyr Cys Lys Gln  Gly Thr Tyr
    1445                 1450                 1455

Tyr Asp  Pro Val Lys Leu Gln  Cys Phe Asp Met Asp  Glu Cys Gln
    1460                 1465                 1470

Asp Pro  Ser Ser Cys Ile Asp  Gly Gln Cys Val Asn  Thr Glu Gly
    1475                 1480                 1485

Ser Tyr  Asn Cys Phe Cys Thr  His Pro Met Val Leu  Asp Ala Ser
    1490                 1495                 1500

Glu Lys  Arg Cys Ile Arg Pro  Ala Glu Ser Asn Glu  Gln Ile Glu
    1505                 1510                 1515

Glu Thr  Asp Val Tyr Gln Asp  Leu Cys Trp Glu His  Leu Ser Asp
    1520                 1525                 1530

Glu Tyr  Val Cys Ser Arg Pro  Leu Val Gly Lys Gln  Thr Thr Tyr
    1535                 1540                 1545

Thr Glu  Cys Cys Cys Leu Tyr  Gly Glu Ala Trp Gly  Met Gln Cys
    1550                 1555                 1560

Ala Leu  Cys Pro Leu Lys Asp  Ser Asp Asp Tyr Ala  Gln Leu Cys
    1565                 1570                 1575

Asn Ile  Pro Val Thr Gly Arg  Arg Gln Pro Tyr Gly  Arg Asp Ala
    1580                 1585                 1590

Leu Val  Asp Phe Ser Glu Gln  Tyr Thr Pro Glu Ala  Asp Pro Tyr
    1595                 1600                 1605

Phe Ile  Gln Asp Arg Phe Leu  Asn Ser Phe Glu Glu  Leu Gln Ala
    1610                 1615                 1620

Glu Glu  Cys Gly Ile Leu Asn  Gly Cys Glu Asn Gly  Arg Cys Val
    1625                 1630                 1635

Arg Val  Gln Glu Gly Tyr Thr  Cys Asp Cys Phe Asp  Gly Tyr His
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    1640                 1645                 1650

Leu Asp  Thr Ala Lys Met Thr  Cys Val Asp Val Asn  Glu Cys Asp
    1655                 1660                 1665

Glu Leu  Asn Asn Arg Met Ser  Leu Cys Lys Asn Ala  Lys Cys Ile
    1670                 1675                 1680

Asn Thr  Asp Gly Ser Tyr Lys  Cys Leu Cys Leu Pro  Gly Tyr Val
    1685                 1690                 1695

Pro Ser  Asp Lys Pro Asn Tyr  Cys Thr Pro Leu Asn  Thr Ala Leu
    1700                 1705                 1710

Asn Leu  Glu Lys Asp Ser Asp  Leu Glu
    1715                 1720


<210> SEQ ID NO 32
<211> LENGTH: 496
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Met Arg Val Leu Ser Gly Thr Ser Leu Met Leu Cys Ser Leu Leu Leu
1               5                   10                  15

Leu Leu Gln Ala Leu Cys Ser Pro Gly Leu Ala Pro Gln Ser Arg Gly
            20                  25                  30

His Leu Cys Arg Thr Arg Pro Thr Asp Leu Val Phe Val Val Asp Ser
        35                  40                  45

Ser Arg Ser Val Arg Pro Val Glu Phe Glu Lys Val Lys Val Phe Leu
    50                  55                  60

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

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

Ala His Val Ser Lys Ala Ala Leu Leu Gln Ala Val Arg Arg Ile Gln
            100                 105                 110

Pro Leu Ser Thr Gly Thr Met Thr Gly Leu Ala Ile Gln Phe Ala Ile
        115                 120                 125

Thr Lys Ala Phe Gly Asp Ala Glu Gly Gly Arg Ser Arg Ser Pro Asp
    130                 135                 140

Ile Ser Lys Val Val Ile Val Val Thr Asp Gly Arg Pro Gln Asp Ser
145                 150                 155                 160

Val Gln Asp Val Ser Ala Arg Ala Arg Ala Ser Gly Val Glu Leu Phe
                165                 170                 175

Ala Ile Gly Val Gly Ser Val Asp Lys Ala Thr Leu Arg Gln Ile Ala
            180                 185                 190

Ser Glu Pro Gln Asp Glu His Val Asp Tyr Val Glu Ser Tyr Ser Val
        195                 200                 205

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

Asp Leu Cys Ala Thr Gly Asp His Asp Cys Glu Gln Val Cys Ile Ser
225                 230                 235                 240

Ser Pro Gly Ser Tyr Thr Cys Ala Cys His Glu Gly Phe Thr Leu Asn
                245                 250                 255

Ser Asp Gly Lys Thr Cys Asn Val Cys Ser Gly Gly Gly Gly Ser Ser
            260                 265                 270
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Ala Thr Asp Leu Val Phe Leu Ile Asp Gly Ser Lys Ser Val Arg Pro
        275                 280                 285

Glu Asn Phe Glu Leu Val Lys Lys Phe Ile Ser Gln Ile Val Asp Thr
    290                 295                 300

Leu Asp Val Ser Asp Lys Leu Ala Gln Val Gly Leu Val Gln Tyr Ser
305                 310                 315                 320

Ser Ser Val Arg Gln Glu Phe Pro Leu Gly Arg Phe His Thr Lys Lys
                325                 330                 335

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

Met Thr Gly Ala Ala Leu Lys Tyr Leu Ile Asp Asn Ser Phe Thr Val
        355                 360                 365

Ser Ser Gly Ala Arg Pro Gly Ala Gln Lys Val Gly Ile Val Phe Thr
    370                 375                 380

Asp Gly Arg Ser Gln Asp Tyr Ile Asn Asp Ala Ala Lys Lys Ala Lys
385                 390                 395                 400

Asp Leu Gly Phe Lys Met Phe Ala Val Gly Val Gly Asn Ala Val Glu
                405                 410                 415

Asp Glu Leu Arg Glu Ile Ala Ser Glu Pro Val Ala Glu His Tyr Phe
            420                 425                 430

Tyr Thr Ala Asp Phe Lys Thr Ile Asn Gln Ile Gly Lys Lys Leu Gln
        435                 440                 445

Lys Lys Ile Cys Val Glu Glu Asp Pro Cys Ala Cys Glu Ser Leu Val
    450                 455                 460

Lys Phe Gln Ala Lys Val Glu Gly Leu Leu Gln Ala Leu Thr Arg Lys
465                 470                 475                 480

Leu Glu Ala Val Ser Lys Arg Leu Ala Ile Leu Glu Asn Thr Val Val
                485                 490                 495
```

<210> SEQ ID NO 33
<211> LENGTH: 486
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

```
Met Pro Arg Pro Ala Pro Ala Arg Arg Leu Pro Gly Leu Leu Leu Leu
1               5                   10                  15

Leu Trp Pro Leu Leu Leu Leu Pro Ser Ala Ala Pro Asp Pro Val Ala
            20                  25                  30

Arg Pro Gly Phe Arg Arg Leu Glu Thr Arg Gly Pro Gly Gly Ser Pro
        35                  40                  45

Gly Arg Arg Pro Ser Pro Ala Ala Pro Asp Gly Ala Pro Ala Ser Gly
    50                  55                  60

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

Pro Leu Asp Leu Val Phe Ile Ile Asp Ser Ser Arg Ser Val Arg Pro
                85                  90                  95

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

Leu Asp Ile Gly Pro Ala Asp Thr Arg Val Ala Val Val Asn Tyr Ala
        115                 120                 125

Ser Thr Val Lys Ile Glu Phe Gln Leu Gln Ala Tyr Thr Asp Lys Gln
    130                 135                 140
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Ser Leu Lys Gln Ala Val Gly Arg Ile Thr Pro Leu Ser Thr Gly Thr
145                 150                 155                 160

Met Ser Gly Leu Ala Ile Gln Thr Ala Met Asp Glu Ala Phe Thr Val
                165                 170                 175

Glu Ala Gly Ala Arg Glu Pro Ser Ser Asn Ile Pro Lys Val Ala Ile
            180                 185                 190

Ile Val Thr Asp Gly Arg Pro Gln Asp Gln Val Asn Glu Val Ala Ala
        195                 200                 205

Arg Ala Gln Ala Ser Gly Ile Glu Leu Tyr Ala Val Gly Val Asp Arg
    210                 215                 220

Ala Asp Met Ala Ser Leu Lys Met Met Ala Ser Glu Pro Leu Glu Glu
225                 230                 235                 240

His Val Phe Tyr Val Glu Thr Tyr Gly Val Ile Glu Lys Leu Ser Ser
                245                 250                 255

Arg Phe Gln Glu Thr Phe Cys Ala Leu Asp Pro Cys Val Leu Gly Thr
            260                 265                 270

His Gln Cys Gln His Val Cys Ile Ser Asp Gly Glu Gly Lys His His
        275                 280                 285

Cys Glu Cys Ser Gln Gly Tyr Thr Leu Asn Ala Asp Lys Lys Thr Cys
    290                 295                 300

Ser Ala Leu Asp Arg Cys Ala Leu Asn Thr His Gly Cys Glu His Ile
305                 310                 315                 320

Cys Val Asn Asp Arg Ser Gly Ser Tyr His Cys Glu Cys Tyr Glu Gly
                325                 330                 335

Tyr Thr Leu Asn Glu Asp Arg Lys Thr Cys Ser Ala Gln Asp Lys Cys
            340                 345                 350

Ala Leu Gly Thr His Gly Cys Gln His Ile Cys Val Asn Asp Arg Thr
        355                 360                 365

Gly Ser His His Cys Glu Cys Tyr Glu Gly Tyr Thr Leu Asn Ala Asp
    370                 375                 380

Lys Lys Thr Cys Ser Val Arg Asp Lys Cys Ala Leu Gly Ser His Gly
385                 390                 395                 400

Cys Gln His Ile Cys Val Ser Asp Gly Ala Ala Ser Tyr His Cys Asp
                405                 410                 415

Cys Tyr Pro Gly Tyr Thr Leu Asn Glu Asp Lys Lys Thr Cys Ser Ala
            420                 425                 430

Thr Glu Glu Ala Arg Arg Leu Val Ser Thr Glu Asp Ala Cys Gly Cys
        435                 440                 445

Glu Ala Thr Leu Ala Phe Gln Asp Lys Val Ser Ser Tyr Leu Gln Arg
    450                 455                 460

Leu Asn Thr Lys Leu Asp Asp Ile Leu Glu Lys Leu Lys Ile Asn Glu
465                 470                 475                 480

Tyr Gly Gln Ile His Arg
                485


<210> SEQ ID NO 34
<211> LENGTH: 525
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Met Arg Val Phe Cys Val Gly Leu Leu Leu Phe Ser Val Thr Trp Ala
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1               5                   10                  15

Ala Pro Thr Phe Gln Pro Gln Thr Glu Lys Thr Lys Gln Ser Cys Val
            20                  25                  30

Glu Glu Gln Arg Gln Glu Glu Lys Asn Lys Asp Asn Ile Gly Phe His
        35                  40                  45

His Leu Gly Lys Arg Ile Asn Gln Glu Leu Ser Ser Lys Glu Asn Ile
    50                  55                  60

Val Gln Glu Arg Lys Lys Asp Leu Ser Leu Ser Glu Ala Ser Glu Asn
65                  70                  75                  80

Lys Gly Ser Ser Lys Ser Gln Asn Tyr Phe Thr Asn Arg Gln Arg Leu
                85                  90                  95

Asn Lys Glu Tyr Ser Ile Ser Asn Lys Glu Asn Thr His Asn Gly Leu
            100                 105                 110

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

Gly Asp Asp Ala Ile Ser Lys Leu His Asp Gln Glu Glu Tyr Gly Ala
    130                 135                 140

Ala Leu Ile Arg Asn Asn Met Gln His Ile Met Gly Pro Val Thr Ala
145                 150                 155                 160

Ile Lys Leu Leu Gly Glu Glu Asn Lys Glu Asn Thr Pro Arg Asn Val
                165                 170                 175

Leu Asn Ile Ile Pro Ala Ser Met Asn Tyr Ala Lys Ala His Ser Lys
            180                 185                 190

Asp Lys Lys Lys Pro Gln Arg Asp Ser Gln Ala Gln Lys Ser Pro Val
        195                 200                 205

Lys Ser Lys Ser Thr His Arg Ile Gln His Asn Ile Asp Tyr Leu Lys
    210                 215                 220

His Leu Ser Lys Val Lys Lys Ile Pro Ser Asp Phe Glu Gly Ser Gly
225                 230                 235                 240

Tyr Thr Asp Leu Gln Glu Arg Gly Asp Asn Asp Ile Ser Pro Phe Ser
                245                 250                 255

Gly Asp Gly Gln Pro Phe Lys Asp Ile Pro Gly Lys Gly Glu Ala Thr
            260                 265                 270

Gly Pro Asp Leu Glu Gly Lys Asp Ile Gln Thr Gly Phe Ala Gly Pro
        275                 280                 285

Ser Glu Ala Glu Ser Thr His Leu Asp Thr Lys Lys Pro Gly Tyr Asn
    290                 295                 300

Glu Ile Pro Glu Arg Glu Glu Asn Gly Gly Asn Thr Ile Gly Thr Arg
305                 310                 315                 320

Asp Glu Thr Ala Lys Glu Ala Asp Ala Val Asp Val Ser Leu Val Glu
                325                 330                 335

Gly Ser Asn Asp Ile Met Gly Ser Thr Asn Phe Lys Glu Leu Pro Gly
            340                 345                 350

Arg Glu Gly Asn Arg Val Asp Ala Gly Ser Gln Asn Ala His Gln Gly
        355                 360                 365

Lys Val Glu Phe His Tyr Pro Pro Ala Pro Ser Lys Glu Lys Arg Lys
    370                 375                 380

Glu Gly Ser Ser Asp Ala Ala Glu Ser Thr Asn Tyr Asn Glu Ile Pro
385                 390                 395                 400

Lys Asn Gly Lys Gly Ser Thr Arg Lys Gly Val Asp His Ser Asn Arg
                405                 410                 415
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Asn Gln Ala Thr Leu Asn Glu Lys Gln Arg Phe Pro Ser Lys Gly Lys
420 425 430

Ser Gln Gly Leu Pro Ile Pro Ser Arg Gly Leu Asp Asn Glu Ile Lys
435 440 445

Asn Glu Met Asp Ser Phe Asn Gly Pro Ser His Glu Asn Ile Ile Thr
450 455 460

His Gly Arg Lys Tyr His Tyr Val Pro His Arg Gln Asn Asn Ser Thr
465 470 475 480

Arg Asn Lys Gly Met Pro Gln Gly Lys Gly Ser Trp Gly Arg Gln Pro
485 490 495

His Ser Asn Arg Arg Phe Ser Ser Arg Arg Arg Asp Asp Ser Ser Glu
500 505 510

Ser Ser Asp Ser Gly Ser Ser Ser Glu Ser Asp Gly Asp
515 520 525

<210> SEQ ID NO 35
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Met Lys Ser Leu Ile Leu Leu Ala Ile Leu Ala Ala Leu Ala Val Val
1 5 10 15

Thr Leu Cys Tyr Glu Ser His Glu Ser Met Glu Ser Tyr Glu Leu Asn
20 25 30

Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Ile Ser Pro Gln Gln
35 40 45

Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro
50 55 60

Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu
65 70 75 80

Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe
85 90 95

Arg Lys Arg Arg Gly Thr Lys
100

<210> SEQ ID NO 36
<211> LENGTH: 2828
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Met Pro Lys Arg Ala His Trp Gly Ala Leu Ser Val Val Leu Ile Leu
1 5 10 15

Leu Trp Gly His Pro Arg Val Ala Leu Ala Cys Pro His Pro Cys Ala
20 25 30

Cys Tyr Val Pro Ser Glu Val His Cys Thr Phe Arg Ser Leu Ala Ser
35 40 45

Val Pro Ala Gly Ile Ala Lys His Val Glu Arg Ile Asn Leu Gly Phe
50 55 60

Asn Ser Ile Gln Ala Leu Ser Glu Thr Ser Phe Ala Gly Leu Thr Lys
65 70 75 80

Leu Glu Leu Leu Met Ile His Gly Asn Glu Ile Pro Ser Ile Pro Asp
85 90 95

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Gly Ala Leu Arg Asp Leu Ser Ser Leu Gln Val Phe Lys Phe Ser Tyr
            100                 105                 110

Asn Lys Leu Arg Val Ile Thr Gly Gln Thr Leu Gln Gly Leu Ser Asn
        115                 120                 125

Leu Met Arg Leu His Ile Asp His Asn Lys Ile Glu Phe Ile His Pro
    130                 135                 140

Gln Ala Phe Asn Gly Leu Thr Ser Leu Arg Leu Leu His Leu Glu Gly
145                 150                 155                 160

Asn Leu Leu His Gln Leu His Pro Ser Thr Phe Ser Thr Phe Thr Phe
                165                 170                 175

Leu Asp Tyr Phe Arg Leu Ser Thr Ile Arg His Leu Tyr Leu Ala Glu
            180                 185                 190

Asn Met Val Arg Thr Leu Pro Ala Ser Met Leu Arg Asn Met Pro Leu
        195                 200                 205

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

Met Arg Trp Phe Leu Glu Trp Asp Ala Lys Ser Arg Gly Ile Leu Lys
225                 230                 235                 240

Cys Lys Lys Asp Lys Ala Tyr Glu Gly Gly Gln Leu Cys Ala Met Cys
                245                 250                 255

Phe Ser Pro Lys Lys Leu Tyr Lys His Glu Ile His Lys Leu Lys Asp
            260                 265                 270

Met Thr Cys Leu Lys Pro Ser Ile Glu Ser Pro Leu Arg Gln Asn Arg
        275                 280                 285

Ser Arg Ser Ile Glu Glu Glu Gln Glu Gln Glu Glu Asp Gly Gly Ser
    290                 295                 300

Gln Leu Ile Leu Glu Lys Phe Gln Leu Pro Gln Trp Ser Ile Ser Leu
305                 310                 315                 320

Asn Met Thr Asp Glu His Gly Asn Met Val Asn Leu Val Cys Asp Ile
                325                 330                 335

Lys Lys Pro Met Asp Val Tyr Lys Ile His Leu Asn Gln Thr Asp Pro
            340                 345                 350

Pro Asp Ile Asp Ile Asn Ala Thr Val Ala Leu Asp Phe Glu Cys Pro
        355                 360                 365

Met Thr Arg Glu Asn Tyr Glu Lys Leu Trp Lys Leu Ile Ala Tyr Tyr
    370                 375                 380

Ser Glu Val Pro Val Lys Leu His Arg Glu Leu Met Leu Ser Lys Asp
385                 390                 395                 400

Pro Arg Val Ser Tyr Gln Tyr Arg Gln Asp Ala Asp Glu Glu Ala Leu
                405                 410                 415

Tyr Tyr Thr Gly Val Arg Ala Gln Ile Leu Ala Glu Pro Glu Trp Val
            420                 425                 430

Met Gln Pro Ser Ile Asp Ile Gln Leu Asn Arg Arg Gln Ser Thr Ala
        435                 440                 445

Lys Lys Val Leu Leu Ser Tyr Tyr Thr Gln Tyr Ser Gln Thr Ile Ser
    450                 455                 460

Thr Lys Asp Thr Arg Gln Ala Arg Gly Arg Ser Trp Val Met Ile Glu
465                 470                 475                 480

Pro Ser Gly Ala Val Gln Arg Asp Gln Thr Val Leu Glu Gly Gly Pro
                485                 490                 495
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Cys Gln Leu Ser Cys Asn Val Lys Ala Ser Glu Ser Pro Ser Ile Phe
            500                 505                 510

Trp Val Leu Pro Asp Gly Ser Ile Leu Lys Ala Pro Met Asp Asp Pro
        515                 520                 525

Asp Ser Lys Phe Ser Ile Leu Ser Ser Gly Trp Leu Arg Ile Lys Ser
    530                 535                 540

Met Glu Pro Ser Asp Ser Gly Leu Tyr Gln Cys Ile Ala Gln Val Arg
545                 550                 555                 560

Asp Glu Met Asp Arg Met Val Tyr Arg Val Leu Val Gln Ser Pro Ser
                565                 570                 575

Thr Gln Pro Ala Glu Lys Asp Thr Val Thr Ile Gly Lys Asn Pro Gly
            580                 585                 590

