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(54) METHOD OF EXAMINING EFFICACY OF THERAPY WITH NUCLEIC ACID

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(57) ABSTRACT

The present invention provides a method of examining efficacy of treatment with a nucleotide or a nucleoside having antitumor- or antivirus activity in individual patients beforehand, which method is mainly connected to tailor-made therapy, a method of screening for agents potentially having antitumor or antivirus activity, and method of investigating the mechanism of action of an antitumor or antivirus agent in vivo.

Fig. 1

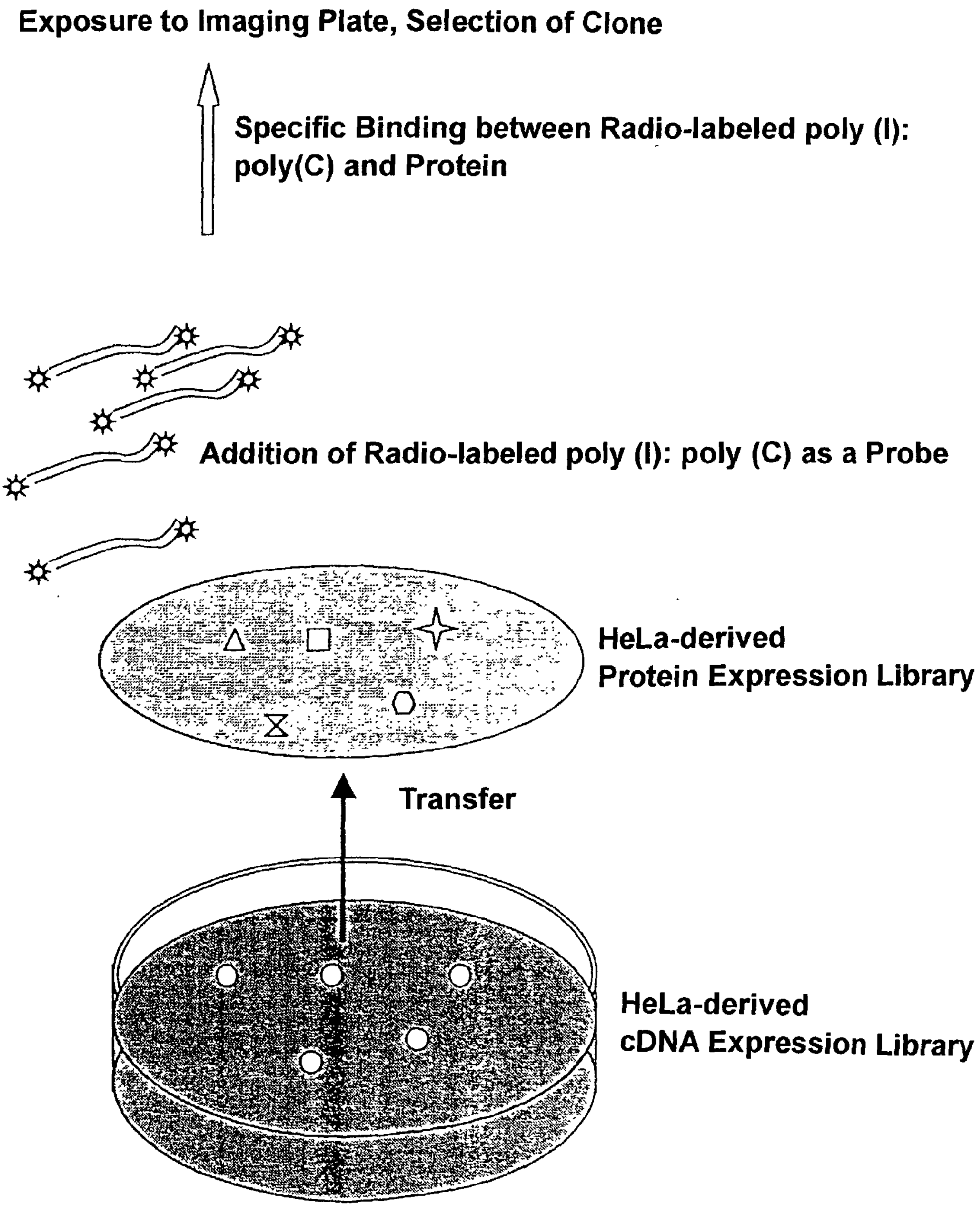

Exposure to Imaging Plate, Selection of Clone
Specific Binding between Radio-labeled poly (I): poly(C) and Protein
Addition of Radio-labeled poly (I): poly (C) as a Probe
HeLa-derived Protein Expression Library
Transfer
HeLa-derived cDNA Expression Library