Glu Ser Val Thr Leu Pro Cys Asn Ala Leu Ala Ile Pro Glu Ala His
        595                 600                 605

Leu Ser Trp Ile Leu Pro Asn Arg Arg Ile Ile Asn Asp Leu Ala Asn
    610                 615                 620

Thr Ser His Val Tyr Met Leu Pro Asn Gly Thr Leu Ser Ile Pro Lys
625                 630                 635                 640

Val Gln Val Ser Asp Ser Gly Tyr Tyr Arg Cys Val Ala Val Asn Gln
                645                 650                 655

Gln Gly Ala Asp His Phe Thr Val Gly Ile Thr Val Thr Lys Lys Gly
            660                 665                 670

Ser Gly Leu Pro Ser Lys Arg Gly Arg Arg Pro Gly Ala Lys Ala Leu
        675                 680                 685

Ser Arg Val Arg Glu Asp Ile Val Glu Asp Glu Gly Gly Ser Gly Met
    690                 695                 700

Gly Asp Glu Glu Asn Thr Ser Arg Arg Leu Leu His Pro Lys Asp Gln
705                 710                 715                 720

Glu Val Phe Leu Lys Thr Lys Asp Asp Ala Ile Asn Gly Asp Lys Lys
                725                 730                 735

Ala Lys Lys Gly Arg Arg Lys Leu Lys Leu Trp Lys His Ser Glu Lys
            740                 745                 750

Glu Pro Glu Thr Asn Val Ala Glu Gly Arg Arg Val Phe Glu Ser Arg
        755                 760                 765

Arg Arg Ile Asn Met Ala Asn Lys Gln Ile Asn Pro Glu Arg Trp Ala
    770                 775                 780

Asp Ile Leu Ala Lys Val Arg Gly Lys Asn Leu Pro Lys Gly Thr Glu
785                 790                 795                 800

Val Pro Pro Leu Ile Lys Thr Thr Ser Pro Pro Ser Leu Ser Leu Glu
                805                 810                 815

Val Thr Pro Pro Phe Pro Ala Ile Ser Pro Pro Ser Ala Ser Pro Val
            820                 825                 830

Gln Thr Val Thr Ser Ala Glu Glu Ser Ser Ala Asp Val Pro Leu Leu
        835                 840                 845

Gly Glu Glu Glu His Val Leu Gly Thr Ile Ser Ser Ala Ser Met Gly
    850                 855                 860

Leu Glu His Asn His Asn Gly Val Ile Leu Val Glu Pro Glu Val Thr
865                 870                 875                 880

Ser Thr Pro Leu Glu Glu Val Val Asp Asp Leu Ser Glu Lys Thr Glu
                885                 890                 895

Glu Ile Thr Ser Thr Glu Gly Asp Leu Lys Gly Thr Ala Ala Pro Thr
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            900                 905                 910

Leu Ile Ser Glu Pro Tyr Glu Pro Ser Pro Thr Leu His Thr Leu Asp
        915                 920                 925

Thr Val Tyr Glu Lys Pro Thr His Glu Glu Thr Ala Thr Glu Gly Trp
    930                 935                 940

Ser Ala Ala Asp Val Gly Ser Ser Pro Glu Pro Thr Ser Ser Glu Tyr
945                 950                 955                 960

Glu Pro Pro Leu Asp Ala Val Ser Leu Ala Glu Ser Glu Pro Met Gln
                965                 970                 975

Tyr Phe Asp Pro Asp Leu Glu Thr Lys Ser Gln Pro Asp Glu Asp Lys
            980                 985                 990

Met Lys Glu Asp Thr Phe Ala His  Leu Thr Pro Thr Pro  Thr Ile Trp
        995                 1000                 1005

Val Asn  Asp Ser Ser Thr Ser  Gln Leu Phe Glu Asp  Ser Thr Ile
    1010                 1015                 1020

Gly Glu  Pro Gly Val Pro Gly  Gln Ser His Leu Gln  Gly Leu Thr
    1025                 1030                 1035

Asp Asn  Ile His Leu Val Lys  Ser Ser Leu Ser Thr  Gln Asp Thr
    1040                 1045                 1050

Leu Leu  Ile Lys Lys Gly Met  Lys Glu Met Ser Gln  Thr Leu Gln
    1055                 1060                 1065

Gly Gly  Asn Met Leu Glu Gly  Asp Pro Thr His Ser  Arg Ser Ser
    1070                 1075                 1080

Glu Ser  Glu Gly Gln Glu Ser  Lys Ser Ile Thr Leu  Pro Asp Ser
    1085                 1090                 1095

Thr Leu  Gly Ile Met Ser Ser  Met Ser Pro Val Lys  Lys Pro Ala
    1100                 1105                 1110

Glu Thr  Thr Val Gly Thr Leu  Leu Asp Lys Asp Thr  Thr Thr Ala
    1115                 1120                 1125

Thr Thr  Thr Pro Arg Gln Lys  Val Ala Pro Ser Ser  Thr Met Ser
    1130                 1135                 1140

Thr His  Pro Ser Arg Arg Arg  Pro Asn Gly Arg Arg  Arg Leu Arg
    1145                 1150                 1155

Pro Asn  Lys Phe Arg His Arg  His Lys Gln Thr Pro  Pro Thr Thr
    1160                 1165                 1170

Phe Ala  Pro Ser Glu Thr Phe  Ser Thr Gln Pro Thr  Gln Ala Pro
    1175                 1180                 1185

Asp Ile  Lys Ile Ser Ser Gln  Val Glu Ser Ser Leu  Val Pro Thr
    1190                 1195                 1200

Ala Trp  Val Asp Asn Thr Val  Asn Thr Pro Lys Gln  Leu Glu Met
    1205                 1210                 1215

Glu Lys  Asn Ala Glu Pro Thr  Ser Lys Gly Thr Pro  Arg Arg Lys
    1220                 1225                 1230

His Gly  Lys Arg Pro Asn Lys  His Arg Tyr Thr Pro  Ser Thr Val
    1235                 1240                 1245

Ser Ser  Arg Ala Ser Gly Ser  Lys Pro Ser Pro Ser  Pro Glu Asn
    1250                 1255                 1260

Lys His  Arg Asn Ile Val Thr  Pro Ser Ser Glu Thr  Ile Leu Leu
    1265                 1270                 1275

Pro Arg  Thr Val Ser Leu Lys  Thr Glu Gly Pro Tyr  Asp Ser Leu
    1280                 1285                 1290
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Asp Tyr  Met Thr Thr Thr Arg  Lys Ile Tyr Ser Ser  Tyr Pro Lys
    1295                 1300                 1305

Val Gln  Glu Thr Leu Pro Val  Thr Tyr Lys Pro Thr  Ser Asp Gly
    1310                 1315                 1320

Lys Glu  Ile Lys Asp Asp Val  Ala Thr Asn Val Asp  Lys His Lys
    1325                 1330                 1335

Ser Asp  Ile Leu Val Thr Gly  Glu Ser Ile Thr Asn  Ala Ile Pro
    1340                 1345                 1350

Thr Ser  Arg Ser Leu Val Ser  Thr Met Gly Glu Phe  Lys Glu Glu
    1355                 1360                 1365

Ser Ser  Pro Val Gly Phe Pro  Gly Thr Pro Thr Trp  Asn Pro Ser
    1370                 1375                 1380

Arg Thr  Ala Gln Pro Gly Arg  Leu Gln Thr Gly Ile  Pro Val Thr
    1385                 1390                 1395

Thr Ser  Gly Glu Asn Leu Thr  Asp Pro Pro Leu Leu  Lys Glu Leu
    1400                 1405                 1410

Glu Asp  Val Asp Phe Thr Ser  Glu Phe Leu Ser Ser  Leu Thr Val
    1415                 1420                 1425

Ser Thr  Pro Phe His Gln Glu  Glu Ala Gly Ser Ser  Thr Thr Leu
    1430                 1435                 1440

Ser Ser  Ile Lys Val Glu Val  Ala Ser Ser Gln Ala  Glu Thr Thr
    1445                 1450                 1455

Thr Leu  Asp Gln Asp His Leu  Glu Thr Thr Val Ala  Ile Leu Leu
    1460                 1465                 1470

Ser Glu  Thr Arg Pro Gln Asn  His Thr Pro Thr Ala  Ala Arg Met
    1475                 1480                 1485

Lys Glu  Pro Ala Ser Ser Ser  Pro Ser Thr Ile Leu  Met Ser Leu
    1490                 1495                 1500

Gly Gln  Thr Thr Thr Thr Lys  Pro Ala Leu Pro Ser  Pro Arg Ile
    1505                 1510                 1515

Ser Gln  Ala Ser Arg Asp Ser  Lys Glu Asn Val Phe  Leu Asn Tyr
    1520                 1525                 1530

Val Gly  Asn Pro Glu Thr Glu  Ala Thr Pro Val Asn  Asn Glu Gly
    1535                 1540                 1545

Thr Gln  His Met Ser Gly Pro  Asn Glu Leu Ser Thr  Pro Ser Ser
    1550                 1555                 1560

Asp Gln  Asp Ala Phe Asn Leu  Ser Thr Lys Leu Glu  Leu Glu Lys
    1565                 1570                 1575

Gln Val  Phe Gly Ser Arg Ser  Leu Pro Arg Gly Pro  Asp Ser Gln
    1580                 1585                 1590

Arg Gln  Asp Gly Arg Val His  Ala Ser His Gln Leu  Thr Arg Val
    1595                 1600                 1605

Pro Ala  Lys Pro Ile Leu Pro  Thr Ala Thr Val Arg  Leu Pro Glu
    1610                 1615                 1620

Met Ser  Thr Gln Ser Ala Ser  Arg Tyr Phe Val Thr  Ser Gln Ser
    1625                 1630                 1635

Pro Arg  His Trp Thr Asn Lys  Pro Glu Ile Thr Thr  Tyr Pro Ser
    1640                 1645                 1650

Gly Ala  Leu Pro Glu Asn Lys  Gln Phe Thr Thr Pro  Arg Leu Ser
    1655                 1660                 1665
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Ser Thr  Thr Ile Pro Leu Pro  Leu His Met Ser Lys  Pro Ser Ile
    1670                 1675                 1680

Pro Ser  Lys Phe Thr Asp Arg  Arg Thr Asp Gln Phe  Asn Gly Tyr
    1685                 1690                 1695

Ser Lys  Val Phe Gly Asn Asn  Asn Ile Pro Glu Ala  Arg Asn Pro
    1700                 1705                 1710

Val Gly  Lys Pro Pro Ser Pro  Arg Ile Pro His Tyr  Ser Asn Gly
    1715                 1720                 1725

Arg Leu  Pro Phe Phe Thr Asn  Lys Thr Leu Ser Phe  Pro Gln Leu
    1730                 1735                 1740

Gly Val  Thr Arg Arg Pro Gln  Ile Pro Thr Ser Pro  Ala Pro Val
    1745                 1750                 1755

Met Arg  Glu Arg Lys Val Ile  Pro Gly Ser Tyr Asn  Arg Ile His
    1760                 1765                 1770

Ser His  Ser Thr Phe His Leu  Asp Phe Gly Pro Pro  Ala Pro Pro
    1775                 1780                 1785

Leu Leu  His Thr Pro Gln Thr  Thr Gly Ser Pro Ser  Thr Asn Leu
    1790                 1795                 1800

Gln Asn  Ile Pro Met Val Ser  Ser Thr Gln Ser Ser  Ile Ser Phe
    1805                 1810                 1815

Ile Thr  Ser Ser Val Gln Ser  Ser Gly Ser Phe His  Gln Ser Ser
    1820                 1825                 1830

Ser Lys  Phe Phe Ala Gly Gly  Pro Pro Ala Ser Lys  Phe Trp Ser
    1835                 1840                 1845

Leu Gly  Glu Lys Pro Gln Ile  Leu Thr Lys Ser Pro  Gln Thr Val
    1850                 1855                 1860

Ser Val  Thr Ala Glu Thr Asp  Thr Val Phe Pro Cys  Glu Ala Thr
    1865                 1870                 1875

Gly Lys  Pro Lys Pro Phe Val  Thr Trp Thr Lys Val  Ser Thr Gly
    1880                 1885                 1890

Ala Leu  Met Thr Pro Asn Thr  Arg Ile Gln Arg Phe  Glu Val Leu
    1895                 1900                 1905

Lys Asn  Gly Thr Leu Val Ile  Arg Lys Val Gln Val  Gln Asp Arg
    1910                 1915                 1920

Gly Gln  Tyr Met Cys Thr Ala  Ser Asn Leu His Gly  Leu Asp Arg
    1925                 1930                 1935

Met Val  Val Leu Leu Ser Val  Thr Val Gln Gln Pro  Gln Ile Leu
    1940                 1945                 1950

Ala Ser  His Tyr Gln Asp Val  Thr Val Tyr Leu Gly  Asp Thr Ile
    1955                 1960                 1965

Ala Met  Glu Cys Leu Ala Lys  Gly Thr Pro Ala Pro  Gln Ile Ser
    1970                 1975                 1980

Trp Ile  Phe Pro Asp Arg Arg  Val Trp Gln Thr Val  Ser Pro Val
    1985                 1990                 1995

Glu Gly  Arg Ile Thr Leu His  Glu Asn Arg Thr Leu  Ser Ile Lys
    2000                 2005                 2010

Glu Ala  Ser Phe Ser Asp Arg  Gly Val Tyr Lys Cys  Val Ala Ser
    2015                 2020                 2025

Asn Ala  Ala Gly Ala Asp Ser  Leu Ala Ile Arg Leu  His Val Ala
    2030                 2035                 2040

Ala Leu  Pro Pro Val Ile His  Gln Glu Lys Leu Glu  Asn Ile Ser
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    2045                2050                2055

Leu Pro  Pro Gly Leu Ser Ile  His Ile His Cys Thr  Ala Lys Ala
    2060                2065                2070

Ala Pro  Leu Pro Ser Val Arg  Trp Val Leu Gly Asp  Gly Thr Gln
    2075                2080                2085

Ile Arg  Pro Ser Gln Phe Leu  His Gly Asn Leu Phe  Val Phe Pro
    2090                2095                2100

Asn Gly  Thr Leu Tyr Ile Arg  Asn Leu Ala Pro Lys  Asp Ser Gly
    2105                2110                2115

Arg Tyr  Glu Cys Val Ala Ala  Asn Leu Val Gly Ser  Ala Arg Arg
    2120                2125                2130

Thr Val  Gln Leu Asn Val Gln  Arg Ala Ala Ala Asn  Ala Arg Ile
    2135                2140                2145

Thr Gly  Thr Ser Pro Arg Arg  Thr Asp Val Arg Tyr  Gly Gly Thr
    2150                2155                2160

Leu Lys  Leu Asp Cys Ser Ala  Ser Gly Asp Pro Trp  Pro Arg Ile
    2165                2170                2175

Leu Trp  Arg Leu Pro Ser Lys  Arg Met Ile Asp Ala  Leu Phe Ser
    2180                2185                2190

Phe Asp  Ser Arg Ile Lys Val  Phe Ala Asn Gly Thr  Leu Val Val
    2195                2200                2205

Lys Ser  Val Thr Asp Lys Asp  Ala Gly Asp Tyr Leu  Cys Val Ala
    2210                2215                2220

Arg Asn  Lys Val Gly Asp Asp  Tyr Val Val Leu Lys  Val Asp Val
    2225                2230                2235

Val Met  Lys Pro Ala Lys Ile  Glu His Lys Glu Glu  Asn Asp His
    2240                2245                2250

Lys Val  Phe Tyr Gly Gly Asp  Leu Lys Val Asp Cys  Val Ala Thr
    2255                2260                2265

Gly Leu  Pro Asn Pro Glu Ile  Ser Trp Ser Leu Pro  Asp Gly Ser
    2270                2275                2280

Leu Val  Asn Ser Phe Met Gln  Ser Asp Asp Ser Gly  Gly Arg Thr
    2285                2290                2295

Lys Arg  Tyr Val Val Phe Asn  Asn Gly Thr Leu Tyr  Phe Asn Glu
    2300                2305                2310

Val Gly  Met Arg Glu Glu Gly  Asp Tyr Thr Cys Phe  Ala Glu Asn
    2315                2320                2325

Gln Val  Gly Lys Asp Glu Met  Arg Val Arg Val Lys  Val Val Thr
    2330                2335                2340

Ala Pro  Ala Thr Ile Arg Asn  Lys Thr Tyr Leu Ala  Val Gln Val
    2345                2350                2355

Pro Tyr  Gly Asp Val Val Thr  Val Ala Cys Glu Ala  Lys Gly Glu
    2360                2365                2370

Pro Met  Pro Lys Val Thr Trp  Leu Ser Pro Thr Asn  Lys Val Ile
    2375                2380                2385

Pro Thr  Ser Ser Glu Lys Tyr  Gln Ile Tyr Gln Asp  Gly Thr Leu
    2390                2395                2400

Leu Ile  Gln Lys Ala Gln Arg  Ser Asp Ser Gly Asn  Tyr Thr Cys
    2405                2410                2415

Leu Val  Arg Asn Ser Ala Gly  Glu Asp Arg Lys Thr  Val Trp Ile
    2420                2425                2430
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His Val Asn Val Gln Pro Pro Lys Ile Asn Gly Asn Pro Asn Pro
2435 2440 2445

Ile Thr Thr Val Arg Glu Ile Ala Ala Gly Gly Ser Arg Lys Leu
2450 2455 2460

Ile Asp Cys Lys Ala Glu Gly Ile Pro Thr Pro Arg Val Leu Trp
2465 2470 2475

Ala Phe Pro Glu Gly Val Val Leu Pro Ala Pro Tyr Tyr Gly Asn
2480 2485 2490

Arg Ile Thr Val His Gly Asn Gly Ser Leu Asp Ile Arg Ser Leu
2495 2500 2505

Arg Lys Ser Asp Ser Val Gln Leu Val Cys Met Ala Arg Asn Glu
2510 2515 2520

Gly Gly Glu Ala Arg Leu Ile Leu Gln Leu Thr Val Leu Glu Pro
2525 2530 2535

Met Glu Lys Pro Ile Phe His Asp Pro Ile Ser Glu Lys Ile Thr
2540 2545 2550

Ala Met Ala Gly His Thr Ile Ser Leu Asn Cys Ser Ala Ala Gly
2555 2560 2565

Thr Pro Thr Pro Ser Leu Val Trp Val Leu Pro Asn Gly Thr Asp
2570 2575 2580

Leu Gln Ser Gly Gln Gln Leu Gln Arg Phe Tyr His Lys Ala Asp
2585 2590 2595

Gly Met Leu His Ile Ser Gly Leu Ser Ser Val Asp Ala Gly Ala
2600 2605 2610

Tyr Arg Cys Val Ala Arg Asn Ala Ala Gly His Thr Glu Arg Leu
2615 2620 2625

Val Ser Leu Lys Val Gly Leu Lys Pro Glu Ala Asn Lys Gln Tyr
2630 2635 2640

His Asn Leu Val Ser Ile Ile Asn Gly Glu Thr Leu Lys Leu Pro
2645 2650 2655

Cys Thr Pro Pro Gly Ala Gly Gln Gly Arg Phe Ser Trp Thr Leu
2660 2665 2670

Pro Asn Gly Met His Leu Glu Gly Pro Gln Thr Leu Gly Arg Val
2675 2680 2685

Ser Leu Leu Asp Asn Gly Thr Leu Thr Val Arg Glu Ala Ser Val
2690 2695 2700

Phe Asp Arg Gly Thr Tyr Val Cys Arg Met Glu Thr Glu Tyr Gly
2705 2710 2715

Pro Ser Val Thr Ser Ile Pro Val Ile Val Ile Ala Tyr Pro Pro
2720 2725 2730

Arg Ile Thr Ser Glu Pro Thr Pro Val Ile Tyr Thr Arg Pro Gly
2735 2740 2745

Asn Thr Val Lys Leu Asn Cys Met Ala Met Gly Ile Pro Lys Ala
2750 2755 2760

Asp Ile Thr Trp Glu Leu Pro Asp Lys Ser His Leu Lys Ala Gly
2765 2770 2775

Val Gln Ala Arg Leu Tyr Gly Asn Arg Phe Leu His Pro Gln Gly
2780 2785 2790

Ser Leu Thr Ile Gln His Ala Thr Gln Arg Asp Ala Gly Phe Tyr
2795 2800 2805

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Lys Cys  Met Ala Lys Asn Ile  Leu Gly Ser Asp Ser  Lys Thr Thr
    2810                 2815                 2820

Tyr Ile  His Val Phe
    2825


<210> SEQ ID NO 37
<211> LENGTH: 442
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Met Ala Leu Pro Ser Arg Ile Leu Leu Trp Lys Leu Val Leu Leu Gln
1               5                   10                  15

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

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

Arg Ala Val Leu Arg Cys Gln Ser Pro Arg Met Val Trp Thr Gln Asp
    50                  55                  60

Arg Leu His Asp Arg Gln Arg Val Leu His Trp Asp Leu Arg Gly Pro
65                  70                  75                  80

Gly Gly Gly Pro Ala Arg Arg Leu Leu Asp Leu Tyr Ser Ala Gly Glu
                85                  90                  95

Gln Arg Val Tyr Glu Ala Arg Asp Arg Gly Arg Leu Glu Leu Ser Ala
            100                 105                 110

Ser Ala Phe Asp Asp Gly Asn Phe Ser Leu Leu Ile Arg Ala Val Glu
        115                 120                 125

Glu Thr Asp Ala Gly Leu Tyr Thr Cys Asn Leu His His His Tyr Cys
    130                 135                 140

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

Pro Ala Thr Pro Ala Tyr Trp Asp Gly Glu Lys Glu Val Leu Ala Val
                165                 170                 175

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

Trp Thr Asp Arg His Val Glu Glu Ala Gln Gln Val Val His Trp Asp
        195                 200                 205

Arg Gln Pro Pro Gly Val Pro His Asp Arg Ala Asp Arg Leu Leu Asp
    210                 215                 220

Leu Tyr Ala Ser Gly Glu Arg Arg Ala Tyr Gly Pro Leu Phe Leu Arg
225                 230                 235                 240

Asp Arg Val Ala Val Gly Ala Asp Ala Phe Glu Arg Gly Asp Phe Ser
                245                 250                 255

Leu Arg Ile Glu Pro Leu Glu Val Ala Asp Glu Gly Thr Tyr Ser Cys
            260                 265                 270

His Leu His His His Tyr Cys Gly Leu His Glu Arg Arg Val Phe His
        275                 280                 285

Leu Thr Val Ala Glu Pro His Ala Glu Pro Pro Pro Arg Gly Ser Pro
    290                 295                 300

Gly Asn Gly Ser Ser His Ser Gly Ala Pro Gly Pro Asp Pro Thr Leu
305                 310                 315                 320

Ala Arg Gly His Asn Val Ile Asn Val Ile Val Pro Glu Ser Arg Ala
                325                 330                 335
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His Phe Phe Gln Gln Leu Gly Tyr Val Leu Ala Thr Leu Leu Leu Phe
            340                 345                 350

Ile Leu Leu Leu Val Thr Val Leu Leu Ala Ala Arg Arg Arg Arg Gly
        355                 360                 365

Gly Tyr Glu Tyr Ser Asp Gln Lys Ser Gly Lys Ser Lys Gly Lys Asp
    370                 375                 380

Val Asn Leu Ala Glu Phe Ala Val Ala Ala Gly Asp Gln Met Leu Tyr
385                 390                 395                 400

Arg Ser Glu Asp Ile Gln Leu Asp Tyr Lys Asn Asn Ile Leu Lys Glu
                405                 410                 415

Arg Ala Glu Leu Ala His Ser Pro Leu Pro Ala Lys Tyr Ile Asp Leu
            420                 425                 430

Asp Lys Gly Phe Arg Lys Glu Asn Cys Lys
        435                 440


<210> SEQ ID NO 38
<211> LENGTH: 1375
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

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

Val Leu Leu Leu Leu Pro Leu Leu Met Leu Arg Ala Ala Ala Leu His
            20                  25                  30

Pro Asp Glu Leu Phe Pro His Gly Glu Ser Trp Gly Asp Gln Leu Leu
        35                  40                  45

Gln Glu Gly Asp Asp Glu Ser Ser Ala Val Val Lys Leu Ala Asn Pro
    50                  55                  60

Leu His Phe Tyr Glu Ala Arg Phe Ser Asn Leu Tyr Val Gly Thr Asn
65                  70                  75                  80

Gly Ile Ile Ser Thr Gln Asp Phe Pro Arg Glu Thr Gln Tyr Val Asp
                85                  90                  95

Tyr Asp Phe Pro Thr Asp Phe Pro Ala Ile Ala Pro Phe Leu Ala Asp
            100                 105                 110

Ile Asp Thr Ser His Gly Arg Gly Arg Val Leu Tyr Arg Glu Asp Thr
        115                 120                 125

Ser Pro Ala Val Leu Gly Leu Ala Ala Arg Tyr Val Arg Ala Gly Phe
    130                 135                 140

Pro Arg Ser Ala Arg Phe Thr Pro Thr His Ala Phe Leu Ala Thr Trp
145                 150                 155                 160

Glu Gln Val Gly Ala Tyr Glu Glu Val Lys Arg Gly Ala Leu Pro Ser
                165                 170                 175

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

Ser Tyr Ala Leu Phe Leu Tyr Pro Ala Asn Gly Leu Gln Phe Leu Gly
        195                 200                 205

Thr Arg Pro Lys Glu Ser Tyr Asn Val Gln Leu Gln Leu Pro Ala Arg
    210                 215                 220

Val Gly Phe Cys Arg Gly Glu Ala Asp Asp Leu Lys Ser Glu Gly Pro
225                 230                 235                 240

Tyr Phe Ser Leu Thr Ser Thr Glu Gln Ser Val Lys Asn Leu Tyr Gln
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                245                 250                 255

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

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

Ala Ala His Ser Ser Val Pro Leu Gly Arg Ser Phe Ser His Ala Thr
    290                 295                 300

Ala Leu Glu Ser Asp Tyr Asn Glu Asp Asn Leu Asp Tyr Tyr Asp Val
305                 310                 315                 320

Asn Glu Glu Glu Ala Glu Tyr Leu Pro Gly Glu Pro Glu Glu Ala Leu
                325                 330                 335

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

Lys Pro Leu Glu Glu Ser Ser Thr Leu Asp Pro His Thr Lys Glu Gly
        355                 360                 365

Thr Ser Leu Gly Glu Val Gly Gly Pro Asp Leu Lys Gly Gln Val Glu
    370                 375                 380

Pro Trp Asp Glu Arg Glu Thr Arg Ser Pro Ala Pro Pro Glu Val Asp
385                 390                 395                 400

Arg Asp Ser Leu Ala Pro Ser Trp Glu Thr Pro Pro Pro Tyr Pro Glu
                405                 410                 415

Asn Gly Ser Ile Gln Pro Tyr Pro Asp Gly Gly Pro Val Pro Ser Glu
            420                 425                 430

Met Asp Val Pro Pro Ala His Pro Glu Glu Glu Ile Val Leu Arg Ser
        435                 440                 445

Tyr Pro Ala Ser Gly His Thr Thr Pro Leu Ser Arg Gly Thr Tyr Glu
    450                 455                 460

Val Gly Leu Glu Asp Asn Ile Gly Ser Asn Thr Glu Val Phe Thr Tyr
465                 470                 475                 480

Asn Ala Ala Asn Lys Glu Thr Cys Glu His Asn His Arg Gln Cys Ser
                485                 490                 495

Arg His Ala Phe Cys Thr Asp Tyr Ala Thr Gly Phe Cys Cys His Cys
            500                 505                 510

Gln Ser Lys Phe Tyr Gly Asn Gly Lys His Cys Leu Pro Glu Gly Ala
        515                 520                 525

Pro His Arg Val Asn Gly Lys Val Ser Gly His Leu His Val Gly His
    530                 535                 540

Thr Pro Val His Phe Thr Asp Val Asp Leu His Ala Tyr Ile Val Gly
545                 550                 555                 560

Asn Asp Gly Arg Ala Tyr Thr Ala Ile Ser His Ile Pro Gln Pro Ala
                565                 570                 575

Ala Gln Ala Leu Leu Pro Leu Thr Pro Ile Gly Gly Leu Phe Gly Trp
            580                 585                 590

Leu Phe Ala Leu Glu Lys Pro Gly Ser Glu Asn Gly Phe Ser Leu Ala
        595                 600                 605

Gly Ala Ala Phe Thr His Asp Met Glu Val Thr Phe Tyr Pro Gly Glu
    610                 615                 620

Glu Thr Val Arg Ile Thr Gln Thr Ala Glu Gly Leu Asp Pro Glu Asn
625                 630                 635                 640

Tyr Leu Ser Ile Lys Thr Asn Ile Gln Gly Gln Val Pro Tyr Val Ser
                645                 650                 655
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Ala Asn Phe Thr Ala His Ile Ser Pro Tyr Lys Glu Leu Tyr His Tyr
            660                 665                 670

Ser Asp Ser Thr Val Thr Ser Thr Ser Ser Arg Asp Tyr Ser Leu Thr
        675                 680                 685

Phe Gly Ala Ile Asn Gln Thr Trp Ser Tyr Arg Ile His Gln Asn Ile
    690                 695                 700

Thr Tyr Gln Val Cys Arg His Ala Pro Arg His Pro Ser Phe Pro Thr
705                 710                 715                 720

Thr Gln Gln Leu Asn Val Asp Arg Val Phe Ala Leu Tyr Asn Asp Glu
                725                 730                 735

Glu Arg Val Leu Arg Phe Ala Val Thr Asn Gln Ile Gly Pro Val Lys
            740                 745                 750

Glu Asp Ser Asp Pro Thr Pro Gly Asn Pro Cys Tyr Asp Gly Ser His
        755                 760                 765

Met Cys Asp Thr Thr Ala Arg Cys His Pro Gly Thr Gly Val Asp Tyr
    770                 775                 780

Thr Cys Glu Cys Ala Ser Gly Tyr Gln Gly Asp Gly Arg Asn Cys Val
785                 790                 795                 800

Asp Glu Asn Glu Cys Ala Thr Gly Phe His Arg Cys Gly Pro Asn Ser
                805                 810                 815

Val Cys Ile Asn Leu Pro Gly Ser Tyr Arg Cys Glu Cys Arg Ser Gly
            820                 825                 830

Tyr Glu Phe Ala Asp Asp Arg His Thr Cys Ile Leu Ile Thr Pro Pro
        835                 840                 845

Ala Asn Pro Cys Glu Asp Gly Ser His Thr Cys Ala Pro Ala Gly Gln
    850                 855                 860

Ala Arg Cys Val His His Gly Gly Ser Thr Phe Ser Cys Ala Cys Leu
865                 870                 875                 880

Pro Gly Tyr Ala Gly Asp Gly His Gln Cys Thr Asp Val Asp Glu Cys
                885                 890                 895

Ser Glu Asn Arg Cys His Pro Ala Ala Thr Cys Tyr Asn Thr Pro Gly
            900                 905                 910

Ser Phe Ser Cys Arg Cys Gln Pro Gly Tyr Tyr Gly Asp Gly Phe Gln
        915                 920                 925

Cys Ile Pro Asp Ser Thr Ser Ser Leu Thr Pro Cys Glu Gln Gln Gln
    930                 935                 940

Arg His Ala Gln Ala Gln Tyr Ala Tyr Pro Gly Ala Arg Phe His Ile
945                 950                 955                 960

Pro Gln Cys Asp Glu Gln Gly Asn Phe Leu Pro Leu Gln Cys His Gly
                965                 970                 975

Ser Thr Gly Phe Cys Trp Cys Val Asp Pro Asp Gly His Glu Val Pro
            980                 985                 990

Gly Thr Gln Thr Pro Pro Gly Ser  Thr Pro Pro His Cys  Gly Pro Ser
        995                 1000                 1005

Pro Glu  Pro Thr Gln Arg Pro  Pro Thr Ile Cys Glu  Arg Trp Arg
    1010                 1015                 1020

Glu Asn  Leu Leu Glu His Tyr  Gly Gly Thr Pro Arg  Asp Asp Gln
    1025                 1030                 1035

Tyr Val  Pro Gln Cys Asp Asp  Leu Gly His Phe Ile  Pro Leu Gln
    1040                 1045                 1050
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Cys His Gly Lys Ser Asp Phe Cys Trp Cys Val Asp Lys Asp Gly
1055 1060 1065

Arg Glu Val Gln Gly Thr Arg Ser Gln Pro Gly Thr Thr Pro Ala
1070 1075 1080

Cys Ile Pro Thr Val Ala Pro Pro Met Val Arg Pro Thr Pro Arg
1085 1090 1095

Pro Asp Val Thr Pro Pro Ser Val Gly Thr Phe Leu Leu Tyr Thr
1100 1105 1110

Gln Gly Gln Gln Ile Gly Tyr Leu Pro Leu Asn Gly Thr Arg Leu
1115 1120 1125

Gln Lys Asp Ala Ala Lys Thr Leu Leu Ser Leu His Gly Ser Ile
1130 1135 1140

Ile Val Gly Ile Asp Tyr Asp Cys Arg Glu Arg Met Val Tyr Trp
1145 1150 1155

Thr Asp Val Ala Gly Arg Thr Ile Ser Arg Ala Gly Leu Glu Leu
1160 1165 1170

Gly Ala Glu Pro Glu Thr Ile Val Asn Ser Gly Leu Ile Ser Pro
1175 1180 1185

Glu Gly Leu Ala Ile Asp His Ile Arg Arg Thr Met Tyr Trp Thr
1190 1195 1200

Asp Ser Val Leu Asp Lys Ile Glu Ser Ala Leu Leu Asp Gly Ser
1205 1210 1215

Glu Arg Lys Val Leu Phe Tyr Thr Asp Leu Val Asn Pro Arg Ala
1220 1225 1230

Ile Ala Val Asp Pro Ile Arg Gly Asn Leu Tyr Trp Thr Asp Trp
1235 1240 1245

Asn Arg Glu Ala Pro Lys Ile Glu Thr Ser Ser Leu Asp Gly Glu
1250 1255 1260

Asn Arg Arg Ile Leu Ile Asn Thr Asp Ile Gly Leu Pro Asn Gly
1265 1270 1275

Leu Thr Phe Asp Pro Phe Ser Lys Leu Leu Cys Trp Ala Asp Ala
1280 1285 1290

Gly Thr Lys Lys Leu Glu Cys Thr Leu Pro Asp Gly Thr Gly Arg
1295 1300 1305

Arg Val Ile Gln Asn Asn Leu Lys Tyr Pro Phe Ser Ile Val Ser
1310 1315 1320

Tyr Ala Asp His Phe Tyr His Thr Asp Trp Arg Arg Asp Gly Val
1325 1330 1335

Val Ser Val Asn Lys His Ser Gly Gln Phe Thr Asp Glu Tyr Leu
1340 1345 1350

Pro Glu Gln Arg Ser His Leu Tyr Gly Ile Thr Ala Val Tyr Pro
1355 1360 1365

Tyr Cys Pro Thr Gly Arg Lys
1370 1375

<210> SEQ ID NO 39
<211> LENGTH: 1200
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Met Lys Val Ala Gly Gly Leu Glu Leu Gly Ala Ala Ala Leu Leu Ser
1 5 10 15

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

Ile Leu Pro Lys Asn Pro Leu Phe Pro Gln Asn Leu Ser Ser Gln Pro
        35                  40                  45

Cys Ile Lys Met Glu Gly Asp Lys Ser Leu Thr Phe Ser Ser Tyr Gly
    50                  55                  60

Leu Gln Trp Cys Leu Tyr Glu Leu Asp Lys Glu Glu Phe Gln Thr Phe
65                  70                  75                  80

Lys Glu Leu Leu Lys Lys Lys Ser Ser Glu Ser Thr Thr Cys Ser Ile
                85                  90                  95

Pro Gln Phe Glu Ile Glu Asn Ala Asn Val Glu Cys Leu Ala Leu Leu
            100                 105                 110

Leu His Glu Tyr Tyr Gly Ala Ser Leu Ala Trp Ala Thr Ser Ile Ser
        115                 120                 125

Ile Phe Glu Asn Met Asn Leu Arg Thr Leu Ser Glu Lys Ala Arg Asp
    130                 135                 140

Asp Met Lys Arg His Ser Pro Glu Asp Pro Glu Ala Thr Met Thr Asp
145                 150                 155                 160

Gln Gly Pro Ser Lys Glu Lys Val Pro Gly Ile Ser Gln Ala Val Gln
                165                 170                 175

Gln Asp Ser Ala Thr Ala Ala Glu Thr Lys Glu Gln Glu Ile Ser Gln
            180                 185                 190

Ala Met Glu Gln Glu Gly Ala Thr Ala Ala Glu Thr Glu Glu Gln Glu
        195                 200                 205

Ile Ser Gln Ala Met Glu Gln Glu Gly Ala Thr Ala Ala Glu Thr Glu
    210                 215                 220

Glu Gln Gly His Gly Gly Asp Thr Trp Asp Tyr Lys Ser His Val Met
225                 230                 235                 240

Thr Lys Phe Ala Glu Glu Glu Asp Val Arg Arg Ser Phe Glu Asn Thr
                245                 250                 255

Ala Ala Asp Trp Pro Glu Met Gln Thr Leu Ala Gly Ala Phe Asp Ser
            260                 265                 270

Asp Arg Trp Gly Phe Arg Pro Arg Thr Val Val Leu His Gly Lys Ser
        275                 280                 285

Gly Ile Gly Lys Ser Ala Leu Ala Arg Arg Ile Val Leu Cys Trp Ala
    290                 295                 300

Gln Gly Gly Leu Tyr Gln Gly Met Phe Ser Tyr Val Phe Phe Leu Pro
305                 310                 315                 320

Val Arg Glu Met Gln Arg Lys Lys Glu Ser Ser Val Thr Glu Phe Ile
                325                 330                 335

Ser Arg Glu Trp Pro Asp Ser Gln Ala Pro Val Thr Glu Ile Met Ser
            340                 345                 350

Arg Pro Glu Arg Leu Leu Phe Ile Ile Asp Gly Phe Asp Asp Leu Gly
        355                 360                 365

Ser Val Leu Asn Asn Asp Thr Lys Leu Cys Lys Asp Trp Ala Glu Lys
    370                 375                 380

Gln Pro Pro Phe Thr Leu Ile Arg Ser Leu Leu Arg Lys Val Leu Leu
385                 390                 395                 400

Pro Glu Ser Phe Leu Ile Val Thr Val Arg Asp Val Gly Thr Glu Lys
                405                 410                 415
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Leu Lys Ser Glu Val Val Ser Pro Arg Tyr Leu Leu Val Arg Gly Ile
            420                 425                 430

Ser Gly Glu Gln Arg Ile His Leu Leu Leu Glu Arg Gly Ile Gly Glu
        435                 440                 445

His Gln Lys Thr Gln Gly Leu Arg Ala Ile Met Asn Asn Arg Glu Leu
    450                 455                 460

Leu Asp Gln Cys Gln Val Pro Ala Val Gly Ser Leu Ile Cys Val Ala
465                 470                 475                 480

Leu Gln Leu Gln Asp Val Val Gly Glu Ser Val Ala Pro Phe Asn Gln
                485                 490                 495

Thr Leu Thr Gly Leu His Ala Ala Phe Val Phe His Gln Leu Thr Pro
            500                 505                 510

Arg Gly Val Val Arg Arg Cys Leu Asn Leu Glu Glu Arg Val Val Leu
        515                 520                 525

Lys Arg Phe Cys Arg Met Ala Val Glu Gly Val Trp Asn Arg Lys Ser
    530                 535                 540

Val Phe Asp Gly Asp Asp Leu Met Val Gln Gly Leu Gly Glu Ser Glu
545                 550                 555                 560

Leu Arg Ala Leu Phe His Met Asn Ile Leu Leu Pro Asp Ser His Cys
                565                 570                 575

Glu Glu Tyr Tyr Thr Phe Phe His Leu Ser Leu Gln Asp Phe Cys Ala
            580                 585                 590

Ala Leu Tyr Tyr Val Leu Glu Gly Leu Glu Ile Glu Pro Ala Leu Cys
        595                 600                 605

Pro Leu Tyr Val Glu Lys Thr Lys Arg Ser Met Glu Leu Lys Gln Ala
    610                 615                 620

Gly Phe His Ile His Ser Leu Trp Met Lys Arg Phe Leu Phe Gly Leu
625                 630                 635                 640

Val Ser Glu Asp Val Arg Arg Pro Leu Glu Val Leu Leu Gly Cys Pro
                645                 650                 655