Fig. 2

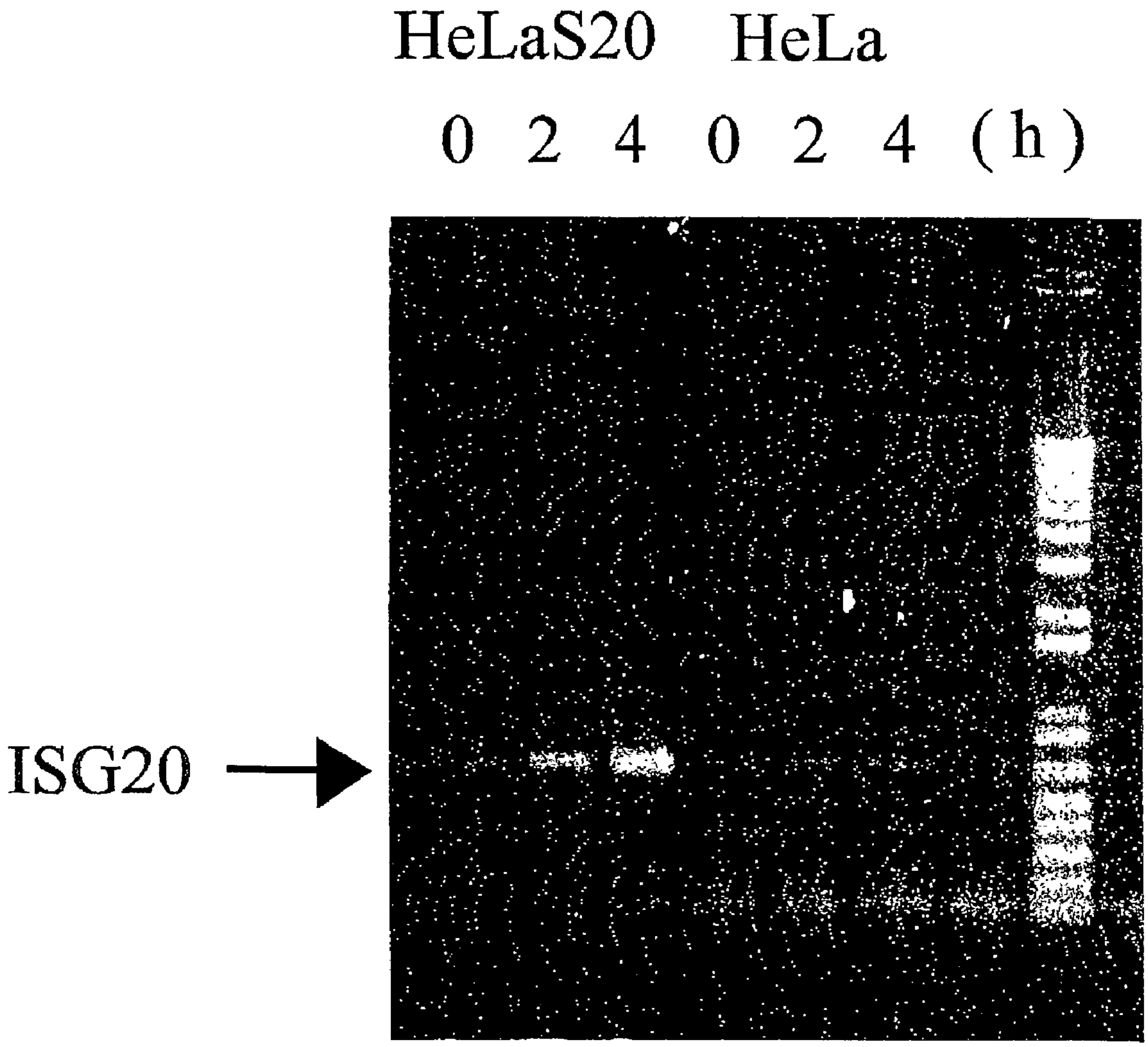
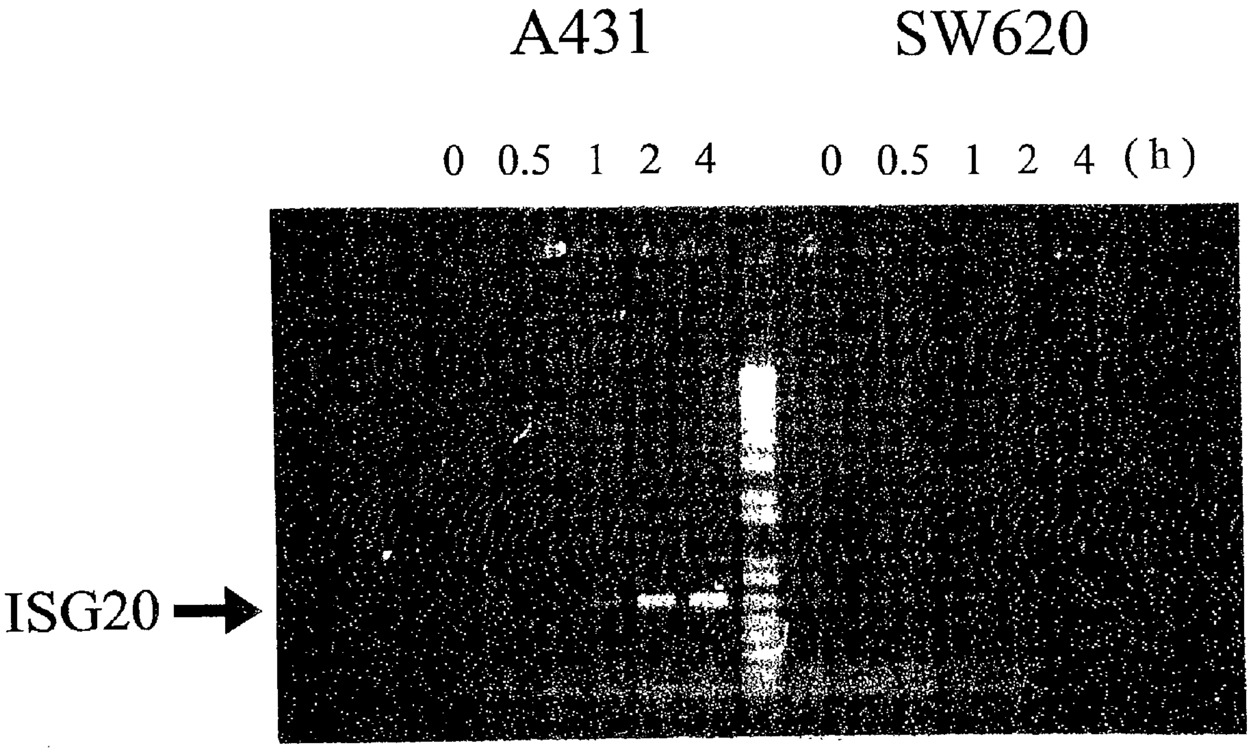


Fig. 3



METHOD OF EXAMINING EFFICACY OF THERAPY WITH NUCLEIC ACID

TECHNICAL FIELD

[0001] The present invention is related to a method of examining efficacy of treatment with an antitumor- or antivirus agent in individual patients. The present invention is also related to a method of screening for a candidate antitumor or antivirus agent.

BACKGROUND OF THE INVENTION

[0002] For example, synthetic nucleic acid polymers typified by polyinosinic—polycytidylic acid (i.e., polyinosinic acid•polycytidylic acid) have excellent antitumor and/or antivirus activity. Such a synthetic nucleic acid polymer has been reported that, when administered into a living body as a complex with an appropriate cationic liposome carrier, it attacks specifically cancer cells and activates an intracellular nuclease thereby leads the cells into apoptosis and that it has prominent antivirus effect on hepatitis virus (WO99/20283, WO99/48531)

[0003] However, the reactivity to antitumor agent administered differs from one patient to another, irrespective of the high potency of the drug administered, and an agent having sufficient effects in a patient while shows only poor effect in another.

[0004] Recently, tailor-made therapy, which is a method of treatment adapted to individual patients, has been proposed. The tailor-made therapy wherein treatment is conducted while confirming the efficacy or predicting side effects of a drug is a promising new therapeutic system.

SUMMARY OF THE INVENTION

[0005] The present invention provides a method of examining efficacy (effectiveness) of treatment with antitumor- or antivirus agent in individual patients, which method is mainly connected to tailor-made therapy. The present invention also provides a method of screening for agents potentially having antitumor or antivirus activity.

[0006] The present inventors have intensively studied and found that there exist in a living body proteins capable of binding to or induced to express by a double-stranded RNA, which is polyinosinic—polycytidylic acid known to be an excellent antitumor or antivirus agent, and established the present invention. In the present application, three proteins of the former type and one protein of the latter type will be disclosed.

[0007] The present invention, for example, includes the following embodiments.