Val Pro Leu Gly Val Lys Gln Lys Leu Leu His Trp Val Ser Leu Leu
            660                 665                 670

Gly Gln Gln Pro Asn Ala Thr Thr Pro Gly Asp Thr Leu Asp Ala Phe
        675                 680                 685

His Cys Leu Phe Glu Thr Gln Asp Lys Glu Phe Val Arg Leu Ala Leu
    690                 695                 700

Asn Ser Phe Gln Glu Val Trp Leu Pro Ile Asn Gln Asn Leu Asp Leu
705                 710                 715                 720

Ile Ala Ser Ser Phe Cys Leu Gln His Cys Pro Tyr Leu Arg Lys Ile
                725                 730                 735

Arg Val Asp Val Lys Gly Ile Phe Pro Arg Asp Glu Ser Ala Glu Ala
            740                 745                 750

Cys Pro Val Val Pro Leu Trp Met Arg Asp Lys Thr Leu Ile Glu Glu
        755                 760                 765

Gln Trp Glu Asp Phe Cys Ser Met Leu Gly Thr His Pro His Leu Arg
    770                 775                 780

Gln Leu Asp Leu Gly Ser Ser Ile Leu Thr Glu Arg Ala Met Lys Thr
785                 790                 795                 800

Leu Cys Ala Lys Leu Arg His Pro Thr Cys Lys Ile Gln Thr Leu Met
                805                 810                 815

Phe Arg Asn Ala Gln Ile Thr Pro Gly Val Gln His Leu Trp Arg Ile
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            820                 825                 830

Val Met Ala Asn Arg Asn Leu Arg Ser Leu Asn Leu Gly Gly Thr His
        835                 840                 845

Leu Lys Glu Glu Asp Val Arg Met Ala Cys Glu Ala Leu Lys His Pro
    850                 855                 860

Lys Cys Leu Leu Glu Ser Leu Arg Leu Asp Cys Cys Gly Leu Thr His
865                 870                 875                 880

Ala Cys Tyr Leu Lys Ile Ser Gln Ile Leu Thr Thr Ser Pro Ser Leu
                885                 890                 895

Lys Ser Leu Ser Leu Ala Gly Asn Lys Val Thr Asp Gln Gly Val Met
            900                 905                 910

Pro Leu Ser Asp Ala Leu Arg Val Ser Gln Cys Ala Leu Gln Lys Leu
        915                 920                 925

Ile Leu Glu Asp Cys Gly Ile Thr Ala Thr Gly Cys Gln Ser Leu Ala
    930                 935                 940

Ser Ala Leu Val Ser Asn Arg Ser Leu Thr His Leu Cys Leu Ser Asn
945                 950                 955                 960

Asn Ser Leu Gly Asn Glu Gly Val Asn Leu Leu Cys Arg Ser Met Arg
                965                 970                 975

Leu Pro His Cys Ser Leu Gln Arg Leu Met Leu Asn Gln Cys His Leu
            980                 985                 990

Asp Thr Ala Gly Cys Gly Phe Leu  Ala Leu Ala Leu Met  Gly Asn Ser
        995                 1000                 1005

Trp Leu  Thr His Leu Ser Leu  Ser Met Asn Pro Val  Glu Asp Asn
    1010                 1015                 1020

Gly Val  Lys Leu Leu Cys Glu  Val Met Arg Glu Pro  Ser Cys His
    1025                 1030                 1035

Leu Gln  Asp Leu Glu Leu Val  Lys Cys His Leu Thr  Ala Ala Cys
    1040                 1045                 1050

Cys Glu  Ser Leu Ser Cys Val  Ile Ser Arg Ser Arg  His Leu Lys
    1055                 1060                 1065

Ser Leu  Asp Leu Thr Asp Asn  Ala Leu Gly Asp Gly  Gly Val Ala
    1070                 1075                 1080

Ala Leu  Cys Glu Gly Leu Lys  Gln Lys Asn Ser Val  Leu Ala Arg
    1085                 1090                 1095

Leu Gly  Leu Lys Ala Cys Gly  Leu Thr Ser Asp Cys  Cys Glu Ala
    1100                 1105                 1110

Leu Ser  Leu Ala Leu Ser Cys  Asn Arg His Leu Thr  Ser Leu Asn
    1115                 1120                 1125

Leu Val  Gln Asn Asn Phe Ser  Pro Lys Gly Met Met  Lys Leu Cys
    1130                 1135                 1140

Ser Ala  Phe Ala Cys Pro Thr  Ser Asn Leu Gln Ile  Ile Gly Leu
    1145                 1150                 1155

Trp Lys  Trp Gln Tyr Pro Val  Gln Ile Arg Lys Leu  Leu Glu Glu
    1160                 1165                 1170

Val Gln  Leu Leu Lys Pro Arg  Val Val Ile Asp Gly  Ser Trp His
    1175                 1180                 1185

Ser Phe  Asp Glu Asp Asp Arg  Tyr Trp Trp Lys Asn
    1190                 1195                 1200


<210> SEQ ID NO 40
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<211> LENGTH: 565
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Met Asp Phe Leu Leu Ala Leu Val Leu Val Ser Ser Leu Tyr Leu Gln
1               5                   10                  15

Ala Ala Ala Glu Phe Asp Gly Arg Trp Pro Arg Gln Ile Val Ser Ser
            20                  25                  30

Ile Gly Leu Cys Arg Tyr Gly Gly Arg Ile Asp Cys Cys Trp Gly Trp
        35                  40                  45

Ala Arg Gln Ser Trp Gly Gln Cys Gln Pro Val Cys Gln Pro Arg Cys
    50                  55                  60

Lys His Gly Glu Cys Ile Gly Pro Asn Lys Cys Lys Cys His Pro Gly
65                  70                  75                  80

Tyr Ala Gly Lys Thr Cys Asn Gln Asp Leu Asn Glu Cys Gly Leu Lys
                85                  90                  95

Pro Arg Pro Cys Lys His Arg Cys Met Asn Thr Tyr Gly Ser Tyr Lys
            100                 105                 110

Cys Tyr Cys Leu Asn Gly Tyr Met Leu Met Pro Asp Gly Ser Cys Ser
        115                 120                 125

Ser Ala Leu Thr Cys Ser Met Ala Asn Cys Gln Tyr Gly Cys Asp Val
    130                 135                 140

Val Lys Gly Gln Ile Arg Cys Gln Cys Pro Ser Pro Gly Leu Gln Leu
145                 150                 155                 160

Ala Pro Asp Gly Arg Thr Cys Val Asp Val Asp Glu Cys Ala Thr Gly
                165                 170                 175

Arg Ala Ser Cys Pro Arg Phe Arg Gln Cys Val Asn Thr Phe Gly Ser
            180                 185                 190

Tyr Ile Cys Lys Cys His Lys Gly Phe Asp Leu Met Tyr Ile Gly Gly
        195                 200                 205

Lys Tyr Gln Cys His Asp Ile Asp Glu Cys Ser Leu Gly Gln Tyr Gln
    210                 215                 220

Cys Ser Ser Phe Ala Arg Cys Tyr Asn Ile Arg Gly Ser Tyr Lys Cys
225                 230                 235                 240

Lys Cys Lys Glu Gly Tyr Gln Gly Asp Gly Leu Thr Cys Val Tyr Ile
                245                 250                 255

Pro Lys Val Met Ile Glu Pro Ser Gly Pro Ile His Val Pro Lys Gly
            260                 265                 270

Asn Gly Thr Ile Leu Lys Gly Asp Thr Gly Asn Asn Asn Trp Ile Pro
        275                 280                 285

Asp Val Gly Ser Thr Trp Trp Pro Pro Lys Thr Pro Tyr Ile Pro Pro
    290                 295                 300

Ile Ile Thr Asn Arg Pro Thr Ser Lys Pro Thr Thr Arg Pro Thr Pro
305                 310                 315                 320

Lys Pro Thr Pro Ile Pro Thr Pro Pro Pro Pro Pro Pro Leu Pro Thr
                325                 330                 335

Glu Leu Arg Thr Pro Leu Pro Pro Thr Thr Pro Glu Arg Pro Thr Thr
            340                 345                 350

Gly Leu Thr Thr Ile Ala Pro Ala Ala Ser Thr Pro Pro Gly Gly Ile
        355                 360                 365

Thr Val Asp Asn Arg Val Gln Thr Asp Pro Gln Lys Pro Arg Gly Asp
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    370                 375                 380

Val Phe Ile Pro Arg Gln Pro Ser Asn Asp Leu Phe Glu Ile Phe Glu
385                 390                 395                 400

Ile Glu Arg Gly Val Ser Ala Asp Asp Glu Ala Lys Asp Asp Pro Gly
                405                 410                 415

Val Leu Val His Ser Cys Asn Phe Asp His Gly Leu Cys Gly Trp Ile
            420                 425                 430

Arg Glu Lys Asp Asn Asp Leu His Trp Glu Pro Ile Arg Asp Pro Ala
        435                 440                 445

Gly Gly Gln Tyr Leu Thr Val Ser Ala Ala Lys Ala Pro Gly Gly Lys
    450                 455                 460

Ala Ala Arg Leu Val Leu Pro Leu Gly Arg Leu Met His Ser Gly Asp
465                 470                 475                 480

Leu Cys Leu Ser Phe Arg His Lys Val Thr Gly Leu His Ser Gly Thr
                485                 490                 495

Leu Gln Val Phe Val Arg Lys His Gly Ala His Gly Ala Ala Leu Trp
            500                 505                 510

Gly Arg Asn Gly Gly His Gly Trp Arg Gln Thr Gln Ile Thr Leu Arg
        515                 520                 525

Gly Ala Asp Ile Lys Ser Val Val Phe Lys Gly Glu Lys Arg Arg Gly
    530                 535                 540

His Thr Gly Glu Ile Gly Leu Asp Asp Val Ser Leu Lys Lys Gly His
545                 550                 555                 560

Cys Ser Glu Glu Arg
                565


<210> SEQ ID NO 41
<211> LENGTH: 298
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Met Lys Thr Leu Gln Ser Thr Leu Leu Leu Leu Leu Leu Val Pro Leu
1               5                   10                  15

Ile Lys Pro Ala Pro Pro Thr Gln Gln Asp Ser Arg Ile Ile Tyr Asp
            20                  25                  30

Tyr Gly Thr Asp Asn Phe Glu Glu Ser Ile Phe Ser Gln Asp Tyr Glu
        35                  40                  45

Asp Lys Tyr Leu Asp Gly Lys Asn Ile Lys Glu Lys Glu Thr Val Ile
    50                  55                  60

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

Pro Leu Pro Pro Lys Lys Glu Asn Asp Glu Met Pro Thr Cys Leu Leu
                85                  90                  95

Cys Val Cys Leu Ser Gly Ser Val Tyr Cys Glu Glu Val Asp Ile Asp
            100                 105                 110

Ala Val Pro Pro Leu Pro Lys Glu Ser Ala Tyr Leu Tyr Ala Arg Phe
        115                 120                 125

Asn Lys Ile Lys Lys Leu Thr Ala Lys Asp Phe Ala Asp Ile Pro Asn
    130                 135                 140

Leu Arg Arg Leu Asp Phe Thr Gly Asn Leu Ile Glu Asp Ile Glu Asp
145                 150                 155                 160
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Gly Thr Phe Ser Lys Leu Ser Leu Leu Glu Glu Leu Ser Leu Ala Glu
                165                 170                 175

Asn Gln Leu Leu Lys Leu Pro Val Leu Pro Pro Lys Leu Thr Leu Phe
            180                 185                 190

Asn Ala Lys Tyr Asn Lys Ile Lys Ser Arg Gly Ile Lys Ala Asn Ala
        195                 200                 205

Phe Lys Lys Leu Asn Asn Leu Thr Phe Leu Tyr Leu Asp His Asn Ala
    210                 215                 220

Leu Glu Ser Val Pro Leu Asn Leu Pro Glu Ser Leu Arg Val Ile His
225                 230                 235                 240

Leu Gln Phe Asn Asn Ile Ala Ser Ile Thr Asp Asp Thr Phe Cys Lys
                245                 250                 255

Ala Asn Asp Thr Ser Tyr Ile Arg Asp Arg Ile Glu Glu Ile Arg Leu
            260                 265                 270

Glu Gly Asn Pro Ile Val Leu Gly Lys His Pro Asn Ser Phe Ile Cys
        275                 280                 285

Leu Lys Arg Leu Pro Ile Gly Ser Tyr Phe
    290                 295


<210> SEQ ID NO 42
<211> LENGTH: 421
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Met Gly Phe Leu Ser Pro Ile Tyr Val Ile Phe Phe Phe Phe Gly Val
1               5                   10                  15

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

Gln Glu Pro Asp Asp Asp Tyr Gln Thr Gly Phe Pro Phe Arg Gln Asn
        35                  40                  45

Val Asp Tyr Gly Val Pro Phe His Gln Tyr Thr Leu Gly Cys Val Ser
    50                  55                  60

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

Arg Lys Leu Lys Thr Ile Pro Asn Ile Pro Met His Ile Gln Gln Leu
                85                  90                  95

Tyr Leu Gln Phe Asn Glu Ile Glu Ala Val Thr Ala Asn Ser Phe Ile
            100                 105                 110

Asn Ala Thr His Leu Lys Glu Ile Asn Leu Ser His Asn Lys Ile Lys
        115                 120                 125

Ser Gln Lys Ile Asp Tyr Gly Val Phe Ala Lys Leu Pro Asn Leu Leu
    130                 135                 140

Gln Leu His Leu Glu His Asn Asn Leu Glu Glu Phe Pro Phe Pro Leu
145                 150                 155                 160

Pro Lys Ser Leu Glu Arg Leu Leu Leu Gly Tyr Asn Glu Ile Ser Lys
                165                 170                 175

Leu Gln Thr Asn Ala Met Asp Gly Leu Val Asn Leu Thr Met Leu Asp
            180                 185                 190

Leu Cys Tyr Asn Tyr Leu His Asp Ser Leu Leu Lys Asp Lys Ile Phe
        195                 200                 205

Ala Lys Met Glu Lys Leu Met Gln Leu Asn Leu Cys Ser Asn Arg Leu
    210                 215                 220
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Glu Ser Met Pro Pro Gly Leu Pro Ser Ser Leu Met Tyr Leu Ser Leu
225                 230                 235                 240

Glu Asn Asn Ser Ile Ser Ser Ile Pro Glu Lys Tyr Phe Asp Lys Leu
                245                 250                 255

Pro Lys Leu His Thr Leu Arg Met Ser His Asn Lys Leu Gln Asp Ile
            260                 265                 270

Pro Tyr Asn Ile Phe Asn Leu Pro Asn Ile Val Glu Leu Ser Val Gly
        275                 280                 285

His Asn Lys Leu Lys Gln Ala Phe Tyr Ile Pro Arg Asn Leu Glu His
    290                 295                 300

Leu Tyr Leu Gln Asn Asn Glu Ile Glu Lys Met Asn Leu Thr Val Met
305                 310                 315                 320

Cys Pro Ser Ile Asp Pro Leu His Tyr His His Leu Thr Tyr Ile Arg
                325                 330                 335

Val Asp Gln Asn Lys Leu Lys Glu Pro Ile Ser Ser Tyr Ile Phe Phe
            340                 345                 350

Cys Phe Pro His Ile His Thr Ile Tyr Tyr Gly Glu Gln Arg Ser Thr
        355                 360                 365

Asn Gly Gln Thr Ile Gln Leu Lys Thr Gln Val Phe Arg Arg Phe Pro
    370                 375                 380

Asp Asp Asp Asp Glu Ser Glu Asp His Asp Asp Pro Asp Asn Ala His
385                 390                 395                 400

Glu Ser Pro Glu Gln Glu Gly Ala Glu Gly His Phe Asp Leu His Tyr
                405                 410                 415

Tyr Glu Asn Gln Glu
            420


<210> SEQ ID NO 43
<211> LENGTH: 979
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

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

Ser Leu Arg Thr Tyr Gln Ser Glu Val Leu Ala Glu Arg Leu Pro Leu
            20                  25                  30

Thr Pro Val Ser Leu Lys Val Ser Thr Asn Ser Thr Arg Gln Ser Leu
        35                  40                  45

His Leu Gln Trp Thr Val His Asn Leu Pro Tyr His Gln Glu Leu Lys
    50                  55                  60

Met Val Phe Gln Ile Gln Ile Ser Arg Ile Glu Thr Ser Asn Val Ile
65                  70                  75                  80

Trp Val Gly Asn Tyr Ser Thr Thr Val Lys Trp Asn Gln Val Leu His
                85                  90                  95

Trp Ser Trp Glu Ser Glu Leu Pro Leu Glu Cys Ala Thr His Phe Val
            100                 105                 110

Arg Ile Lys Ser Leu Val Asp Asp Ala Lys Phe Pro Glu Pro Asn Phe
        115                 120                 125

Trp Ser Asn Trp Ser Ser Trp Glu Glu Val Ser Val Gln Asp Ser Thr
    130                 135                 140

Gly Gln Asp Ile Leu Phe Val Phe Pro Lys Asp Lys Leu Val Glu Glu
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145                 150                 155                 160

Gly Thr Asn Val Thr Ile Cys Tyr Val Ser Arg Asn Ile Gln Asn Asn
                165                 170                 175

Val Ser Cys Tyr Leu Glu Gly Lys Gln Ile His Gly Glu Gln Leu Asp
            180                 185                 190

Pro His Val Thr Ala Phe Asn Leu Asn Ser Val Pro Phe Ile Arg Asn
        195                 200                 205

Lys Gly Thr Asn Ile Tyr Cys Glu Ala Ser Gln Gly Asn Val Ser Glu
    210                 215                 220

Gly Met Lys Gly Ile Val Leu Phe Val Ser Lys Val Leu Glu Glu Pro
225                 230                 235                 240

Lys Asp Phe Ser Cys Glu Thr Glu Asp Phe Lys Thr Leu His Cys Thr
                245                 250                 255

Trp Asp Pro Gly Thr Asp Thr Ala Leu Gly Trp Ser Lys Gln Pro Ser
            260                 265                 270

Gln Ser Tyr Thr Leu Phe Glu Ser Phe Ser Gly Glu Lys Lys Leu Cys
        275                 280                 285

Thr His Lys Asn Trp Cys Asn Trp Gln Ile Thr Gln Asp Ser Gln Glu
    290                 295                 300

Thr Tyr Asn Phe Thr Leu Ile Ala Glu Asn Tyr Leu Arg Lys Arg Ser
305                 310                 315                 320

Val Asn Ile Leu Phe Asn Leu Thr His Arg Val Tyr Leu Met Asn Pro
                325                 330                 335

Phe Ser Val Asn Phe Glu Asn Val Asn Ala Thr Asn Ala Ile Met Thr
            340                 345                 350

Trp Lys Val His Ser Ile Arg Asn Asn Phe Thr Tyr Leu Cys Gln Ile
        355                 360                 365

Glu Leu His Gly Glu Gly Lys Met Met Gln Tyr Asn Val Ser Ile Lys
    370                 375                 380

Val Asn Gly Glu Tyr Phe Leu Ser Glu Leu Glu Pro Ala Thr Glu Tyr
385                 390                 395                 400

Met Ala Arg Val Arg Cys Ala Asp Ala Ser His Phe Trp Lys Trp Ser
                405                 410                 415

Glu Trp Ser Gly Gln Asn Phe Thr Thr Leu Glu Ala Ala Pro Ser Glu
            420                 425                 430

Ala Pro Asp Val Trp Arg Ile Val Ser Leu Glu Pro Gly Asn His Thr
        435                 440                 445

Val Thr Leu Phe Trp Lys Pro Leu Ser Lys Leu His Ala Asn Gly Lys
    450                 455                 460

Ile Leu Phe Tyr Asn Val Val Val Glu Asn Leu Asp Lys Pro Ser Ser
465                 470                 475                 480

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

Leu Asp Arg Cys Ser Tyr Gln Ile Cys Val Ile Ala Asn Asn Ser Val
            500                 505                 510

Gly Ala Ser Pro Ala Ser Val Ile Val Ile Ser Ala Asp Pro Glu Asn
        515                 520                 525

Lys Glu Val Glu Glu Glu Arg Ile Ala Gly Thr Glu Gly Gly Phe Ser
    530                 535                 540

Leu Ser Trp Lys Pro Gln Pro Gly Asp Val Ile Gly Tyr Val Val Asp
545                 550                 555                 560
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Trp Cys Asp His Thr Gln Asp Val Leu Gly Asp Phe Gln Trp Lys Asn
                565                 570                 575

Val Gly Pro Asn Thr Thr Ser Thr Val Ile Ser Thr Asp Ala Phe Arg
            580                 585                 590

Pro Gly Val Arg Tyr Asp Phe Arg Ile Tyr Gly Leu Ser Thr Lys Arg
        595                 600                 605

Ile Ala Cys Leu Leu Glu Lys Lys Thr Gly Tyr Ser Gln Glu Leu Ala
    610                 615                 620

Pro Ser Asp Asn Pro His Val Leu Val Asp Thr Leu Thr Ser His Ser
625                 630                 635                 640

Phe Thr Leu Ser Trp Lys Asp Tyr Ser Thr Glu Ser Gln Pro Gly Phe
                645                 650                 655

Ile Gln Gly Tyr His Val Tyr Leu Lys Ser Lys Ala Arg Gln Cys His
            660                 665                 670

Pro Arg Phe Glu Lys Ala Val Leu Ser Asp Gly Ser Glu Cys Cys Lys
        675                 680                 685

Tyr Lys Ile Asp Asn Pro Glu Glu Lys Ala Leu Ile Val Asp Asn Leu
    690                 695                 700

Lys Pro Glu Ser Phe Tyr Glu Phe Phe Ile Thr Pro Phe Thr Ser Ala
705                 710                 715                 720

Gly Glu Gly Pro Ser Ala Thr Phe Thr Lys Val Thr Thr Pro Asp Glu
                725                 730                 735

His Ser Ser Met Leu Ile His Ile Leu Leu Pro Met Val Phe Cys Val
            740                 745                 750

Leu Leu Ile Met Val Met Cys Tyr Leu Lys Ser Gln Trp Ile Lys Glu
        755                 760                 765

Thr Cys Tyr Pro Asp Ile Pro Asp Pro Tyr Lys Ser Ser Ile Leu Ser
    770                 775                 780

Leu Ile Lys Phe Lys Glu Asn Pro His Leu Ile Ile Met Asn Val Ser
785                 790                 795                 800

Asp Cys Ile Pro Asp Ala Ile Glu Val Val Ser Lys Pro Glu Gly Thr
                805                 810                 815

Lys Ile Gln Phe Leu Gly Thr Arg Lys Ser Leu Thr Glu Thr Glu Leu
            820                 825                 830

Thr Lys Pro Asn Tyr Leu Tyr Leu Leu Pro Thr Glu Lys Asn His Ser
        835                 840                 845

Gly Pro Gly Pro Cys Ile Cys Phe Glu Asn Leu Thr Tyr Asn Gln Ala
    850                 855                 860

Ala Ser Asp Ser Gly Ser Cys Gly His Val Pro Val Ser Pro Lys Ala
865                 870                 875                 880

Pro Ser Met Leu Gly Leu Met Thr Ser Pro Glu Asn Val Leu Lys Ala
                885                 890                 895

Leu Glu Lys Asn Tyr Met Asn Ser Leu Gly Glu Ile Pro Ala Gly Glu
            900                 905                 910

Thr Ser Leu Asn Tyr Val Ser Gln Leu Ala Ser Pro Met Phe Gly Asp
        915                 920                 925

Lys Asp Ser Leu Pro Thr Asn Pro Val Glu Ala Pro His Cys Ser Glu
    930                 935                 940

Tyr Lys Met Gln Met Ala Val Ser Leu Arg Leu Ala Leu Pro Pro Pro
945                 950                 955                 960
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Thr Glu Asn Ser Ser Leu Ser Ser Ile Thr Leu Leu Asp Pro Gly Glu
                965                 970                 975

His Tyr Cys


<210> SEQ ID NO 44
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Met Leu Asp Trp Arg Leu Ala Ser Ala His Phe Ile Leu Ala Val Thr
1               5                   10                  15

Leu Thr Leu Trp Ser Ser Gly Lys Val Leu Ser Val Asp Val Thr Thr
            20                  25                  30

Thr Glu Ala Phe Asp Ser Gly Val Ile Asp Val Gln Ser Thr Pro Thr
        35                  40                  45

Val Arg Glu Glu Lys Ser Ala Thr Asp Leu Thr Ala Lys Leu Leu Leu
    50                  55                  60

Leu Asp Glu Leu Val Ser Leu Glu Asn Asp Val Ile Glu Thr Lys Lys
65                  70                  75                  80

Lys Arg Ser Phe Ser Gly Phe Gly Ser Pro Leu Asp Arg Leu Ser Ala
                85                  90                  95

Gly Ser Val Asp His Lys Gly Lys Gln Arg Lys Val Val Asp His Pro
            100                 105                 110

Lys Arg Arg Phe Gly Ile Pro Met Asp Arg Ile Gly Arg Asn Arg Leu
        115                 120                 125

Ser Asn Ser Arg Gly
    130


<210> SEQ ID NO 45
<211> LENGTH: 836
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val
1               5                   10                  15

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
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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
    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
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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
                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


<210> SEQ ID NO 46
<211> LENGTH: 1404
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Met Ala Trp Lys Thr Leu Pro Ile Tyr Leu Leu Leu Leu Leu Ser Val
1               5                   10                  15

Phe Val Ile Gln Gln Val Ser Ser Gln Asp Leu Ser Ser Cys Ala Gly
            20                  25                  30

Arg Cys Gly Glu Gly Tyr Ser Arg Asp Ala Thr Cys Asn Cys Asp Tyr
        35                  40                  45

Asn Cys Gln His Tyr Met Glu Cys Cys Pro Asp Phe Lys Arg Val Cys
    50                  55                  60

Thr Ala Glu Leu Ser Cys Lys Gly Arg Cys Phe Glu Ser Phe Glu Arg
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65                  70                  75                  80

Gly Arg Glu Cys Asp Cys Asp Ala Gln Cys Lys Lys Tyr Asp Lys Cys
                85                  90                  95

Cys Pro Asp Tyr Glu Ser Phe Cys Ala Glu Val His Asn Pro Thr Ser
            100                 105                 110

Pro Pro Ser Ser Lys Lys Ala Pro Pro Pro Ser Gly Ala Ser Gln Thr
        115                 120                 125

Ile Lys Ser Thr Thr Lys Arg Ser Pro Lys Pro Pro Asn Lys Lys Lys
    130                 135                 140

Thr Lys Lys Val Ile Glu Ser Glu Glu Ile Thr Glu Glu His Ser Val
145                 150                 155                 160

Ser Glu Asn Gln Glu Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser
                165                 170                 175

Ser Thr Ile Arg Lys Ile Lys Ser Ser Lys Asn Ser Ala Ala Asn Arg
            180                 185                 190

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

Lys Lys Lys Pro Thr Pro Lys Pro Pro Val Val Asp Glu Ala Gly Ser
    210                 215                 220

Gly Leu Asp Asn Gly Asp Phe Lys Val Thr Thr Pro Asp Thr Ser Thr
225                 230                 235                 240

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

Pro Ile Asn Pro Arg Pro Ser Leu Pro Pro Asn Ser Asp Thr Ser Lys
            260                 265                 270

Glu Thr Ser Leu Thr Val Asn Lys Glu Thr Thr Val Glu Thr Lys Glu
        275                 280                 285

Thr Thr Thr Thr Asn Lys Gln Thr Ser Thr Asp Gly Lys Glu Lys Thr
    290                 295                 300

Thr Ser Ala Lys Glu Thr Gln Ser Ile Glu Lys Thr Ser Ala Lys Asp
305                 310                 315                 320

Leu Ala Pro Thr Ser Lys Val Leu Ala Lys Pro Thr Pro Lys Ala Glu
                325                 330                 335

Thr Thr Thr Lys Gly Pro Ala Leu Thr Thr Pro Lys Glu Pro Thr Pro
            340                 345                 350

Thr Thr Pro Lys Glu Pro Ala Ser Thr Thr Pro Lys Glu Pro Thr Pro
        355                 360                 365

Thr Thr Ile Lys Ser Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr
    370                 375                 380

Thr Thr Lys Ser Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr
385                 390                 395                 400

Thr Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr
                405                 410                 415

Thr Lys Glu Pro Ala Pro Thr Thr Thr Lys Ser Ala Pro Thr Thr Pro
            420                 425                 430

Lys Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Thr Thr Pro
        435                 440                 445

Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro Thr Pro Thr Thr Pro
    450                 455                 460

Lys Glu Pro Ala Pro Thr Thr Lys Glu Pro Ala Pro Thr Thr Pro Lys
465                 470                 475                 480
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Glu Pro Ala Pro Thr Ala Pro Lys Lys Pro Ala Pro Thr Thr Pro Lys
                485                 490                 495

Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Thr Lys
            500                 505                 510

Glu Pro Ser Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Thr Lys
        515                 520                 525

Ser Ala Pro Thr Thr Thr Lys Glu Pro Ala Pro Thr Thr Thr Lys Ser
    530                 535                 540

Ala Pro Thr Thr Pro Lys Glu Pro Ser Pro Thr Thr Thr Lys Glu Pro
545                 550                 555                 560

Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro
                565                 570                 575

Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro
            580                 585                 590

Ala Pro Thr Thr Thr Lys Lys Pro Ala Pro Thr Thr Pro Lys Glu Pro
        595                 600                 605

Ala Pro Thr Thr Pro Lys Glu Thr Ala Pro Thr Thr Pro Lys Lys Leu
    610                 615                 620

Thr Pro Thr Thr Pro Glu Lys Leu Ala Pro Thr Thr Pro Glu Lys Pro
625                 630                 635                 640

Ala Pro Thr Thr Pro Glu Glu Leu Ala Pro Thr Thr Pro Glu Glu Pro
                645                 650                 655

Thr Pro Thr Thr Pro Glu Glu Pro Ala Pro Thr Thr Pro Lys Ala Ala
            660                 665                 670

Ala Pro Asn Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro
        675                 680                 685

Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Thr
    690                 695                 700

Ala Pro Thr Thr Pro Lys Gly Thr Ala Pro Thr Thr Leu Lys Glu Pro
705                 710                 715                 720

Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Lys Glu Leu Ala Pro Thr
                725                 730                 735

Thr Thr Lys Glu Pro Thr Ser Thr Thr Cys Asp Lys Pro Ala Pro Thr
            740                 745                 750

Thr Pro Lys Gly Thr Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr
        755                 760                 765

Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Gly Thr Ala Pro Thr
    770                 775                 780

Thr Leu Lys Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Lys
785                 790                 795                 800

Glu Leu Ala Pro Thr Thr Thr Lys Gly Pro Thr Ser Thr Thr Ser Asp
                805                 810                 815

Lys Pro Ala Pro Thr Thr Pro Lys Glu Thr Ala Pro Thr Thr Pro Lys
            820                 825                 830

Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Thr Thr Pro Glu
        835                 840                 845

Thr Pro Pro Pro Thr Thr Ser Glu Val Ser Thr Pro Thr Thr Thr Lys
    850                 855                 860

Glu Pro Thr Thr Ile His Lys Ser Pro Asp Glu Ser Thr Pro Glu Leu
865                 870                 875                 880
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Ser Ala Glu Pro Thr Pro Lys Ala Leu Glu Asn Ser Pro Lys Glu Pro
                885                 890                 895

Gly Val Pro Thr Thr Lys Thr Pro Ala Ala Thr Lys Pro Glu Met Thr
            900                 905                 910

Thr Thr Ala Lys Asp Lys Thr Thr Glu Arg Asp Leu Arg Thr Thr Pro
        915                 920                 925

Glu Thr Thr Thr Ala Ala Pro Lys Met Thr Lys Glu Thr Ala Thr Thr
    930                 935                 940

Thr Glu Lys Thr Thr Glu Ser Lys Ile Thr Ala Thr Thr Thr Gln Val
945                 950                 955                 960

Thr Ser Thr Thr Thr Gln Asp Thr Thr Pro Phe Lys Ile Thr Thr Leu
                965                 970                 975

Lys Thr Thr Thr Leu Ala Pro Lys Val Thr Thr Thr Lys Lys Thr Ile
            980                 985                 990

Thr Thr Thr Glu Ile Met Asn Lys  Pro Glu Glu Thr Ala  Lys Pro Lys
        995                 1000                1005

Asp Arg  Ala Thr Asn Ser Lys  Ala Thr Thr Pro Lys  Pro Gln Lys
    1010                1015                1020

Pro Thr  Lys Ala Pro Lys Lys  Pro Thr Ser Thr Lys  Lys Pro Lys
    1025                1030                1035

Thr Met  Pro Arg Val Arg Lys  Pro Lys Thr Thr Pro  Thr Pro Arg
    1040                1045                1050

Lys Met  Thr Ser Thr Met Pro  Glu Leu Asn Pro Thr  Ser Arg Ile
    1055                1060                1065

Ala Glu  Ala Met Leu Gln Thr  Thr Thr Arg Pro Asn  Gln Thr Pro
    1070                1075                1080

Asn Ser  Lys Leu Val Glu Val  Asn Pro Lys Ser Glu  Asp Ala Gly
    1085                1090                1095

Gly Ala  Glu Gly Glu Thr Pro  His Met Leu Leu Arg  Pro His Val
    1100                1105                1110

Phe Met  Pro Glu Val Thr Pro  Asp Met Asp Tyr Leu  Pro Arg Val
    1115                1120                1125

Pro Asn  Gln Gly Ile Ile Ile  Asn Pro Met Leu Ser  Asp Glu Thr
    1130                1135                1140

Asn Ile  Cys Asn Gly Lys Pro  Val Asp Gly Leu Thr  Thr Leu Arg
    1145                1150                1155

Asn Gly  Thr Leu Val Ala Phe  Arg Gly His Tyr Phe  Trp Met Leu
    1160                1165                1170

Ser Pro  Phe Ser Pro Pro Ser  Pro Ala Arg Arg Ile  Thr Glu Val
    1175                1180                1185

Trp Gly  Ile Pro Ser Pro Ile  Asp Thr Val Phe Thr  Arg Cys Asn
    1190                1195                1200

Cys Glu  Gly Lys Thr Phe Phe  Phe Lys Asp Ser Gln  Tyr Trp Arg
    1205                1210                1215

Phe Thr  Asn Asp Ile Lys Asp  Ala Gly Tyr Pro Lys  Pro Ile Phe
    1220                1225                1230

Lys Gly  Phe Gly Gly Leu Thr  Gly Gln Ile Val Ala  Ala Leu Ser
    1235                1240                1245

Thr Ala  Lys Tyr Lys Asn Trp  Pro Glu Ser Val Tyr  Phe Phe Lys
    1250                1255                1260

Arg Gly  Gly Ser Ile Gln Gln  Tyr Ile Tyr Lys Gln  Glu Pro Val
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    1265                 1270                 1275

Gln Lys  Cys Pro Gly Arg Arg  Pro Ala Leu Asn Tyr  Pro Val Tyr
    1280                 1285                 1290

Gly Glu  Thr Thr Gln Val Arg  Arg Arg Arg Phe Glu  Arg Ala Ile
    1295                 1300                 1305

Gly Pro  Ser Gln Thr His Thr  Ile Arg Ile Gln Tyr  Ser Pro Ala
    1310                 1315                 1320

Arg Leu  Ala Tyr Gln Asp Lys  Gly Val Leu His Asn  Glu Val Lys
    1325                 1330                 1335

Val Ser  Ile Leu Trp Arg Gly  Leu Pro Asn Val Val  Thr Ser Ala
    1340                 1345                 1350

Ile Ser  Leu Pro Asn Ile Arg  Lys Pro Asp Gly Tyr  Asp Tyr Tyr
    1355                 1360                 1365

Ala Phe  Ser Lys Asp Gln Tyr  Tyr Asn Ile Asp Val  Pro Ser Arg
    1370                 1375                 1380

Thr Ala  Arg Ala Ile Thr Thr  Arg Ser Gly Gln Thr  Leu Ser Lys
    1385                 1390                 1395

Val Trp  Tyr Asn Cys Pro
    1400


<210> SEQ ID NO 47
<211> LENGTH: 168
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Met Gln Ala Gln Gln Tyr Gln Gln Gln Arg Arg Lys Phe Ala Ala Ala
1               5                   10                  15

Phe Leu Ala Phe Ile Phe Ile Leu Ala Ala Val Asp Thr Ala Glu Ala
            20                  25                  30

Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser Asp Cys Gly
        35                  40                  45

Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly Asp Cys Gly Leu
    50                  55                  60

Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu Cys Lys Gln Thr Met
65                  70                  75                  80

Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn Trp Lys Lys Gln Phe Gly
                85                  90                  95

Ala Glu Cys Lys Tyr Gln Phe Gln Ala Trp Gly Glu Cys Asp Leu Asn
            100                 105                 110

Thr Ala Leu Lys Thr Arg Thr Gly Ser Leu Lys Arg Ala Leu His Asn
        115                 120                 125

Ala Glu Cys Gln Lys Thr Val Thr Ile Ser Lys Pro Cys Gly Lys Leu
    130                 135                 140

Thr Lys Pro Lys Pro Gln Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly
145                 150                 155                 160

Lys Lys Gln Glu Lys Met Leu Asp
                165


<210> SEQ ID NO 48
<211> LENGTH: 328
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 48

Met Met Trp Arg Trp Thr Leu Met Leu Leu Leu Leu Leu Leu Arg His
1               5                   10                  15

Trp Ala Leu Gly Lys Pro Ser Pro Asp Ala Gly Pro His Gly Gln Asp
            20                  25                  30

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

His Gly Asn Phe Gln Tyr Asp His Glu Ala Phe Leu Gly Arg Asp Val
    50                  55                  60

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

Gly Arg Ile Val Asp Arg Met Asp Leu Ala Gly Asp Ser Asp Gly Trp
                85                  90                  95

Val Ser Leu Ala Glu Leu Arg Ala Trp Ile Ala His Thr Gln Gln Arg
            100                 105                 110

His Ile Arg Asp Ser Val Ser Ala Ala Trp His Thr Tyr Asp Thr Asp
        115                 120                 125

Arg Asp Gly Arg Val Gly Trp Glu Glu Leu Arg Asn Ala Thr Tyr Gly
    130                 135                 140

His Tyr Glu Pro Gly Glu Glu Phe His Asp Val Glu Asp Ala Glu Thr
145                 150                 155                 160

Tyr Lys Lys Met Leu Ala Arg Asp Glu Arg Arg Phe Arg Val Ala Asp
                165                 170                 175

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

His Pro Glu Glu Phe Pro His Met Arg Asp Ile Val Val Ala Glu Thr
        195                 200                 205

Leu Glu Asp Leu Asp Lys Asn Lys Asp Gly Tyr Val Gln Val Glu Glu
    210                 215                 220

Tyr Ile Ala Asp Leu Tyr Ser Ala Glu Pro Gly Glu Glu Glu Pro Ala
225                 230                 235                 240

Trp Val Gln Thr Glu Arg Gln Gln Phe Arg Asp Phe Arg Asp Leu Asn
                245                 250                 255

Lys Asp Gly Arg Leu Asp Gly Ser Glu Val Gly Tyr Trp Val Leu Pro
            260                 265                 270

Pro Ser Gln Asp Gln Pro Leu Val Glu Ala Asn His Leu Leu His Glu
        275                 280                 285

Ser Asp Thr Asp Lys Asp Gly Arg Leu Ser Lys Ala Glu Ile Leu Ser
    290                 295                 300

Asn Trp Asn Met Phe Val Gly Ser Gln Ala Thr Asn Tyr Gly Glu Asp
305                 310                 315                 320

Leu Thr Arg His His Asp Glu Leu
                325


<210> SEQ ID NO 49
<211> LENGTH: 1073
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

Met Arg Val Phe Leu Leu Cys Ala Tyr Ile Leu Leu Leu Met Val Ser
1               5                   10                  15
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Gln Leu Arg Ala Val Ser Phe Pro Glu Asp Asp Glu Pro Leu Asn Thr
            20                  25                  30

Val Asp Tyr His Tyr Ser Arg Gln Tyr Pro Val Phe Arg Gly Arg Pro
        35                  40                  45

Ser Gly Asn Glu Ser Gln His Arg Leu Asp Phe Gln Leu Met Leu Lys
    50                  55                  60

Ile Arg Asp Thr Leu Tyr Ile Ala Gly Arg Asp Gln Val Tyr Thr Val
65                  70                  75                  80

Asn Leu Asn Glu Met Pro Lys Thr Glu Val Ile Pro Asn Lys Lys Leu
                85                  90                  95