> **[0008]** (1) A method of examining efficacy of treatment with a nucleotide or a nucleoside in a given subject comprising:
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> > **[0009]** (a) measuring the amount of expression or activity of at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4 in a blood or tissue sample previously taken from the subject;
> >
> > **[0010]** (b) administering the nucleotide or the nucleoside into a tissue of the subject or a tissue taken from the subject followed by measuring the amount of expression or activity of the same protein as that measured in (a) in blood or treated tissue after 3-48 hours from administration; and
> >
> > **[0011]** (c) comparing the measurement obtained in step (a) with that obtained in step (b) and evaluating the change in the amount of expression or the activity of the protein.
>
> **[0012]** (2) A method of examining efficacy of treatment with a nucleotide or a nucleoside in a given subject comprising:
>
> > **[0013]** (a) measuring the amount of expression or activity of at least one protein among those each having amino acid sequences of SEQ ID NO: 5-30 in a blood or tissue sample previously taken from the subject;
> >
> > **[0014]** (b) administering the nucleotide or the nucleoside into a tissue of the subject or a tissue taken from the subject followed by measuring the amount of expression or activity of the same protein as that measured in (a) in blood or treated tissue after 3-48 hours from administration; and
> >
> > **[0015]** (c) comparing the measurement obtained in step (a) with that obtained in step (b) and evaluating the change in the amount of expression or the activity of the protein.
>
> **[0016]** (3) A method of screening for agents potentially having antitumor or antivirus activity comprising examining a test compound for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4.
>
> **[0017]** (4) A method of screening for agents potentially having antitumor or antivirus activity comprising examining a test compound for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 5-30.
>
> **[0018]** (5) A method of investigating the mechanism of action of an antitumor or antivirus agent in vivo comprising examining the antitumor or antivirus agent for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4.
>
> **[0019]** (6) A method of investigating the mechanism of action of an antitumor or antivirus agent in vivo comprising examining the antitumor or antivirus agent for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 5-30.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **FIG. 1** is a schematic diagram of the process for detecting proteins each having amino acid sequences of SEQ ID NO: 1-3 described in Experiment 1.

[0021] **FIG. 2** is an electrophoretogram showing expression of mRNA for ISG20 in carcinoma cells, HeLaS3 (left lane) and HeLa (right lane) following the addition of a complex comprising polyinosinic—polycytidylic acid. The figures at the upper side indicate the time (hour) after administration of the complex. The bands at the rightmost lane indicate markers. The white arrow indicates the site where mRNA for ISG20 is expressed.

[0022] **FIG. 3** is an electrophoretogram showing expression of mRNA for ISG20 in carcinoma cells, A431 (left lane) and SW620 (right lane) following the addition of a complex comprising polyinosinic—polycytidylic acid. The figures at the upper side indicate the time (hour) after administration of the complex. The bands at the middle lane indicate markers. The white arrow indicates the site where mRNA for ISG20 is expressed.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0023] Nucleotides or nucleosides of which antitumor or antivirus activity is evaluated by the present method are those that exert activity when entered into a cell.

[0024] Such a nucleotide or nucleoside is, for example, administered into a tissue as an aqueous solution containing the same as it is, or as a pharmaceutical composition containing the same in association with an appropriate carrier. The proteins usable in the present method can be obtained, for example, according to the screening method illustrated hereinafter in the Experimental Examples.

[0025] I. Proteins

[0026] Examples of proteins usable in the present method include those each having amino acid sequences of SEQ ID NO: 1-30.

[0027] The proteins having amino acid sequences of SEQ ID NO: 1-4 are all known proteins.

[0028] The protein of SEQ ID NO: 1 exists in a living body and comprises 490 amino acids. A gene encoding the protein is deposited at GenBank under accession number AK002169 (gene name: AK002169). This protein is known to comprise motifs of ribonuclease III family, receptor tyrosine kinase class III, receptor tyrosine kinase class V, dsRNA binding motif, and the like. Since the motifs of nuclease and ribonuclease exist, the protein is considered to induce apoptosis in cells when activated.

[0029] The proteins of SEQ ID NO: 5-16 are all known proteins, of which amino acid sequences are highly identical with the amino acid sequence of the protein of SEQ ID NO: 1 wherein the sequence identity is 60% or more, and considered to have activity equivalent to that of the protein of SEQ ID NO: 1. Genes encoding these proteins are deposited at GenBank, wherein the GenBank accession number of a gene encoding the protein of SEQ ID NO: 5 is AL136866 (gene name; HSM801834), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 6 is AK024285 (gene name; AK024285), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 7 is AF167569 (gene name; AF167569), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 8 is AF141870 (gene name; AF141870), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 9 is AJ271745 (gene name; HSA271745), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 10 is AJ271746 (gene name; HSA271746), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 11 is AF167570 (gene name; AF167570), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 12 is AJ271744 (gene name; HSA271744), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 13 is U10324 (gene name; HSU10324), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 14 is X98265 (gene name; HSMPP4II), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 15 is AF147209 (gene name; AF147209), and the GenBank accession number of a gene encoding the protein of SEQ ID NO: 16 is X98264 or X98265 (gene name; HSMPP4I).

[0030] The protein having amino acid sequence of SEQ ID NO: 2 exists in a living body and comprises 366 amino acids and is referred to as human TAR RNA binding protein 2 (TRBP2). A gene encoding the protein is deposited at GenBank under accession number U08998 (gene name: HSU08998). This protein is also known to have motifs such as a motif of ribonuclease III family, dsRNA binding motif, and the like. Since the motifs of nuclease and kinase exist, the protein is considered to induce apoptosis in cells when activated.

[0031] The proteins of SEQ ID NO: 17-24 are all known proteins, which comprise amino acid sequences having high sequence identity to the amino acid sequence of dsRNA binding motif portion of the protein of SEQ ID NO: 2, and are considered to have activity equivalent to that of the protein of SEQ ID NO: 2. Genes encoding these proteins are deposited at GenBank, wherein the GenBank accession number of a gene encoding the protein of SEQ ID NO: 17 is M60801 (gene name; HUMTRBP), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 18 is AF083033 (gene name; AF083033), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 19 is X99227 (gene name; HSHRED1A), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 20 is U18121 (gene name; HSU18121), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 21 is AJ271745 (gene name; HSA271745), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 22 is AF141870 (gene name; AF141870), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 23 is AJ271747 (gene name; HSA271747), the GenBank accession number of a gene encoding the protein defined by SEQ ID NO: 24 is AF202445 (gene name; AF202445),

[0032] The protein having amino acid sequence of SEQ ID NO: 3 exists in a living body, comprises 803 amino acids, and is referred to as human TRAL. A gene encoding the protein is deposited at GenBank under accession number X15187 (gene name: HSTRA1). This protein is presumed to participate in the transmission of a signal for cell growth or cell death in association with other protein(s) (Saishin Igaku, vol. 56, p. 21, 2001). Examples of the other proteins include IRE1 β having nuclease motif (e.g., Nature Cell Biology, vol. 3, p. 158, 2001). It is considered that, when the protein of SEQ ID NO: 3 is activated, the activity of IRE1 β is controlled and apoptosis in a cell is induced. A partial sequence of a DNA encoding IRE1 β is deposited at GenBank under accession number AA088547 (protein name: IRE1 β) (SEQ ID NO: 31).

[0033] The protein having amino acid sequence of SEQ ID NO: 4 exists in a living body, comprises 181 amino acids and is also referred to as ISG20. A gene encoding the protein is deposited at GenBank under accession number X89773 (gene name: HSISG20GN). This protein is reported to have the both of ribonuclease activity (RNase) and deoxyribonuclease activity (DNase) (e.g., Biochemistry, 40(24), p.7174, 2001). The present inventors have found that, when a complex comprising polyinosinic—polycytidylic acid double stranded RNA and cationic liposomes is added to a certain cancer cell, mRNA for said protein is expressed, which cationic liposomes are formed from 2-O-(2-diethylaminoethyl)carbamoyl-1,3-O-dioleoyl glycerol (hereinafter, referred to as "cationic glycerol") and a phospholipid as essential components, as shown in Experimental Example 2 below.

[0034] The proteins of SEQ ID NO: 25-30 are all known proteins, which comprise amino acid sequences having high sequence identity to the amino acid sequence of nuclease motif of the protein of SEQ ID NO: 4. Genes encoding these proteins are deposited at GenBank, wherein the GenBank accession number of a gene encoding the protein of SEQ ID NO: 25 is AK025493 (gene name; AK025493), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 26 is AF273304 (gene name; AF273304), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 27 is AF295774 (gene name; AF295774), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 28 is AL136894 (gene name; HSM801862), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 29 is AK022733 (gene name; AK022733), the GenBank accession number of a gene encoding the protein of SEQ ID NO: 30 is AK022546 (gene name; AK022546).

[0035] II. Nucleotide or Nucleoside, or Composition Containing the Same

[0036] The nucleotides or nucleosides usable in the present method are not particularly restricted as long as they can exert antitumor or antivirus activity when entered into a cell. There are mono-, oligo- and poly-nucleotides, and the present invention encompasses all of them without any particular limitations.

[0037] Examples of the nucleotides or nucleoside are shown below.

[0038] (1) Homopolymer•homopolymer Double-stranded RNA

[0039] Polyinosinic acid•polycytidylic acid,

[0040] Polyinosinic acid•poly(5-bromocytidylic acid),

[0041] Polyinosinic acid•poly (2-thiocytidylic acid),

[0042] Poly(7-deazainosinic acid)•polycytidylic acid,

[0043] Poly(7-deazainosinic acid)•poly(5-bromocytidylic acid),

[0044] Poly(2'-azidoinosinic acid)•polycytidylic acid,

[0045] Polyinosinic acid•poly(cytidine-5'-thiophosphoric acid), and

[0046] Polyinosinic acid•poly(1-vinylcytidylic acid)

[0047] (2) Homopolymer•copolymer Double-stranded RNA

[0048] Polyinosinic acid•poly(cytidylic acid, uridylic acid), and

[0049] Polyinosinic acid•poly(cytidylic acid, 4-thiouridylic acid).

[0050] (3) Copolymer Single-stranded RNA

[0051] Poly(adenylic acid, uridylic acid).

[0052] (4) Others

[0053] 5-Fluorouracil, and

[0054] Cytosine arabinoside.

[0055] Most of single-stranded or double-stranded RNAs among these substances cannot enter into cells directly since they are a polymer and need to be converted into a complex with, for example, a carrier for transferring/introducing a drug into cells. A polynucleotide which formed a complex with a particular drug carrier can enter into a cell. Such a carrier is available in the art or can be prepared according to a method known to one of ordinary skill in the art.

[0056] Examples of carriers useful for transferring/introducing a substance into a cell include cationic liposome carriers. Specific examples of cationic liposome carriers include a cationic liposome carrier comprising as basic essential components cationic glycerol and a phospholipid (e.g., phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl inositol, phosphatidyl serine, lecithin) in the ratio of 1:3 to 2:1 (cationic glycerol:phospholipid) by weight; Lipofectin® (a cationic liposome carrier comprising as basic essential components N-[1-(2,3-dioleyloxy)propyl]-n,n,n-trimethylammonium chloride (DOTMA) and dioleoyl phosphatidylethanolamine (DOPE) in the ratio of 1:1 by weight), Lipofectamine® (a cationic liposome carrier comprising as basic essential components 2,3-dioleyloxy-N-[2-(sperminecarboxamido) ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA) and dioleoyl phosphatidylethanolamine (DOPE) in the ratio of 3:1 by weight), Cellfectin® (a cationic liposome carrier comprising as basic essential components N, N^{I}, N^{II}, N^{III}-tetramethyl-N, N^{I}, N^{II}, N^{III}-tetrapalmitylspermine (TMTPS) and dioleoyl phosphatidylethanolamine (DOPE) in the ratio of 1:1.5 by weight), DMRIE-C® (a cationic liposome carrier comprising as basic essential components 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DMRIE) and cholesterol in the molar ratio of 1:1). Also included are cationic liposome carriers comprising as basic essential components any one of various glycerol derivatives described in WO94/19314 and a phospholipid (ibid). Among them, a cationic liposome carrier comprising as basic essential components a cationic glycerol and a phospholipid (e.g., lecithin) in the ratio of 1:2 to 1:1 (cationic glycerol:phospholipid) by weight is preferred.

[0057] The cationic liposome carrier consists of a lipid bilayer similarly to ordinary liposomes and is an endoplasmic reticulum that is positively charged in aqueous solution. Accordingly, the cationic liposome carrier easily forms a complex with a compound that is negatively charged in aqueous solution such as a nucleic acid.

[0058] When the nucleotide used in the present invention is a polynucleotide such as polyinosinic—polycytidylic acid, it can have various chain lengths or molecular weights, and the present invention is by no means restricted to a polynucleotide of any particular chain length or molecular weight. As to a copolymer polynucleotide such as poly(cytidylic acid, uridylic acid), it may contain two nucleotides in various constitutions or ratios, and the present invention is by no means restricted to a polynucleotide of any particular constitution or ratio. However, in the preferred constitution for the polyinosinic acid•poly(cytidylic acid, uridylic acid), one uridylic acid appears as compared with about 12 cytidylic acids (poly $C_{12}U$). With regard to a copolymer single-stranded RNA such as poly(adenylic acid, uridylic acid), it is preferably a constitution where two nucleotides appear alternately.

[0059] The present method is applicable to examination of efficacy of treatment with any types of nucleotide or nucleoside; however, it is suitable for examining or evaluating efficacy of treatment with polyinosinic—polycytidylic acid, and is more suitable for examining efficacy of treatment with polyinosinic—polycytidylic acid of average chain length between 100 bp and 500 bp (base pairs). As mentioned above, polyinosinic—polycytidylic acid cannot enter into a cell directly and should be administered as a complex with a cationic liposome carrier which, for example, comprises as basic essential components a cationic glycerol and a phospholipid (e.g., lecithin) in the ratio of 1:2 to 1:1 (cationic glycerol:phospholipid) by weight so that it can enter into a cell.

[0060] The present method can be conducted both in vivo and in vitro. In the former case, examples of tissues of a subject to which a nucleotide or a nucleoside is administered include vein, hepatic artery, portal vein and tumor tissues. In the latter case, examples of tissues to be taken from a subject include a carcinoma tissue and a tissue infected with virus. Specific examples of carcinoma tissues include hepatic carcinoma, lung cancer, carcinoma of colon and rectum, gastric cancer, bladder carcinoma, ovarian carcinoma, uterine cancer, breast cancer, prostatic cancer, brain tumor, kidney cancer, pancreas cancer, skin cancer and myosarcoma. However, the present invention is not limited to the above tissues, and one can select tissues appropriately depending on the purpose.