Thr Trp Arg Ser Arg Gln Gln Asp Arg Glu Asn Cys Ala Met Lys Gly
            100                 105                 110

Lys His Lys Asp Glu Cys His Asn Phe Ile Lys Val Phe Val Pro Arg
        115                 120                 125

Asn Asp Glu Met Val Phe Val Cys Gly Thr Asn Ala Phe Asn Pro Met
    130                 135                 140

Cys Arg Tyr Tyr Arg Leu Ser Thr Leu Glu Tyr Asp Gly Glu Glu Ile
145                 150                 155                 160

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

Leu Phe Ala Asp Gly Lys Leu Tyr Ser Ala Thr Val Ala Asp Phe Leu
            180                 185                 190

Ala Ser Asp Ala Val Ile Tyr Arg Ser Met Gly Asp Gly Ser Ala Leu
        195                 200                 205

Arg Thr Ile Lys Tyr Asp Ser Lys Trp Ile Lys Glu Pro His Phe Leu
    210                 215                 220

His Ala Ile Glu Tyr Gly Asn Tyr Val Tyr Phe Phe Phe Arg Glu Ile
225                 230                 235                 240

Ala Val Glu His Asn Asn Leu Gly Lys Ala Val Tyr Ser Arg Val Ala
                245                 250                 255

Arg Ile Cys Lys Asn Asp Met Gly Gly Ser Gln Arg Val Leu Glu Lys
            260                 265                 270

His Trp Thr Ser Phe Leu Lys Ala Arg Leu Asn Cys Ser Val Pro Gly
        275                 280                 285

Asp Ser Phe Phe Tyr Phe Asp Val Leu Gln Ser Ile Thr Asp Ile Ile
    290                 295                 300

Gln Ile Asn Gly Ile Pro Thr Val Val Gly Val Phe Thr Thr Gln Leu
305                 310                 315                 320

Asn Ser Ile Pro Gly Ser Ala Val Cys Ala Phe Ser Met Asp Asp Ile
                325                 330                 335

Glu Lys Val Phe Lys Gly Arg Phe Lys Glu Gln Lys Thr Pro Asp Ser
            340                 345                 350

Val Trp Thr Ala Val Pro Glu Asp Lys Val Pro Lys Pro Arg Pro Gly
        355                 360                 365

Cys Cys Ala Lys His Gly Leu Ala Glu Ala Tyr Lys Thr Ser Ile Asp
    370                 375                 380

Phe Pro Asp Glu Thr Leu Ser Phe Ile Lys Ser His Pro Leu Met Asp
385                 390                 395                 400

Ser Ala Val Pro Pro Ile Ala Asp Glu Pro Trp Phe Thr Lys Thr Arg
                405                 410                 415

Val Arg Tyr Arg Leu Thr Ala Ile Ser Val Asp His Ser Ala Gly Pro
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            420                 425                 430

Tyr Gln Asn Tyr Thr Val Ile Phe Val Gly Ser Glu Ala Gly Met Val
        435                 440                 445

Leu Lys Val Leu Ala Lys Thr Ser Pro Phe Ser Leu Asn Asp Ser Val
    450                 455                 460

Leu Leu Glu Glu Ile Glu Ala Tyr Asn His Ala Lys Cys Ser Ala Glu
465                 470                 475                 480

Asn Glu Glu Asp Lys Lys Val Ile Ser Leu Gln Leu Asp Lys Asp His
                485                 490                 495

His Ala Leu Tyr Val Ala Phe Ser Ser Cys Ile Ile Arg Ile Pro Leu
            500                 505                 510

Ser Arg Cys Glu Arg Tyr Gly Ser Cys Lys Lys Ser Cys Ile Ala Ser
        515                 520                 525

Arg Asp Pro Tyr Cys Gly Trp Leu Ser Gln Gly Ser Cys Gly Arg Val
    530                 535                 540

Thr Pro Gly Met Leu Ala Glu Gly Tyr Glu Gln Asp Thr Glu Phe Gly
545                 550                 555                 560

Asn Thr Ala His Leu Gly Asp Cys His Glu Ile Leu Pro Thr Ser Thr
                565                 570                 575

Thr Pro Asp Tyr Lys Ile Phe Gly Gly Pro Thr Ser Asp Met Glu Val
            580                 585                 590

Ser Ser Ser Ser Val Thr Thr Met Ala Ser Ile Pro Glu Ile Thr Pro
        595                 600                 605

Lys Val Ile Asp Thr Trp Arg Pro Lys Leu Thr Ser Ser Arg Lys Phe
    610                 615                 620

Val Val Gln Asp Asp Pro Asn Thr Ser Asp Phe Thr Asp Pro Leu Ser
625                 630                 635                 640

Gly Ile Pro Lys Gly Val Arg Trp Glu Val Gln Ser Gly Glu Ser Asn
                645                 650                 655

Gln Met Val His Met Asn Val Leu Ile Thr Cys Val Phe Ala Ala Phe
            660                 665                 670

Val Leu Gly Ala Phe Ile Ala Gly Val Ala Val Tyr Cys Tyr Arg Asp
        675                 680                 685

Met Phe Val Arg Lys Asn Arg Lys Ile His Lys Asp Ala Glu Ser Ala
    690                 695                 700

Gln Ser Cys Thr Asp Ser Ser Gly Ser Phe Ala Lys Leu Asn Gly Leu
705                 710                 715                 720

Phe Asp Ser Pro Val Lys Glu Tyr Gln Gln Asn Ile Asp Ser Pro Lys
                725                 730                 735

Leu Tyr Ser Asn Leu Leu Thr Ser Arg Lys Glu Leu Pro Pro Asn Gly
            740                 745                 750

Asp Thr Lys Ser Met Val Met Asp His Arg Gly Gln Pro Pro Glu Leu
        755                 760                 765

Ala Ala Leu Pro Thr Pro Glu Ser Thr Pro Val Leu His Gln Lys Thr
    770                 775                 780

Leu Gln Ala Met Lys Ser His Ser Glu Lys Ala His Gly His Gly Ala
785                 790                 795                 800

Ser Arg Lys Glu Thr Pro Gln Phe Phe Pro Ser Ser Pro Pro Pro His
                805                 810                 815

Ser Pro Leu Ser His Gly His Ile Pro Ser Ala Ile Val Leu Pro Asn
            820                 825                 830
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Ala Thr His Asp Tyr Asn Thr Ser Phe Ser Asn Ser Asn Ala His Lys
        835                 840                 845

Ala Glu Lys Lys Leu Gln Asn Ile Asp His Pro Leu Thr Lys Ser Ser
    850                 855                 860

Ser Lys Arg Asp His Arg Arg Ser Val Asp Ser Arg Asn Thr Leu Asn
865                 870                 875                 880

Asp Leu Leu Lys His Leu Asn Asp Pro Asn Ser Asn Pro Lys Ala Ile
                885                 890                 895

Met Gly Asp Ile Gln Met Ala His Gln Asn Leu Met Leu Asp Pro Met
            900                 905                 910

Gly Ser Met Ser Glu Val Pro Pro Lys Val Pro Asn Arg Glu Ala Ser
        915                 920                 925

Leu Tyr Ser Pro Pro Ser Thr Leu Pro Arg Asn Ser Pro Thr Lys Arg
    930                 935                 940

Val Asp Val Pro Thr Thr Pro Gly Val Pro Met Thr Ser Leu Glu Arg
945                 950                 955                 960

Gln Arg Gly Tyr His Lys Asn Ser Ser Gln Arg His Ser Ile Ser Ala
                965                 970                 975

Met Pro Lys Asn Leu Asn Ser Pro Asn Gly Val Leu Leu Ser Arg Gln
            980                 985                 990

Pro Ser Met Asn Arg Gly Gly Tyr  Met Pro Thr Pro Thr  Gly Ala Lys
        995                 1000                 1005

Val Asp  Tyr Ile Gln Gly Thr  Pro Val Ser Val His  Leu Gln Pro
    1010                 1015                 1020

Ser Leu  Ser Arg Gln Ser Ser  Tyr Thr Ser Asn Gly  Thr Leu Pro
    1025                 1030                 1035

Arg Thr  Gly Leu Lys Arg Thr  Pro Ser Leu Lys Pro  Asp Val Pro
    1040                 1045                 1050

Pro Lys  Pro Ser Phe Val Pro  Gln Thr Pro Ser Val  Arg Pro Leu
    1055                 1060                 1065

Asn Lys  Tyr Thr Tyr
    1070
```

<210> SEQ ID NO 50
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

```
Met Asn Trp His Leu Pro Leu Phe Leu Leu Ala Ser Val Thr Leu Pro
1               5                   10                  15

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

Asn Thr Gly Ile Gln Val Phe Asn Gln Ile Val Lys Ser Arg Pro His
        35                  40                  45

Asp Asn Ile Val Ile Ser Pro His Gly Ile Ala Ser Val Leu Gly Met
    50                  55                  60

Leu Gln Leu Gly Ala Asp Gly Arg Thr Lys Lys Gln Leu Ala Met Val
65                  70                  75                  80

Met Arg Tyr Gly Val Asn Gly Val Gly Lys Ile Leu Lys Lys Ile Asn
                85                  90                  95

Lys Ala Ile Val Ser Lys Lys Asn Lys Asp Ile Val Thr Val Ala Asn
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            100                 105                 110

Ala Val Phe Val Lys Asn Ala Ser Glu Ile Glu Val Pro Phe Val Thr
        115                 120                 125

Arg Asn Lys Asp Val Phe Gln Cys Glu Val Arg Asn Val Asn Phe Glu
    130                 135                 140

Asp Pro Ala Ser Ala Cys Asp Ser Ile Asn Ala Trp Val Lys Asn Glu
145                 150                 155                 160

Thr Arg Asp Met Ile Asp Asn Leu Leu Ser Pro Asp Leu Ile Asp Gly
                165                 170                 175

Val Leu Thr Arg Leu Val Leu Val Asn Ala Val Tyr Phe Lys Gly Leu
            180                 185                 190

Trp Lys Ser Arg Phe Gln Pro Glu Asn Thr Lys Lys Arg Thr Phe Val
        195                 200                 205

Ala Ala Asp Gly Lys Ser Tyr Gln Val Pro Met Leu Ala Gln Leu Ser
    210                 215                 220

Val Phe Arg Cys Gly Ser Thr Ser Ala Pro Asn Asp Leu Trp Tyr Asn
225                 230                 235                 240

Phe Ile Glu Leu Pro Tyr His Gly Glu Ser Ile Ser Met Leu Ile Ala
                245                 250                 255

Leu Pro Thr Glu Ser Ser Thr Pro Leu Ser Ala Ile Ile Pro His Ile
            260                 265                 270

Ser Thr Lys Thr Ile Asp Ser Trp Met Ser Ile Met Val Pro Lys Arg
        275                 280                 285

Val Gln Val Ile Leu Pro Lys Phe Thr Ala Val Ala Gln Thr Asp Leu
    290                 295                 300

Lys Glu Pro Leu Lys Val Leu Gly Ile Thr Asp Met Phe Asp Ser Ser
305                 310                 315                 320

Lys Ala Asn Phe Ala Lys Ile Thr Thr Gly Ser Glu Asn Leu His Val
                325                 330                 335

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

Lys Ala Ser Ala Ala Thr Thr Ala Ile Leu Ile Ala Arg Ser Ser Pro
        355                 360                 365

Pro Trp Phe Ile Val Asp Arg Pro Phe Leu Phe Phe Ile Arg His Asn
    370                 375                 380

Pro Thr Gly Ala Val Leu Phe Met Gly Gln Ile Asn Lys Pro
385                 390                 395
```

<210> SEQ ID NO 51
<211> LENGTH: 581
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

```
Met Pro Ala Pro Arg Ala Arg Glu Gln Pro Arg Val Pro Gly Glu Arg
1               5                   10                  15

Gln Pro Leu Leu Pro Arg Gly Ala Arg Gly Pro Arg Arg Trp Arg Arg
            20                  25                  30

Ala Ala Gly Ala Ala Val Leu Leu Val Glu Met Leu Glu Arg Ala Ala
        35                  40                  45

Phe Phe Gly Val Thr Ala Asn Leu Val Leu Tyr Leu Asn Ser Thr Asn
    50                  55                  60
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Phe Asn Trp Thr Gly Glu Gln Ala Thr Arg Ala Ala Leu Val Phe Leu
65                  70                  75                  80

Gly Ala Ser Tyr Leu Leu Ala Pro Val Gly Gly Trp Leu Ala Asp Val
                85                  90                  95

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

Ala Ala Ser Gly Leu Leu Pro Ala Thr Ala Phe Pro Asp Gly Arg Ser
        115                 120                 125

Ser Phe Cys Gly Glu Met Pro Ala Ser Pro Leu Gly Pro Ala Cys Pro
    130                 135                 140

Ser Ala Gly Cys Pro Arg Ser Ser Pro Ser Pro Tyr Cys Ala Pro Val
145                 150                 155                 160

Leu Tyr Ala Gly Leu Leu Leu Leu Gly Leu Ala Ala Ser Ser Val Arg
                165                 170                 175

Ser Asn Leu Thr Ser Phe Gly Ala Asp Gln Val Met Asp Leu Gly Arg
            180                 185                 190

Asp Ala Thr Arg Arg Phe Phe Asn Trp Phe Tyr Trp Ser Ile Asn Leu
        195                 200                 205

Gly Ala Val Leu Ser Leu Leu Val Val Ala Phe Ile Gln Gln Asn Ile
    210                 215                 220

Ser Phe Leu Leu Gly Tyr Ser Ile Pro Val Gly Cys Val Gly Leu Ala
225                 230                 235                 240

Phe Phe Ile Phe Leu Phe Ala Thr Pro Val Phe Ile Thr Lys Pro Pro
                245                 250                 255

Met Gly Ser Gln Val Ser Ser Met Leu Lys Leu Ala Leu Gln Asn Cys
            260                 265                 270

Cys Pro Gln Leu Trp Gln Arg His Ser Ala Arg Asp Arg Gln Cys Ala
        275                 280                 285

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

Glu Asp Ile Ala Asn Phe Gln Val Leu Val Lys Ile Leu Pro Val Met
305                 310                 315                 320

Val Thr Leu Val Pro Tyr Trp Met Val Tyr Phe Gln Met Gln Ser Thr
                325                 330                 335

Tyr Val Leu Gln Gly Leu His Leu His Ile Pro Asn Ile Phe Pro Ala
            340                 345                 350

Asn Pro Ala Asn Ile Ser Val Ala Leu Arg Ala Gln Gly Ser Ser Tyr
        355                 360                 365

Thr Ile Pro Glu Ala Trp Leu Leu Leu Ala Asn Val Val Val Val Leu
    370                 375                 380

Ile Leu Val Pro Leu Lys Asp Arg Leu Ile Asp Pro Leu Leu Leu Arg
385                 390                 395                 400

Cys Lys Leu Leu Pro Ser Ala Leu Gln Lys Met Ala Leu Gly Met Phe
                405                 410                 415

Phe Gly Phe Thr Ser Val Ile Val Ala Gly Val Leu Glu Met Glu Arg
            420                 425                 430

Leu His Tyr Ile His His Asn Glu Thr Val Ser Gln Gln Ile Gly Glu
        435                 440                 445

Val Leu Tyr Asn Ala Ala Pro Leu Ser Ile Trp Trp Gln Ile Pro Gln
    450                 455                 460

Tyr Leu Leu Ile Gly Ile Ser Glu Ile Phe Ala Ser Ile Pro Gly Leu
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465                 470                 475                 480

Glu Phe Ala Tyr Ser Glu Ala Pro Arg Ser Met Gln Gly Ala Ile Met
                485                 490                 495

Gly Ile Phe Phe Cys Leu Ser Gly Val Gly Ser Leu Leu Gly Ser Ser
            500                 505                 510

Leu Val Ala Leu Leu Ser Leu Pro Gly Gly Trp Leu His Cys Pro Lys
        515                 520                 525

Asp Phe Gly Asn Ile Asn Asn Cys Arg Met Asp Leu Tyr Phe Phe Leu
    530                 535                 540

Leu Ala Gly Ile Gln Ala Val Thr Ala Leu Leu Phe Val Trp Ile Ala
545                 550                 555                 560

Gly Arg Tyr Glu Arg Ala Ser Gln Gly Pro Ala Ser His Ser Arg Phe
                565                 570                 575

Ser Arg Asp Arg Gly
            580


<210> SEQ ID NO 52
<211> LENGTH: 691
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

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

Val Gly Phe Gln Asn Glu Glu Asn Phe Leu Glu Asn Glu Asn Thr Ser
            20                  25                  30

Gly Asn Asn Ser Ile Arg Ser Arg Ala Val Gln Ser Arg Glu His Thr
        35                  40                  45

Asn Thr Lys Gln Asp Glu Glu Gln Val Thr Val Glu Gln Asp Ser Pro
    50                  55                  60

Arg Asn Arg Glu His Met Glu Asp Asp Asp Glu Glu Met Gln Gln Lys
65                  70                  75                  80

Gly Cys Leu Glu Arg Arg Tyr Asp Thr Val Cys Gly Phe Cys Arg Lys
                85                  90                  95

His Lys Thr Thr Leu Arg His Ile Ile Trp Gly Ile Leu Leu Ala Gly
            100                 105                 110

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

Leu Pro Leu Phe Val Ile Thr Val Ala Ala Ile Phe Phe Val Val Trp
    130                 135                 140

Asp His Leu Met Ala Lys Tyr Glu His Arg Ile Asp Glu Met Leu Ser
145                 150                 155                 160

Pro Gly Arg Arg Leu Leu Asn Ser His Trp Phe Trp Leu Lys Trp Val
                165                 170                 175

Ile Trp Ser Ser Leu Val Leu Ala Val Ile Phe Trp Leu Ala Phe Asp
            180                 185                 190

Thr Ala Lys Leu Gly Gln Gln Gln Leu Val Ser Phe Gly Gly Leu Ile
        195                 200                 205

Met Tyr Ile Val Leu Leu Phe Leu Phe Ser Lys Tyr Pro Thr Arg Val
    210                 215                 220

Tyr Trp Arg Pro Val Leu Trp Gly Ile Gly Leu Gln Phe Leu Leu Gly
225                 230                 235                 240
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Leu Leu Ile Leu Arg Thr Asp Pro Gly Phe Ile Ala Phe Asp Trp Leu
                245                 250                 255

Gly Arg Gln Val Gln Thr Phe Leu Glu Tyr Thr Asp Ala Gly Ala Ser
            260                 265                 270

Phe Val Phe Gly Glu Lys Tyr Lys Asp His Phe Phe Ala Phe Lys Val
        275                 280                 285

Leu Pro Ile Val Val Phe Phe Ser Thr Val Met Ser Met Leu Tyr Tyr
    290                 295                 300

Leu Gly Leu Met Gln Trp Ile Ile Arg Lys Val Gly Trp Ile Met Leu
305                 310                 315                 320

Val Thr Thr Gly Ser Ser Pro Ile Glu Ser Val Val Ala Ser Gly Asn
                325                 330                 335

Ile Phe Val Gly Gln Thr Glu Ser Pro Leu Leu Val Arg Pro Tyr Leu
            340                 345                 350

Pro Tyr Ile Thr Lys Ser Glu Leu His Ala Ile Met Thr Ala Gly Phe
        355                 360                 365

Ser Thr Ile Ala Gly Ser Val Leu Gly Ala Tyr Ile Ser Phe Gly Val
    370                 375                 380

Pro Ser Ser His Leu Leu Thr Ala Ser Val Met Ser Ala Pro Ala Ser
385                 390                 395                 400

Leu Ala Ala Ala Lys Leu Phe Trp Pro Glu Thr Glu Lys Pro Lys Ile
                405                 410                 415

Thr Leu Lys Asn Ala Met Lys Met Glu Ser Gly Asp Ser Gly Asn Leu
            420                 425                 430

Leu Glu Ala Ala Thr Gln Gly Ala Ser Ser Ser Ile Ser Leu Val Ala
        435                 440                 445

Asn Ile Ala Val Asn Leu Ile Ala Phe Leu Ala Leu Leu Ser Phe Met
    450                 455                 460

Asn Ser Ala Leu Ser Trp Phe Gly Asn Met Phe Asp Tyr Pro Gln Leu
465                 470                 475                 480

Ser Phe Glu Leu Ile Cys Ser Tyr Ile Phe Met Pro Phe Ser Phe Met
                485                 490                 495