[0061] According to the present method, a nucleotide or a nucleoside is generally administered as a solution. The nucleotide or nucleoside can be in any form before being converted into a solution, including liquid preparation, powder preparation and lyophilized preparation. The present invention is not restricted to a particular form.

[0062] In the present examination method, any of known pharmaceutical compositions containing a nucleotide or a nucleoside that can enter into cells can be used as it is, which composition comprises, for example, a complex between a double stranded RNA such as polyinosinic—polycytidylic acid and a cationic liposome carrier. Such a pharmaceutical composition can be prepared in a conventional manner or are commercially available.

[0063] The dose of a nucleotide or a nucleoside should vary depending on the kinds of nucleotide or nucleoside to be used, the disease, conditions of the patient, or the like, and is appropriately determined.

[0064] III. Determination of Expression Amount of Protein

[0065] In the present examination method, the determination of the expression amount of a protein according to the present invention can be conducted by a known method wherein (1) the target protein is measured directly, or (2) the expression of mRNA encoding the target protein is measured, and the like. Specific examples of the former include ELISA method that uses an appropriate antibody and specific examples of the latter include RT-PCR method.

[0066] When carrying out the present method, the expression amount of a protein according to the present invention is measured in vivo or in vitro, before and after the administration of a nucleotide or a nucleoside into a tissue of a subject or into a tissue obtained from the subject. The increase in the amount of expression of the protein as a result of administration of the nucleotide or the nucleoside leads to the evaluation that a pharmaceutical composition containing the nucleotide or the nucleoside possibly has therapeutic effect in said patient.

[0067] Among the proteins according to the present invention, preferred protein of which expression amount is measured varies depending on the kind of nucleotide or nucleoside to be used, the kind of disease (e.g., tumor, infected virus, etc.), conditions of the patient, and the like. To examine therapeutic efficacy of a pharmaceutical composition containing as a double-stranded RNA polyinosinic—polycytidylic acid and cationic liposome carrier, it would be useful to measure the protein having amino acid sequence of SEQ ID NO: 4. When the expression amount of the protein of SEQ ID NO: 4 increases after the administration of said pharmaceutical composition, said composition can be estimated to have therapeutic effect in said patient.

[0068] The criterion of judgment regarding therapeutic efficacy should vary depending on the condition of a patient, kind of nucleotide or nucleoside to be used, the kind of disease (e.g., tumor, infected virus, etc.), a protein to be measured, method of measurement, and the like. However, if the expression amount of a protein measured after the administration increased 1.5 or more times, preferably, 2.0 or more times as compared to what measured before the administration, it can be estimated to be therapeutically effective.

[0069] IV. Determination of Activity of Protein

[0070] In the present examination method, the determination of the activity of a protein according to the present invention can be conducted by a known method. Examples of such activity include nuclease (DNase, RNase) activity, kinase activity and protein-binding activity. Specific examples of the method for determining the activity involve the determination of nuclease (DNase, RNase) activity or kinase activity as hereinafter described.

[0071] (1) Determination of DNase Activity

[0072] Substrate:

> **[0073]** Cell fraction, DNA or DNA plasmid, which are radio-labeled with a radioisotope such as radioactive phosphorous

[0074] Reaction Solution:

> **[0075]** 50 mM MES-NaOH(pH 5.6) or 10 mM Tris-HCl (pH 7.8), 3 mM $CaCl_2$, 3 mM $MgCl_2$, 0.1 mM PMSF, 1 mM mercaptoethanol

[0076] To the substrate and the reaction solution is added a test protein and the mixture is incubated at 37° C. for 10 to 60 minutes. The reaction mixture is centrifuged at 20,000×g for 20 seconds and the supernatant is removed.

The precipitates are treated with RNase and proteinase K, and electrophoresed on agarose. The DNase activity can be determined from the amount of decomposed radio-labeled DNA as an indicator.

[0077] (2) Determination of RNase Activity

[0078] Substrate:

[0079] Ribosomal RNA radio-labeled with a radioisotope such as radioactive phosphorous

[0080] Reaction Solution:

[0081] 10 mM Tris-HCl(pH 7.4), 300 mM NaCl, 5 mM EDTA

[0082] To the substrate and the reaction solution is added a test protein and the mixture is incubated at 37° C. for 10 to 60 minutes. The radio-labeled ribosomal RNA is extracted by guanidium thiocyanate method and electrophoresed on agarose. The RNase activity can be determined from the amount of fragmented radio-labeled RNA as an indicator.

[0083] (3) Determination of Kinase Activity

[0084] Substrate:Peptide

[0085] Reaction solution:

[0086] 20-50 mM Tris-HCl (pH 7.4), 5-10 mM $MgCl_2$, 250-500 μM [γ-^{32}P]ATP, 15 mM mercaptoethanol, 0.1% Tween80

[0087] To the substrate and the reaction solution is added a test protein and the mixture is incubated at 37° C. for 10 to 60 minutes. The substrate peptides are extracted and the kinase activity can be determined from the amount of radio-labeled peptides as an indicator.

[0088] When carrying out the present method, the nuclease activity or the like is measured in vivo or in vitro, before and after the administration of a nucleotide or a nucleoside into a tissue of a subject or into a tissue obtained from the subject. The increase in the activity as a result of administration of the nucleotide or the nucleoside leads to the evaluation that a pharmaceutical composition containing the said nucleotide or the nucleoside possibly has therapeutic effect in said patient.

[0089] Among the proteins according to the present invention, preferred protein of which expression amount should be measured varies depending on the kind of nucleotide or nucleoside to be used, the kind of disease (e.g., tumor, infected virus, etc.), conditions of the patient, and the like. To examine therapeutic efficacy of a pharmaceutical composition containing as a double-stranded RNA polyinosinic—polycytidylic acid and cationic liposome carrier, it would be useful to measure a protein from those having the amino acid sequences of SEQ ID NO: 1-4, preferably SEQ ID NO: 1, 2 and 4. When the expression amount of a protein having an amino acid sequence selected from SEQ ID NO: 1-4 increases after the administration of said pharmaceutical composition, said composition can be estimated as being possibly therapeutically effective in said patient.

[0090] The criterion of judgment regarding therapeutic efficacy varies depending on the kind of nucleotide or nucleoside to be used, condition of a patient, the kind of disease (e.g., tumor, infected virus, etc.), a protein to be measured, method of measurement, and the like. However, if the activity of a protein measured increased 1.5 or more times, preferably, 2.0 or more times as compared to what measured before the administration, it can be estimated as being therapeutically effective.

[0091] V. Determination of Binding Ability to Proteins

[0092] Examples of method for examining the binding ability of a test substance (medical substance) to a protein according to the present invention include West western method with an appropriate antibody, immunoprecipitation method, and a process by means of BIAcore® (Pharmacia Biotech) which is an automated analytic device based on surface plasmon resonance (SPR), an optical phenomenon, as measuring principle. If a test substance proved to bind to a protein(s) according to the present invention, said test substance can be a promising antitumor or antivirus agent.

[0093] A substance known to have antitumor or antivirus activity can also be examined for the ability to bind to a protein of the present invention according to a similar method as the above. If the substance proved to bind to the protein, said substance can be expected to act in vivo through at least a similar reaction mechanism as polyinosinic—polycytidylic acid.

[0094] The experimental examples below provides the detection or identification of a protein(s) according to the present invention, and influence of a nucleic acid on the expression of mRNA for the protein. In the following experimental examples, a double-stranded RNA, polyinosinic acid-polycytidylic acid (polyinosinic—polycytidylic acid, hereinafter, referred to as "poly(I)•poly(C)") was used as a nucleic acid-containing test substance (drug). Poly(I)•poly(C) is known to be efficacious against certain cancer cells (e.g., HeLaS3, A431) but inefficacious against others (e.g., HeLa, SW620) (Cancer Research, 59, pp. 4325-4333 (1999)).

EXPERIMENTAL EXAMPLE 1

[0095] Detection of Binding Ability to Proteins of SEQ ID NO: 1-3

[0096] (1) Each protein was synthesized by plating phages containing cDNA on a petri dish using human HeLa 5'-STRETCH PLUS cDNA library.

[0097] (2) The synthesized protein was transferred to nitrocellulose membrane.

[0098] (3) To the nitrocellulose membrane was added the following test solution containing poly(I)•poly(C) (chain length 100-500 bp) radio-labeled with [γ-^{32}P] ATP, and subjected to hybridization at 42° C., for 5-6 hours.

[0099] <Test Solution>

[0100] 10 mM HEPES, pH 7.5

[0101] 50 mM NaCl

[0102] 1 mM Dithiothreitol

[0103] 1 mM EDTA

[0104] 5% Glycerol

[0105] 1 ng/ml-1 μg/ml [^{32}P]-poly(I)•poly(C)

[0106] (4) The nitrocellulose membrane was washed several times with above-mentioned solution which does not contain [^{32}P]-poly(I)•poly(C) and exposed to imaging plate to screen proteins bound to poly(I)•poly(C). The nucleotide sequence of cDNA corresponding to the screened protein was determined with a sequencer to identify the screened protein.

[0107] As a result, proteins of SEQ ID NO: 1-3 were revealed to that bound to poly(I)•poly(C).

EXPERIMENTAL EXAMPLE 2

[0108] Detection of Expression of mRNA for Protein of SEQ ID NO: 4 (ISG20)

[0109] (1) A test complex comprising poly(I)•poly(C) was added to each of cancer cells, Hela, HeLaS3, A431 and SW620 cells so that the concentration of poly(I)•poly(C) becomes from 10 to 100 ng/ml.

[0110] (2) Following the addition of the test complex, total RNA was extracted from HeLa and HeLaS3 cells at 2 and 4 hours, and from A431 and SW620 cells at 0.5, 1, 2 and 4 hours by guanidium thiocyanate method.

[0111] (3) The extracted RNA was subjected to the Reverse Transcriptase Chain Reaction (RT-PCR) and the reaction solution was electrophoresed on agarose gel. The bands indicated by white arrow in **FIGS. 2 and 3** show ISG20 mRNA.

[0112] <Test Complex>

	Weight ratio
Poly (I) · poly (C) (chain length 100~500 bp)	1
Cationic glycerol	6
Yolk lecithin	10

[0113] As is clear from **FIGS. 2 and 3**, the expression amount of ISG20 mRNA increased with time in cancer cells (HeLaS3, A431) on which the complex comprising poly(I)•poly(C) has effect. On the other hand, ISG20 mRNA was not expressed in cancer cells (HeLa, SW620) on which the complex comprising poly(I)•poly(C) does not have effect. This result shows that it is possible to evaluate whether a test drug is effective as a therapeutic agent in a specific patient on the basis of the presence or absence of expression of ISG20.

INDUSTRIAL APPLICABILITY

[0114] According to the method of the present invention, the efficacy of an antitumor or antivirus agent comprising a nucleic acid in individual patients can be evaluated beforehand, and hence it becomes possible to treat a patient more effectively through tailor-made therapy or the like. Furthermore, according to the present method, a substance potentially having antitumor or antivirus activity can be screened.

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                              SEQUENCE LISTING


<160> NUMBER OF SEQ ID NOS: 31

<210> SEQ ID NO 1
<211> LENGTH: 490
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Met Lys Asp Pro Pro Asp Leu Leu Asp Arg Gln Lys Cys Pro Asn Ala
  1               5                  10                  15

Leu Ala Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly
             20                  25                  30

Leu Lys Ser Cys Val Ile Val Leu Arg Ile Leu Arg Asp Leu Cys Asn
         35                  40                  45

Arg Val Pro Thr Trp Ala Pro Leu Lys Gly Trp Pro Leu Glu Leu Ile
     50                  55                  60

Cys Glu Lys Ser Ile Gly Thr Cys Asn Arg Pro Leu Gly Ala Gly Glu
 65                  70                  75                  80

Ala Leu Arg Arg Val Met Glu Cys Leu Ala Ser Gly Ile Leu Leu Pro
                 85                  90                  95

Gly Gly Pro Gly Leu His Asp Pro Cys Glu Arg Asp Pro Thr Asp Ala
            100                 105                 110

Leu Ser Tyr Met Thr Ile Gln Gln Lys Glu Asp Ile Thr His Ser Ala
        115                 120                 125

Gln His Ala Leu Arg Leu Ser Ala Phe Gly Gln Ile Tyr Lys Val Leu
    130                 135                 140
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Glu Met Asp Pro Leu Pro Ser Ser Lys Pro Phe Gln Lys Tyr Ser Trp
145                 150                 155                 160

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

Phe Glu Asp Gly Leu Gly Asp Asp Lys Asp Pro Asn Lys Lys Met Lys
            180                 185                 190

Arg Asn Leu Arg Lys Ile Leu Asp Ser Lys Ala Ile Asp Leu Met Asn
        195                 200                 205

Ala Leu Met Arg Leu Asn Gln Ile Arg Pro Gly Leu Gln Tyr Lys Leu
    210                 215                 220

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

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

Ala Lys Leu His Val Ala Val Lys Val Leu Gln Ala Met Gly Tyr Pro
            260                 265                 270

Thr Gly Phe Asp Ala Asp Ile Glu Cys Met Ser Ser Asp Glu Lys Ser
        275                 280                 285

Asp Asn Glu Ser Lys Asn Glu Thr Val Ser Ser Asn Ser Ser Asn Asn
    290                 295                 300

Thr Gly Asn Ser Thr Thr Glu Thr Ser Ser Thr Leu Glu Val Arg Thr
305                 310                 315                 320

Gln Gly Pro Ile Leu Thr Ala Ser Gly Lys Asn Pro Val Met Glu Leu
                325                 330                 335

Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile Ser Glu Thr Gly
            340                 345                 350

Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu Val Asp Gly Gln
        355                 360                 365