Met Gly Val Glu Trp Gln Asp Ser Phe Met Val Ala Arg Leu Ile Gly
            500                 505                 510

Tyr Lys Thr Phe Phe Asn Glu Phe Val Ala Tyr Glu His Leu Ser Lys
        515                 520                 525

Trp Ile His Leu Arg Lys Glu Gly Gly Pro Lys Phe Val Asn Gly Val
    530                 535                 540

Gln Gln Tyr Ile Ser Ile Arg Ser Glu Ile Ile Ala Thr Tyr Ala Leu
545                 550                 555                 560

Cys Gly Phe Ala Asn Ile Gly Ser Leu Gly Ile Val Ile Gly Gly Leu
                565                 570                 575

Thr Ser Met Ala Pro Ser Arg Lys Arg Asp Ile Ala Ser Gly Ala Val
            580                 585                 590

Arg Ala Leu Ile Ala Gly Thr Val Ala Cys Phe Met Thr Ala Cys Ile
        595                 600                 605

Ala Gly Ile Leu Ser Ser Thr Pro Val Asp Ile Asn Cys His His Val
    610                 615                 620

Leu Glu Asn Ala Phe Asn Ser Thr Phe Pro Gly Asn Thr Thr Lys Val
625                 630                 635                 640

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

Gly Glu Val Ile Pro Gly Gly Asn His Ser Leu Tyr Ser Leu Lys Gly
            660                 665                 670

Cys Cys Thr Leu Leu Asn Pro Ser Thr Phe Asn Cys Asn Gly Ile Ser
        675                 680                 685

Asn Thr Phe
    690


<210> SEQ ID NO 53
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Met Ala Asp Pro Arg Val Arg Gln Ile Lys Ile Lys Thr Gly Val Val
1               5                   10                  15

Lys Arg Leu Val Lys Glu Lys Val Met Tyr Glu Lys Glu Ala Lys Gln
            20                  25                  30

Gln Glu Glu Lys Ile Glu Lys Met Arg Ala Glu Asp Gly Glu Asn Tyr
        35                  40                  45

Asp Ile Lys Lys Gln Ala Glu Ile Leu Gln Glu Ser Arg Met Met Ile
    50                  55                  60

Pro Asp Cys Gln Arg Arg Leu Glu Ala Ala Tyr Leu Asp Leu Gln Arg
65                  70                  75                  80

Ile Leu Glu Asn Glu Lys Asp Leu Glu Glu Ala Glu Glu Tyr Lys Glu
                85                  90                  95

Ala Arg Leu Val Leu Asp Ser Val Lys Leu Glu Ala
            100                 105


<210> SEQ ID NO 54
<211> LENGTH: 160
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Met Glu Glu Gly Ser Ser Ser Pro Val Ser Pro Val Asp Ser Leu Gly
1               5                   10                  15

Thr Ser Glu Glu Glu Leu Glu Arg Gln Pro Lys Arg Phe Gly Arg Lys
            20                  25                  30

Arg Arg Tyr Ser Lys Lys Ser Ser Glu Asp Gly Ser Pro Thr Pro Gly
        35                  40                  45

Lys Arg Gly Lys Lys Gly Ser Pro Ser Ala Gln Ser Phe Glu Glu Leu
    50                  55                  60

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

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

Pro Ser Asp Lys Leu Ser Lys Ile Gln Thr Leu Lys Leu Ala Ala Arg
            100                 105                 110

Tyr Ile Asp Phe Leu Tyr Gln Val Leu Gln Ser Asp Glu Met Asp Asn
        115                 120                 125

Lys Met Thr Ser Cys Ser Tyr Val Ala His Glu Arg Leu Ser Tyr Ala
    130                 135                 140

Phe Ser Val Trp Arg Met Glu Gly Ala Trp Ser Met Ser Ala Ser His
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145                 150                 155                 160


<210> SEQ ID NO 55
<211> LENGTH: 140
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Leu Tyr His Thr Val Leu Pro Thr Thr Ala Cys Ser Phe Ile Val
1               5                   10                  15

Ala Val Asn Ala Pro Phe Leu Ser Phe Ser Pro Leu Lys Ile Arg Glu
            20                  25                  30

His Ala Gly Leu Ser Cys Ala Arg His Ser Ile Pro His Met Val Asp
        35                  40                  45

Glu Gly Gly Cys Gly Ser Asp Gly Ser Thr Ala Val His Pro Gly Gly
    50                  55                  60

Trp Thr Cys Val Pro Gly Tyr Gln Ser Leu Arg Leu Thr Ser Pro His
65                  70                  75                  80

Val His Ala Ala Leu Pro Leu Ala Val Ser Thr Phe Trp Val Ser Leu
                85                  90                  95

Lys Asp Phe Thr Gly Ala Asp Phe Thr Lys Ala Lys Leu Phe Leu Lys
            100                 105                 110

Glu Val Asp Met Lys Asp Leu Lys Ser Gly Leu Leu Lys Lys Ser Lys
        115                 120                 125

His Arg Leu Met Thr Tyr Leu His Pro Thr Arg Phe
    130                 135                 140


<210> SEQ ID NO 56
<211> LENGTH: 581
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Met Pro Leu Lys His Tyr Leu Leu Leu Leu Val Gly Cys Gln Ala Trp
1               5                   10                  15

Gly Ala Gly Leu Ala Tyr His Gly Cys Pro Ser Glu Cys Thr Cys Ser
            20                  25                  30

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

Thr Pro Leu Pro Trp Asn Ala Met Ser Leu Gln Ile Leu Asn Thr His
    50                  55                  60

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

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

Phe Arg Asn Leu Gly Ser Leu Arg Tyr Leu Ser Leu Ala Asn Asn Lys
            100                 105                 110

Leu Gln Val Leu Pro Ile Gly Leu Phe Gln Gly Leu Asp Ser Leu Glu
        115                 120                 125

Ser Leu Leu Leu Ser Ser Asn Gln Leu Leu Gln Ile Gln Pro Ala His
    130                 135                 140

Phe Ser Gln Cys Ser Asn Leu Lys Glu Leu Gln Leu His Gly Asn His
145                 150                 155                 160

Leu Glu Tyr Ile Pro Asp Gly Ala Phe Asp His Leu Val Gly Leu Thr
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                165                 170                 175

Lys Leu Asn Leu Gly Lys Asn Ser Leu Thr His Ile Ser Pro Arg Val
            180                 185                 190

Phe Gln His Leu Gly Asn Leu Gln Val Leu Arg Leu Tyr Glu Asn Arg
        195                 200                 205

Leu Thr Asp Ile Pro Met Gly Thr Phe Asp Gly Leu Val Asn Leu Gln
    210                 215                 220

Glu Leu Ala Leu Gln Gln Asn Gln Ile Gly Leu Leu Ser Pro Gly Leu
225                 230                 235                 240

Phe His Asn Asn His Asn Leu Gln Arg Leu Tyr Leu Ser Asn Asn His
                245                 250                 255

Ile Ser Gln Leu Pro Pro Ser Ile Phe Met Gln Leu Pro Gln Leu Asn
            260                 265                 270

Arg Leu Thr Leu Phe Gly Asn Ser Leu Lys Glu Leu Ser Leu Gly Ile
        275                 280                 285

Phe Gly Pro Met Pro Asn Leu Arg Glu Leu Trp Leu Tyr Asp Asn His
    290                 295                 300

Ile Ser Ser Leu Pro Asp Asn Val Phe Ser Asn Leu Arg Gln Leu Gln
305                 310                 315                 320

Val Leu Ile Leu Ser Arg Asn Gln Ile Ser Phe Ile Ser Pro Gly Ala
                325                 330                 335

Phe Asn Gly Leu Thr Glu Leu Arg Glu Leu Ser Leu His Thr Asn Ala
            340                 345                 350

Leu Gln Asp Leu Asp Gly Asn Val Phe Arg Met Leu Ala Asn Leu Gln
        355                 360                 365

Asn Ile Ser Leu Gln Asn Asn Arg Leu Arg Gln Leu Pro Gly Asn Ile
    370                 375                 380

Phe Ala Asn Val Asn Gly Leu Met Ala Ile Gln Leu Gln Asn Asn Gln
385                 390                 395                 400

Leu Glu Asn Leu Pro Leu Gly Ile Phe Asp His Leu Gly Lys Leu Cys
                405                 410                 415

Glu Leu Arg Leu Tyr Asp Asn Pro Trp Arg Cys Asp Ser Asp Ile Leu
            420                 425                 430

Pro Leu Arg Asn Trp Leu Leu Leu Asn Gln Pro Arg Leu Gly Thr Asp
        435                 440                 445

Thr Val Pro Val Cys Phe Ser Pro Ala Asn Val Arg Gly Gln Ser Leu
    450                 455                 460

Ile Ile Ile Asn Val Asn Val Ala Val Pro Ser Val His Val Pro Glu
465                 470                 475                 480

Val Pro Ser Tyr Pro Glu Thr Pro Trp Tyr Pro Asp Thr Pro Ser Tyr
                485                 490                 495

Pro Asp Thr Thr Ser Val Ser Ser Thr Thr Glu Leu Thr Ser Pro Val
            500                 505                 510

Glu Asp Tyr Thr Asp Leu Thr Thr Ile Gln Val Thr Asp Asp Arg Ser
        515                 520                 525

Val Trp Gly Met Thr Gln Ala Gln Ser Gly Leu Ala Ile Ala Ala Ile
    530                 535                 540

Val Ile Gly Ile Val Ala Leu Ala Cys Ser Leu Ala Ala Cys Val Gly
545                 550                 555                 560

Cys Cys Cys Cys Lys Lys Arg Ser Gln Ala Val Leu Met Gln Met Lys
                565                 570                 575
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Ala Pro Asn Glu Cys
            580


<210> SEQ ID NO 57
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Cys Tyr Ala Gly Trp Leu Ala Asp Gly Ser Leu Arg
1               5                   10


<210> SEQ ID NO 58
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Leu Glu Gly Glu Val Phe Phe Ala Thr Arg
1               5                   10


<210> SEQ ID NO 59
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

Thr Pro Cys Val Gly Asp Lys Asp Ser Ser Pro Gly Val Arg
1               5                   10


<210> SEQ ID NO 60
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Ala Cys Glu Glu Ala Pro Pro Ser Ala Ala His Phe Arg
1               5                   10


<210> SEQ ID NO 61
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

Cys Ser Ala Ala Cys Gly Gln Thr Gly Val Gln Thr Arg
1               5                   10


<210> SEQ ID NO 62
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

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


<210> SEQ ID NO 63
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 63

Glu Ile Gln Cys Ser Gly Tyr Thr Leu Pro Thr Lys
1               5                   10


<210> SEQ ID NO 64
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Phe Leu Pro Ser Glu Gln Ile Gln Gly Val Val Ile Ser Val Ile Asn
1               5                   10                  15

Leu Glu Pro Arg
            20


<210> SEQ ID NO 65
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Phe Asn Pro Asn Ala Ile Gly Val Pro Gln Pro Tyr Leu Asn Lys
1               5                   10                  15


<210> SEQ ID NO 66
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Phe Tyr Gln Ile Glu Gly Asp Arg
1               5


<210> SEQ ID NO 67
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Ile Val Gly Pro Leu Glu Val Asn Val Arg
1               5                   10


<210> SEQ ID NO 68
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Leu Phe Asn Leu Asp Val Pro Glu Ser Arg
1               5                   10


<210> SEQ ID NO 69
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Pro Arg Pro Asn Ser Ala Glu Glu Ser Asn Gly Pro Ile Tyr Ala Phe
1               5                   10                  15

Glu Asn Leu Arg
            20
```

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<210> SEQ ID NO 70
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Ser Asn Val Gly Val Ala Leu Thr Phe Asn Cys Val Glu Arg
1               5                   10


<210> SEQ ID NO 71
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Thr Ala Phe Gln Ile Ser Met Ala Lys
1               5


<210> SEQ ID NO 72
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Thr Phe Leu Val Gly Asn Leu Glu Ile Arg
1               5                   10


<210> SEQ ID NO 73
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Ala Asp Ala Gly Thr Ala Val Thr Phe Gln Cys Arg
1               5                   10


<210> SEQ ID NO 74
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Ala Tyr Ala Asn Asp Lys Phe Thr Pro Ser Glu Gln Val Glu Gly Val
1               5                   10                  15

Val Val Thr Leu Val Asn Leu Glu Pro Ala Pro Gly Phe Ser Ala Asn
            20                  25                  30

Pro Arg


<210> SEQ ID NO 75
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Glu Cys Gln Gly Ala Pro Val Thr Ala Ser His Phe Arg
1               5                   10


<210> SEQ ID NO 76
<211> LENGTH: 11
<212> TYPE: PRT
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Glu Met Ser Glu Ala Ala Gln Ala Gln Ala Arg
1               5                   10


<210> SEQ ID NO 77
<211> LENGTH: 28
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Phe Thr Pro Ser Glu Gln Val Glu Gly Val Val Val Thr Leu Val Asn
1               5                   10                  15

Leu Glu Pro Ala Pro Gly Phe Ser Ala Asn Pro Arg
            20                  25


<210> SEQ ID NO 78
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Gly Gln Leu Tyr Gly Leu Arg
1               5


<210> SEQ ID NO 79
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

His Pro Pro Pro Val Pro Ala Glu Asp Pro Ala Ala Phe Ser Met Leu
1               5                   10                  15

Ala Pro Leu Asp Pro Leu Gly His Asn Tyr Gly Val Tyr Thr Val Thr
            20                  25                  30

Asp Gln Ser Pro Arg
        35


<210> SEQ ID NO 80
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Leu Leu Glu Ser Pro Ala Thr Ala Leu Gly Asp Ile Arg
1               5                   10


<210> SEQ ID NO 81
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Pro Leu Pro Ala Thr Val Gly Val Thr Gln Pro Tyr Leu Asp Arg
1               5                   10                  15


<210> SEQ ID NO 82
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 82

Arg Thr Asp His Asp Asp Pro Ala Phe Lys
1               5                   10


<210> SEQ ID NO 83
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Ser His Asn Ala Gly Gly Ser His Pro Arg
1               5                   10


<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Thr Asp His Asp Asp Pro Ala Phe Lys
1               5


<210> SEQ ID NO 85
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Val Ala Val Asn Gly Leu Leu Arg
1               5


<210> SEQ ID NO 86
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Val Glu Ala Asp Lys Tyr Glu Tyr Asn Val Val Pro Phe Arg
1               5                   10


<210> SEQ ID NO 87
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Val Phe Leu Val Gly Asn Val Glu Ile Arg
1               5                   10


<210> SEQ ID NO 88
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Ile Thr Gln Thr Ala Glu Gly Leu Asp Pro Glu Asn Tyr Leu Ser Ile
1               5                   10                  15

Lys


<210> SEQ ID NO 89
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-continued

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<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

Ala Gly Asp Gly Asp Gly Trp Val Ser Leu Ala Glu Leu Arg
1               5                   10


<210> SEQ ID NO 90
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

Cys Tyr Tyr Phe Ser Val Glu Lys
1               5


<210> SEQ ID NO 91
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Cys Tyr Tyr Phe Ser Val Glu Lys Glu Ile Phe Glu Asp Ala Lys
1               5                   10                  15


<210> SEQ ID NO 92
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Asp Arg Glu Thr Val Leu Ser Ser Ala Leu
1               5                   10


<210> SEQ ID NO 93
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

Glu Glu Gln Gln Trp Ile Lys
1               5


<210> SEQ ID NO 94
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

Glu Glu Gln Gln Trp Ile Lys Lys
1               5


<210> SEQ ID NO 95
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Glu Ile Phe Glu Asp Ala Lys
1               5
```

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<210> SEQ ID NO 96
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Glu Ser His Trp Ile Gly Leu Thr Asp Ser Glu Arg
1               5                   10


<210> SEQ ID NO 97
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Glu Ser His Trp Ile Gly Leu Thr Asp Ser Glu Arg Glu Asn Glu Trp
1               5                   10                  15

Lys


<210> SEQ ID NO 98
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Ser Ser His Leu Val Phe Ile Asn Thr Arg
1               5                   10


<210> SEQ ID NO 99
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Trp Leu Asp Gly Thr Ser Pro Asp Tyr Lys
1               5                   10


<210> SEQ ID NO 100
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Ala Ala Leu Ala Gln Leu Leu Lys
1               5


<210> SEQ ID NO 101
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

Gly Ile Ala Glu Gly Thr Phe Ser His Leu Thr Lys
1               5                   10


<210> SEQ ID NO 102
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

Leu Glu Glu Leu His Leu Asp Asp Asn Ser Ile Ser Thr Val Gly Val
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1               5                   10                  15

Glu Asp Gly Ala Phe Arg
            20


<210> SEQ ID NO 103
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Leu Ile Val Asp Gly Asn Leu Leu Thr Asn Lys
1               5                   10


<210> SEQ ID NO 104
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Leu Tyr Leu Gln Asp Asn Gln Ile Asn His Ile Pro Leu Thr Ala Phe
1               5                   10                  15

Ser Asn Leu Arg
            20


<210> SEQ ID NO 105
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Met Leu Thr Gln Gly Val Phe Asp Asn Leu Ser Asn Leu Lys
1               5                   10


<210> SEQ ID NO 106
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Asn His Leu Ser Ser Val Pro Val Gly Leu Pro Val Asp Leu Gln Glu
1               5                   10                  15

Leu Arg


<210> SEQ ID NO 107
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Ile Ser Thr Ile Ser Ser Pro Ser Leu Gln Gly Leu Thr Ser Leu Lys
1               5                   10                  15


<210> SEQ ID NO 108
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Ile Tyr Leu Tyr His Asn Ser Leu Asp Glu Phe Pro Thr Asn Leu Pro
1               5                   10                  15
```

```
Lys


<210> SEQ ID NO 109
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Ala Trp Gly Pro His Cys Glu Lys
1               5


<210> SEQ ID NO 110
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Phe Ser Glu Gln Gln Arg Lys
1               5


<210> SEQ ID NO 111
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Met Thr Cys Val Asp Val Asn Glu Cys Asp Glu Leu Asn Asn Arg
1               5                   10                  15


<210> SEQ ID NO 112
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Gln Cys Met His Pro Leu Ser Val His Leu Thr Lys
1               5                   10


<210> SEQ ID NO 113
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Gln Leu Cys Cys Cys Ser Val Gly Lys
1               5


<210> SEQ ID NO 114
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Val Gln Glu Gly Tyr Thr Cys Asp Cys Phe Asp Gly Tyr His Leu Asp
1               5                   10                  15

Thr Ala Lys


<210> SEQ ID NO 115
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 115

Val Met Ile Glu Pro Ser Gly Pro Ile His Val Pro Lys
1               5                   10


<210> SEQ ID NO 116
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

His Gly Glu Cys Ile Gly Pro Asn Lys
1               5


<210> SEQ ID NO 117
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Leu Val Leu Pro Leu Gly Arg
1               5


<210> SEQ ID NO 118
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Glu Lys Asp Asn Asp Leu His Trp Glu Pro Ile Arg Asp Pro Ala Gly
1               5                   10                  15

Gly Gln Tyr Leu Thr Val Ser Ala Ala Lys
            20                  25


<210> SEQ ID NO 119
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Lys His Gly Ala His Gly Ala Ala Leu Trp Gly Arg
1               5                   10


<210> SEQ ID NO 120
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Asp Pro Ala Gly Gly Gln Tyr Leu Thr Val Ser Ala Ala Lys
1               5                   10


<210> SEQ ID NO 121
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

His Gly Ala His Gly Ala Ala Leu Trp Gly Arg
1               5                   10


<210> SEQ ID NO 122
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<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Val Thr Gly Leu His Ser Gly Thr Leu Gln Val Phe Val Arg
1               5                   10


<210> SEQ ID NO 123
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Thr Cys Val Asp Val Asp Glu Cys Ala Thr Gly Arg
1               5                   10


<210> SEQ ID NO 124
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Gln Thr Gln Ile Thr Leu Arg
1               5


<210> SEQ ID NO 125
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

Gln Cys Val Asn Thr Phe Gly Ser Tyr Ile Cys Lys
1               5                   10


<210> SEQ ID NO 126
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Glu Gly Tyr Gln Gly Asp Gly Leu Thr Cys Val Tyr Ile Pro Lys
1               5                   10                  15


<210> SEQ ID NO 127
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Glu Glu Ser Glu Ala Asp Gln Trp Leu Arg
1               5                   10