Lys Phe Arg Gly Ala Gly Pro Asn Lys Lys Val Ala Lys Ala Ser Ala
    370                 375                 380

Ala Leu Ala Ala Leu Glu Lys Leu Phe Ser Gly Pro Asn Ala Ala Asn
385                 390                 395                 400

Asn Lys Lys Lys Lys Ile Ile Pro Gln Ala Lys Gly Val Val Asn Thr
                405                 410                 415

Ala Val Ser Ala Ala Val Gln Ala Val Arg Gly Arg Gly Arg Gly Thr
            420                 425                 430

Leu Thr Arg Gly Ala Phe Val Gly Ala Thr Ala Ala Pro Gly Tyr Ile
        435                 440                 445

Ala Pro Gly Tyr Gly Thr Pro Tyr Gly Tyr Ser Thr Ala Ala Pro Ala
    450                 455                 460

Tyr Gly Leu Pro Lys Arg Met Val Leu Leu Pro Val Met Lys Phe Pro
465                 470                 475                 480

Thr Tyr Pro Val Pro His Tyr Ser Phe Phe
                485                 490


<210> SEQ ID NO 2
<211> LENGTH: 366
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Ser Glu Glu Glu Gln Gly Ser Gly Thr Thr Thr Gly Cys Gly Leu
  1               5                  10                  15
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Pro Ser Ile Glu Gln Met Leu Ala Ala Asn Pro Gly Lys Thr Pro Ile
             20                  25                  30

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

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

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

Lys Ala Ala Lys His Lys Ala Ala Glu Val Ala Leu Lys His Leu Lys
                 85                  90                  95

Gly Gly Ser Met Leu Glu Pro Ala Leu Glu Asp Ser Ser Ser Phe Ser
            100                 105                 110

Pro Leu Asp Ser Ser Leu Pro Glu Asp Ile Pro Val Phe Thr Ala Ala
        115                 120                 125

Ala Ala Ala Thr Pro Val Pro Ser Val Val Leu Thr Arg Ser Pro Pro
    130                 135                 140

Met Glu Leu Gln Pro Pro Val Ser Pro Gln Gln Ser Glu Cys Asn Pro
145                 150                 155                 160

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

Glu Tyr Thr Val Thr Gln Glu Ser Gly Pro Ala His Arg Lys Glu Phe
            180                 185                 190

Thr Met Thr Cys Arg Val Glu Arg Phe Ile Glu Ile Gly Ser Gly Thr
        195                 200                 205

Ser Lys Lys Leu Ala Lys Arg Asn Ala Ala Ala Lys Met Leu Leu Arg
    210                 215                 220

Val His Thr Val Pro Leu Asp Ala Arg Asp Gly Asn Glu Val Glu Pro
225                 230                 235                 240

Asp Asp Asp His Phe Ser Ile Gly Val Gly Phe Arg Leu Asp Gly Leu
                245                 250                 255

Arg Asn Arg Gly Pro Gly Cys Thr Trp Asp Ser Leu Arg Asn Ser Val
            260                 265                 270

Gly Glu Lys Ile Leu Ser Leu Arg Ser Cys Ser Leu Gly Ser Leu Gly
        275                 280                 285

Ala Leu Gly Pro Ala Cys Cys Arg Val Leu Ser Glu Leu Ser Glu Glu
    290                 295                 300

Gln Ala Phe His Val Ser Tyr Leu Asp Ile Glu Glu Leu Ser Leu Ser
305                 310                 315                 320

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

Cys His Gly Ser Ala Thr Thr Arg Glu Ala Ala Arg Gly Glu Ala Ala
            340                 345                 350

Arg Arg Ala Leu Gln Tyr Leu Lys Ile Met Ala Gly Ser Lys
        355                 360                 365

<210> SEQ ID NO 3
<211> LENGTH: 803
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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

Gly Ser Val Arg Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu
             20                  25                  30

Glu Asp Leu Gly Lys Ser Arg Glu Gly Ser Arg Thr Asp Asp Glu Val
         35                  40                  45

Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser
     50                  55                  60

Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala
 65                  70                  75                  80

Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn
                 85                  90                  95

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

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

Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
    130                 135                 140

Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val
145                 150                 155                 160

Lys Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Glu Phe Leu Asn
                165                 170                 175

Lys Met Thr Glu Ala Gln Glu Asp Gly Gln Ser Thr Ser Glu Leu Ile
            180                 185                 190

Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Phe Leu Val Ala Asp Lys
        195                 200                 205

Val Ile Val Thr Ser Lys His Asn Asn Asp Thr Gln His Ile Trp Glu
    210                 215                 220

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

Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu Glu Ala Ser
                245                 250                 255

Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys Lys Tyr Ser
            260                 265                 270

Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys Thr Glu Thr
        275                 280                 285

Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu Glu Lys Glu
    290                 295                 300

Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu Glu Lys Lys
305                 310                 315                 320

Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp Glu Leu Met
                325                 330                 335

Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu Val Glu Glu
            340                 345                 350

Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu Ser Asp Asp
        355                 360                 365

Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val Thr Phe Lys
    370                 375                 380

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

Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val Arg Arg Val
                405                 410                 415
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Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr Leu Asn Phe
            420                 425                 430

Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn Val Ser Arg
        435                 440                 445

Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg Lys Lys Leu
    450                 455                 460

Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp Asp Lys Tyr
465                 470                 475                 480

Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys Leu Gly Val
                485                 490                 495

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

Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp Gln Tyr Val
        515                 520                 525

Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met Ala Gly Ser
    530                 535                 540

Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg Leu Leu Lys
545                 550                 555                 560

Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp Glu Tyr Cys
                565                 570                 575

Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln Asn Val Ala
            580                 585                 590

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

Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp Met Lys Asp
    610                 615                 620

Lys Ala Leu Lys Asp Lys Ile Glu Lys Ala Val Val Ser Gln Arg Leu
625                 630                 635                 640

Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly Trp Ser Gly
                645                 650                 655

Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr Gly Lys Asp
            660                 665                 670

Ile Ser Thr Asn Tyr Tyr Ala Ser Gln Lys Lys Thr Phe Glu Ile Asn
        675                 680                 685

Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile Lys Glu Asp
    690                 695                 700

Glu Asp Asp Lys Thr Val Leu Asp Leu Ala Val Val Leu Phe Glu Thr
705                 710                 715                 720

Ala Thr Leu Arg Ser Gly Tyr Leu Leu Pro Asp Thr Lys Ala Tyr Gly
                725                 730                 735

Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile Asp Pro Asp
            740                 745                 750

Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu Thr Ala Glu
        755                 760                 765

Asp Thr Thr Glu Asp Thr Glu Gln Asp Glu Asp Glu Glu Met Asp Val
    770                 775                 780

Gly Thr Asp Glu Glu Glu Glu Thr Ala Lys Glu Ser Thr Ala Glu Lys
785                 790                 795                 800

Asp Glu Leu
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<210> SEQ ID NO 4
<211> LENGTH: 181
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Ala Gly Ser Arg Glu Val Val Ala Met Asp Cys Glu Met Val Gly
  1               5                  10                  15