<210> SEQ ID NO 128
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Leu Leu Leu Leu Asp Glu Leu Val Ser Leu Glu Asn Asp Val Ile Glu
1               5                   10                  15

Thr Lys
```

```
<210> SEQ ID NO 129
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Ser Ala Thr Asp Leu Thr Ala Lys
1               5


<210> SEQ ID NO 130
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Asp Phe Ala Asp Ile Pro Asn Leu Arg
1               5


<210> SEQ ID NO 131
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Leu Asp Phe Thr Gly Asn Leu Ile Glu Asp Ile Glu Asp Gly Thr Phe
1               5                   10                  15

Ser Lys


<210> SEQ ID NO 132
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Leu Ser Leu Leu Glu Glu Leu Ser Leu Ala Glu Asn Gln Leu Leu Lys
1               5                   10                  15


<210> SEQ ID NO 133
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Arg Leu Asp Phe Thr Gly Asn Leu Ile Glu Asp Ile Glu Asp Gly Thr
1               5                   10                  15

Phe Ser Lys


<210> SEQ ID NO 134
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Leu Leu Gly Glu Glu Asn Lys Glu Asn Thr Pro Arg
1               5                   10


<210> SEQ ID NO 135
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 135

Ala Tyr Gly Pro Leu Phe Leu Arg
1   5

<210> SEQ ID NO 136
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Asp Arg Val Ala Val Gly Ala Asp Ala Phe Glu Arg
1   5   10

<210> SEQ ID NO 137
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Glu Val Leu Ala Val Ala Arg
1   5

<210> SEQ ID NO 138
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Gly Ala Pro Ala Leu Leu Thr Cys Val Asn Arg
1   5   10

<210> SEQ ID NO 139
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Gly His Val Trp Thr Asp Arg
1   5

<210> SEQ ID NO 140
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Gly Pro Gly Gly Gly Pro Ala Arg
1   5

<210> SEQ ID NO 141
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

His Val Glu Glu Ala Gln Gln Val Val His Trp Asp Arg
1   5   10

<210> SEQ ID NO 142
<211> LENGTH: 18
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Leu Glu Val Thr Asp Gly Pro Pro Ala Thr Pro Ala Tyr Trp Asp Gly
1               5                   10                  15

Glu Lys


<210> SEQ ID NO 143
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Leu Glu Val Thr Asp Gly Pro Pro Ala Thr Pro Ala Tyr Trp Asp Gly
1               5                   10                  15

Glu Lys Glu Val Leu Ala Val Ala Arg
            20                  25


<210> SEQ ID NO 144
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

Leu Leu Asp Leu Tyr Ala Ser Gly Glu Arg
1               5                   10


<210> SEQ ID NO 145
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Leu Leu Asp Leu Tyr Ala Ser Gly Glu Arg Arg
1               5                   10


<210> SEQ ID NO 146
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

Leu Leu Asp Leu Tyr Ser Ala Gly Glu Gln Arg
1               5                   10


<210> SEQ ID NO 147
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Met Val Trp Thr Gln Asp Arg
1               5


<210> SEQ ID NO 148
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

Gln Pro Pro Gly Val Pro His Asp Arg
```

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```
1               5


<210> SEQ ID NO 149
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Arg Ala Tyr Gly Pro Leu Phe Leu Arg
1               5


<210> SEQ ID NO 150
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

Arg Leu Leu Asp Leu Tyr Ser Ala Gly Glu Gln Arg
1               5                   10


<210> SEQ ID NO 151
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Arg Val Phe His Leu Thr Val Ala Glu Pro His Ala Glu Pro Pro Pro
1               5                   10                  15

Arg


<210> SEQ ID NO 152
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Val Ala Val Gly Ala Asp Ala Phe Glu Arg
1               5                   10


<210> SEQ ID NO 153
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Val Phe His Leu Thr Val Ala Glu Pro His Ala Glu Pro Pro Pro Arg
1               5                   10                  15


<210> SEQ ID NO 154
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Val Leu His Trp Asp Leu Arg
1               5


<210> SEQ ID NO 155
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

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```
<400> SEQUENCE: 155

Asp Ile Val Thr Val Ala Asn Ala Val Phe Val Lys
1               5                   10


<210> SEQ ID NO 156
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Leu Glu Ala Ala Tyr Leu Asp Leu Gln Arg
1               5                   10


<210> SEQ ID NO 157
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Leu Val Leu Asp Ser Val Lys Leu Glu Ala
1               5                   10


<210> SEQ ID NO 158
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Arg Leu Glu Ala Ala Tyr Leu Asp Leu Gln Arg
1               5                   10


<210> SEQ ID NO 159
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Glu Ala Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys Pro Ala
1               5                   10                  15

Leu Glu Phe Thr Lys
            20


<210> SEQ ID NO 160
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Ile Phe Phe Pro Gly Val Ser Glu Phe Gly Lys
1               5                   10


<210> SEQ ID NO 161
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Asp Lys Gln His Phe Thr Thr Leu Ile Lys
1               5                   10


<210> SEQ ID NO 162
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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg
1 5 10 15

<210> SEQ ID NO 163
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Ile Leu Gly Gln Gln Val Pro Tyr Ala Thr Lys
1 5 10

<210> SEQ ID NO 164
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Gln Leu Leu Leu Ser Ala Ala Leu Ser Ala Gly Lys
1 5 10

<210> SEQ ID NO 165
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Ser Phe Thr Leu Ala Ser Ser Glu Thr Gly Val Gly Ala Pro Ile Ser
1 5 10 15

Gly Pro Gly Ile Pro Gly Arg
20

<210> SEQ ID NO 166
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg
1 5 10 15

<210> SEQ ID NO 167
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

Thr Leu Leu Ser Val Gly Gly Trp Asn Phe Gly Ser Gln Arg
1 5 10

<210> SEQ ID NO 168
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala Lys

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```
1               5                   10


<210> SEQ ID NO 169
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

Gln Asp Ala Asp Glu Glu Ala Leu Tyr Tyr Thr Gly Val Arg
1               5                   10


<210> SEQ ID NO 170
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Tyr Gln Ile Tyr Gln Asp Gly Thr Leu Leu Ile Gln Lys
1               5                   10


<210> SEQ ID NO 171
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

His Leu Tyr Leu Ala Glu Asn Met Val Arg
1               5                   10


<210> SEQ ID NO 172
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Val Asp Val Val Met Lys Pro Ala Lys
1               5


<210> SEQ ID NO 173
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Val Gly Leu Lys Pro Glu Ala Asn Lys
1               5


<210> SEQ ID NO 174
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Val Gln Val Ser Asp Ser Gly Tyr Tyr Arg
1               5                   10


<210> SEQ ID NO 175
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175
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His Ser Glu Lys Glu Pro Glu Thr Asn Val Ala Glu Gly Arg
1               5                   10


<210> SEQ ID NO 176
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Arg Thr Val Gln Leu Asn Val Gln Arg
1               5


<210> SEQ ID NO 177
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Ala Asp Ile Thr Trp Glu Leu Pro Asp Lys
1               5                   10


<210> SEQ ID NO 178
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Thr Val Gln Leu Asn Val Gln Arg
1               5


<210> SEQ ID NO 179
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Leu Ile Ala Tyr Tyr Ser Glu Val Pro Val Lys
1               5                   10


<210> SEQ ID NO 180
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Thr Thr Tyr Ile His Val Phe
1               5


<210> SEQ ID NO 181
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Cys Phe Glu Ser Phe Glu Arg
1               5


<210> SEQ ID NO 182
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182
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Gly Arg Glu Cys Asp Cys Asp Ala Gln Cys Lys
1               5                   10


<210> SEQ ID NO 183
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Val Cys Thr Ala Glu Leu Ser Cys Lys
1               5


<210> SEQ ID NO 184
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Ala Tyr Tyr Asn Gly Ile Ser Leu Phe Asn Asn Pro Val Pro Tyr Trp
1               5                   10                  15

Glu Val Gln Pro Ala Thr Phe Arg
            20


<210> SEQ ID NO 185
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp Leu Gln Asn Asn Asp Ile
1               5                   10                  15

Ser Glu Leu Arg
            20


<210> SEQ ID NO 186
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp Leu Gln Asn Asn Asp Ile
1               5                   10                  15

Ser Glu Leu Arg Lys
            20


<210> SEQ ID NO 187
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Ile Gln Ala Ile Glu Leu Glu Asp Leu Leu Arg
1               5                   10


<210> SEQ ID NO 188
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188
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```
Leu Gly Leu Gly His Asn Gln Ile Arg
1               5


<210> SEQ ID NO 189
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

Asn His Leu Val Glu Ile Pro Pro Asn Leu Pro Ser Ser Leu Val Glu
1               5                   10                  15

Leu Arg


<210> SEQ ID NO 190
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Val Gly Val Asn Asp Phe Cys Pro Met Gly Phe Gly Val Lys
1               5                   10


<210> SEQ ID NO 191
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Val Val Gln Cys Ser Asp Leu Gly Leu Lys
1               5                   10


<210> SEQ ID NO 192
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Leu Leu Leu Gly Tyr Asn Glu Ile Ser Lys
1               5                   10


<210> SEQ ID NO 193
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

Leu Gln Asp Ile Pro Tyr Asn Ile Phe Asn Leu Pro Asn Ile Val Glu
1               5                   10                  15

Leu Ser Val Gly His Asn Lys
            20


<210> SEQ ID NO 194
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic peptide

<400> SEQUENCE: 194

Arg Leu Ile Asp Gly Ser Ser Pro Gln Glu Pro Glu Phe Thr Gly Val
1               5                   10                  15
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Leu Gly Pro His
            20


<210> SEQ ID NO 195
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 195

Ile Asn Lys Asn Asp Phe Ala Ser Leu Ser Asp Leu Lys Arg Ile
1               5                   10                  15


<210> SEQ ID NO 196
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 196

Phe Ile Asp Ile Ser Asn Asn Arg Leu Gly Arg Lys Gly Ile Lys Gln
1               5                   10                  15

Glu Ala


<210> SEQ ID NO 197
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 197

Glu Asn Lys Val Lys Lys Ile Gln Lys Asp Thr
1               5                   10


<210> SEQ ID NO 198
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 198

Leu Lys Lys Ile Pro Ser Gly Leu Pro Glu
1               5                   10


<210> SEQ ID NO 199
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 199

Lys Lys Ser Leu Tyr Ser Ala Ile Ser Leu Phe
1               5                   10


<210> SEQ ID NO 200
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 200

Ile Ser Ser Ser Ala Ser Ser Ser Leu Glu Thr
1 5 10

<210> SEQ ID NO 201
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 201

Asn Asp Ile Glu Ser Lys Ser Leu Val Leu
1 5 10

<210> SEQ ID NO 202
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 202

Pro Val Tyr Ala Ala Ser Ser Gly Gln Lys Lys Gln Gln Gln Ser Lys
1 5 10 15

<210> SEQ ID NO 203
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 203

Ala Ala Glu Glu Asn Cys Leu Ala Ser Ser Ala Arg Ser Ala Asn Trp
1 5 10 15

<210> SEQ ID NO 204
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 204

Ile Leu Thr Pro Asn Gly Thr Lys Val Ala Glu Gly His Lys Ala
1 5 10 15

<210> SEQ ID NO 205
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 205

Glu Leu Glu Arg Gln Pro Lys Arg Phe Gly Arg Lys Arg Arg Tyr Ser
1 5 10 15

Lys Lys Ser Ser Glu Asp Gly Ser Pro Thr Pro Gly Lys Arg
20 25 30

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<210> SEQ ID NO 206
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 206

Lys Ile Ile Pro Thr Leu Pro Ser Asp Lys Leu Ser Lys Ile Gln Thr
1               5                   10                  15

Leu Lys Leu Ala
            20


<210> SEQ ID NO 207
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 207

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

Ser Asp Ile Phe
            20


<210> SEQ ID NO 208
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 208

Val Asn Thr Tyr Gly Ser Tyr Arg Cys Arg Thr Asn Lys Lys Cys Ser
1               5                   10                  15

Arg Gly Tyr Glu
            20


<210> SEQ ID NO 209
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 209

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

Tyr Tyr Ala Leu
            20


<210> SEQ ID NO 210
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 210

Asp Arg Asn Gln Leu Ser Ser Tyr Pro Ser Ala Ala Leu Ser Lys Leu
1               5                   10                  15
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Arg Val Val Glu
            20


<210> SEQ ID NO 211
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 211

Phe Arg Ser Cys Lys Phe Pro Thr Lys Arg Ser Lys Lys Ala Gly Arg
1               5                   10                  15

His
```

1-33. (canceled)

34. A method for diagnosing a bone and/or cartilage disorder in a mammal comprising:

(a) obtaining a test sample from said mammal
(b) contacting the test sample with an antibody or fragment thereof that specifically binds to a polypeptide selected from the group consisting of SEQ ID Nos: 2, 10, 16, 19, 28, 29 and 54;
(c) measuring binding of the antibody or fragment thereof to the test sample; and
(d) comparing binding of step (c) to a normal control level of binding, whereby an alteration in binding of the antibody or fragment thereof to the test sample relative to a normal control level of binding is indicative of a bone and/or cartilage disorder in the mammal

35. The method of claim **34** wherein the antibody or fragment thereof specifically binds to an epitope selected from the group consisting of:

(a) amino acids 180-190 of SEQ ID NO: 2;
(b) amino acids 301-310 of SEQ ID NO: 2;
(c) amino acids 340-350 of SEQ ID NO: 2;
(d) amino acids 203-222 of SEQ ID NO: 10;
(e) amino acids 343-359 of SEQ ID NO: 10;
(f) amino acids 238-257 of SEQ ID NO: 16;
(g) amino acids 578-597 of SEQ ID NO: 16;
(h) amino acids 88-107 of SEQ ID NO: 16;
(i) amino acids 91-110 of SEQ ID NO: 19;
(j) amino acids 158-172 of SEQ ID NO: 19;
(k) amino acids 215-232 of SEQ ID NO: 19;
(l) amino acids 49-59 of SEQ ID NO: 28;
(m) amino acids 158-167 of SEQ ID NO: 28;
(n) amino acids 285-300 of SEQ ID NO: 29;
(o) amino acids 555-570 of SEQ ID NO: 29;
(p) amino acids 621-635 of SEQ ID NO: 29;
(p) amino acids 621-635 of SEQ ID NO: 29;
(q) amino acids 21-50 of SEQ ID NO: 54; and
(r) amino acids 91-110 of SEQ ID NO: 54.

36. The method of claim **34**, wherein the antibody or fragment thereof is immobilized on a support substrate selected from at least one of the group of a bead, a slide, a gel, a multi-well plate and a column.

37. The method of claim **34** wherein the mammal is a human.

38. The method of claim **34** wherein the bone and/or cartilage disorder is selected from the group consisting of osteoporosis and rheumatoid arthritis,.

39. The method of claim **34** wherein the normal control level of binding is determined by measuring binding of the antibody or fragment thereof to a sample from one or more undiseased mammals.

40. The method of claim **34**, wherein the test sample comprises mammalian body fluids selected form the group consisting of blood, urine, synovial fluid, tears, sweat, saliva, serum, lymph, semen, vaginal fluid, cerebro-spinal fluid, cell culture supernatant, cell extract and tissue extract.

41. The method of claim **34** wherein said antibody is a monoclonal antibody.

42. The method of claim **34** wherein said antibody is a polyclonal antibody.

43. A kit for diagnosing a bone and/or cartilage disorder in a mammal said kit comprising:

(a) an antibody or fragment thereof that specifically binds to a polypeptide selected from the group consisting of SEQ ID Nos: 2, 10, 16, 19, 28, 29 and 54; and
(b) means for detecting binding of said antibody to said polypeptide.

44. The kit of claim **43** wherein the antibody specifically binds to an epitope selected from the group consisting of:

(a) amino acids 180-190 of SEQ ID NO: 2;
(b) amino acids 301-310 of SEQ ID NO: 2;
(c) amino acids 340-350 of SEQ ID NO: 2;
(d) amino acids 203-222 of SEQ ID NO: 10;
(e) amino acids 343-359 of SEQ ID NO: 10;
(f) amino acids 238-257 of SEQ ID NO: 16;
(g) amino acids 578-597 of SEQ ID NO: 16;
(h) amino acids 88-107 of SEQ ID NO: 16;
(i) amino acids 91-110 of SEQ ID NO: 19;
(j) amino acids 158-172 of SEQ ID NO: 19;
(k) amino acids 215-232 of SEQ ID NO: 19;
(l) amino acids 49-59 of SEQ ID NO: 28;
(m) amino acids 158-167 of SEQ ID NO: 28;
(n) amino acids 285-300 of SEQ ID NO: 29;
(o) amino acids 555-570 of SEQ ID NO: 29;
(p) amino acids 621-635 of SEQ ID NO: 29;
(q) amino acids 21-50 of SEQ ID NO: 54; and
(r) amino acids 91-110 of SEQ ID NO: 54.

45. The kit of claim **43**, wherein said antibody or fragment thereof is immobilized in a plurality of wells in a multi-well plate.

46. The kit of claim **43**, further comprising instructions for use.

47. The kit of claim **43** wherein said antibody is a monoclonal antibody.

48. The kit of claim **43** wherein said antibody is a polyclonal antibody.

49. An isolated antibody generated by immunizing a mammal with a peptide fragment selected from the group consisting of:

(a) amino acids 180-190 of SEQ ID NO: 2;
(b) amino acids 301-310 of SEQ ID NO: 2;
(c) amino acids 340-350 of SEQ ID NO: 2;
(d) amino acids 203-222 of SEQ ID NO: 10;
(e) amino acids 343-359 of SEQ ID NO: 10;
(f) amino acids 238-257 of SEQ ID NO: 16;
(g) amino acids 578-597 of SEQ ID NO: 16;
(h) amino acids 88-107 of SEQ ID NO: 16;
(i) amino acids 91-110 of SEQ ID NO: 19;
(j) amino acids 158-172 of SEQ ID NO: 19;
(k) amino acids 215-232 of SEQ ID NO: 19;
(l) amino acids 49-59 of SEQ ID NO: 28;
(m) amino acids 158-167 of SEQ ID NO: 28;
(n) amino acids 285-300 of SEQ ID NO: 29;
(o) amino acids 555-570 of SEQ ID NO: 29;
(p) amino acids 621-635 of SEQ ID NO: 29;
(q) amino acids 21-50 of SEQ ID NO: 54; and
(r) amino acids 91-110 of SEQ ID NO: 54, wherein said antibody is capable of binding to said peptide fragment.

50. The isolated antibody of claim **49** wherein said antibody is a monoclonal antibody.

51. The isolated antibody of claim **49** wherein said antibody is a polyclonal antibody.

* * * * *

专利名称(译)	检测和诊断骨或软骨疾病的方法		
公开(公告)号	US20110189694A1	公开(公告)日	2011-08-04
申请号	US13/122541	申请日	2009-10-22
[标]申请(专利权)人(译)	生物标志设计FORSCHUNGS		
申请(专利权)人(译)	生物标志设计FORSCHUNGS GMBH		
当前申请(专利权)人(译)	生物标志设计FORSCHUNGS GMBH		
[标]发明人	WOLOSZCZUK WOLFGANG HAWA GERHARD		
发明人	WOLOSZCZUK, WOLFGANG HAWA, GERHARD		
IPC分类号	G01N33/53 G01N33/566 C07K16/00		
CPC分类号	G01N2800/10 G01N33/6887		
优先权	61/107564 2008-10-22 US		
外部链接	Espacenet USPTO		

摘要(译)

本发明涉及检测和诊断骨和/或软骨疾病的方法，其中通过使测试样品与特异性结合所述多肽的抗体接触并测量，测定测试样品中多肽的表达水平。所述抗体与所述测试样品的结合。

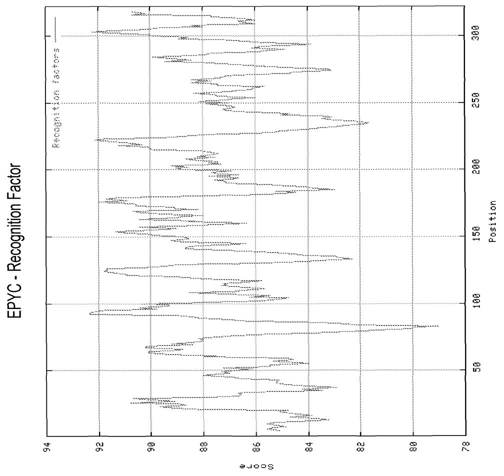

Figure 1A