Leu Gly Pro His Arg Glu Ser Gly Leu Ala Arg Cys Ser Leu Val Asn
             20                  25                  30

Val His Gly Ala Val Leu Tyr Asp Lys Phe Ile Arg Pro Glu Gly Glu
         35                  40                  45

Ile Thr Asp Tyr Arg Thr Arg Val Ser Gly Val Thr Pro Gln His Met
     50                  55                  60

Val Gly Ala Thr Pro Phe Ala Val Ala Arg Leu Glu Ile Leu Gln Leu
 65                  70                  75                  80

Leu Lys Gly Lys Leu Val Val Gly His Asp Leu Lys His Asp Phe Gln
                 85                  90                  95

Ala Leu Lys Glu Asp Met Ser Gly Tyr Thr Ile Tyr Asp Thr Ser Thr
            100                 105                 110

Asp Arg Leu Leu Trp Arg Glu Ala Lys Leu Asp His Cys Arg Arg Val
        115                 120                 125

Ser Leu Arg Val Leu Ser Glu Arg Leu Leu His Lys Ser Ile Gln Asn
    130                 135                 140

Ser Leu Leu Gly His Ser Ser Val Glu Asp Ala Arg Ala Thr Met Glu
145                 150                 155                 160

Leu Tyr Gln Ile Ser Gln Arg Ile Arg Ala Arg Arg Gly Leu Pro Arg
                165                 170                 175

Leu Ala Val Ser Asp
            180


<210> SEQ ID NO 5
<211> LENGTH: 658
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Val Lys His Ser Thr Ile Tyr Pro Ser Pro Glu Glu Leu Glu Ala
  1               5                  10                  15

Val Gln Asn Met Val Ser Thr Val Glu Cys Ala Leu Lys His Val Ser
             20                  25                  30

Asp Trp Leu Asp Glu Thr Asn Lys Gly Thr Lys Thr Glu Gly Glu Thr
         35                  40                  45

Glu Val Lys Lys Asp Glu Ala Gly Glu Asn Tyr Ser Lys Asp Gln Gly
     50                  55                  60

Gly Arg Thr Leu Cys Gly Val Met Arg Ile Gly Leu Val Ala Lys Gly
 65                  70                  75                  80

Leu Leu Ile Lys Asp Asp Met Asp Leu Glu Leu Val Leu Met Cys Lys
                 85                  90                  95

Asp Lys Pro Thr Glu Thr Leu Leu Asn Thr Val Lys Asp Asn Leu Pro
            100                 105                 110

Ile Gln Ile Gln Lys Leu Thr Glu Glu Lys Tyr Gln Val Glu Gln Cys
        115                 120                 125

Val Asn Glu Ala Ser Ile Ile Ile Arg Asn Thr Lys Glu Pro Thr Leu
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    130                 135                 140

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

Lys Lys Asp Gly Glu Asn Val Ser Met Lys Asp Pro Pro Asp Leu Leu
                165                 170                 175

Asp Arg Gln Lys Cys Leu Asn Ala Leu Ala Ser Leu Arg His Ala Lys
            180                 185                 190

Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys Ser Cys Val Ile Val Leu
        195                 200                 205

Arg Ile Leu Arg Asp Leu Cys Asn Arg Val Pro Thr Trp Ala Pro Leu
    210                 215                 220

Lys Gly Trp Pro Leu Glu Leu Ile Cys Glu Lys Ser Ile Gly Thr Cys
225                 230                 235                 240

Asn Arg Pro Leu Gly Ala Gly Glu Ala Leu Arg Arg Val Met Glu Cys
                245                 250                 255

Leu Ala Ser Gly Ile Leu Leu Pro Gly Gly Pro Gly Leu His Asp Pro
            260                 265                 270

Cys Glu Arg Asp Pro Thr Asp Ala Leu Ser Tyr Met Thr Ile Gln Gln
        275                 280                 285

Lys Glu Asp Ile Thr His Ser Ala Gln His Ala Leu Arg Leu Ser Ala
    290                 295                 300

Phe Gly Gln Ile Tyr Lys Val Leu Glu Met Asp Pro Leu Pro Ser Ser
305                 310                 315                 320

Lys Pro Phe Gln Lys Tyr Ser Trp Ser Val Thr Asp Lys Glu Gly Ala
                325                 330                 335

Gly Ser Ser Ala Leu Lys Arg Pro Phe Glu Asp Gly Leu Gly Asp Asp
            340                 345                 350

Lys Asp Pro Asn Lys Lys Met Lys Arg Asn Leu Arg Lys Ile Leu Asp
        355                 360                 365

Ser Lys Ala Ile Asp Leu Met Asn Ala Leu Met Arg Leu Asn Gln Ile
    370                 375                 380

Arg Pro Gly Leu Gln Tyr Lys Leu Leu Ser Gln Ser Gly Pro Val His
385                 390                 395                 400

Ala Pro Val Phe Thr Met Ser Val Asp Val Asp Gly Thr Thr Tyr Glu
                405                 410                 415

Ala Ser Gly Pro Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys
            420                 425                 430

Val Leu Gln Ala Met Gly Tyr Pro Thr Gly Phe Asp Ala Asp Ile Glu
        435                 440                 445

Cys Met Ser Ser Asp Glu Lys Ser Asp Asn Glu Ser Lys Asn Glu Thr
    450                 455                 460

Val Ser Ser Asn Ser Ser Asn Asn Thr Gly Asn Ser Thr Thr Glu Thr
465                 470                 475                 480

Ser Ser Thr Leu Glu Val Arg Thr Gln Gly Pro Ile Leu Thr Ala Ser
                485                 490                 495

Gly Lys Asn Pro Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys
            500                 505                 510

Tyr Glu Leu Ile Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val
        515                 520                 525

Met Glu Val Glu Val Asp Gly Gln Lys Phe Arg Gly Ala Gly Pro Asn
    530                 535                 540
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Lys Lys Val Ala Lys Ala Ser Ala Ala Leu Ala Ala Leu Glu Lys Leu
545                 550                 555                 560

Phe Ser Gly Pro Asn Ala Ala Asn Asn Lys Lys Lys Lys Ile Ile Pro
                565                 570                 575

Gln Ala Lys Gly Val Val Asn Thr Ala Val Ser Ala Ala Val Gln Ala
            580                 585                 590

Val Arg Gly Arg Gly Arg Gly Thr Leu Thr Arg Gly Ala Phe Val Gly
        595                 600                 605

Ala Thr Ala Ala Pro Gly Tyr Ile Ala Pro Gly Tyr Gly Thr Pro Tyr
    610                 615                 620

Gly Tyr Ser Thr Ala Ala Pro Ala Tyr Gly Leu Pro Lys Arg Met Val
625                 630                 635                 640

Leu Leu Pro Val Met Lys Phe Pro Thr Tyr Pro Val Pro His Tyr Ser
                645                 650                 655

Phe Phe


<210> SEQ ID NO 6
<211> LENGTH: 405
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Glu Cys Leu Ala Ser Gly Ile Leu Leu Pro Gly Gly Pro Gly Leu
  1               5                  10                  15

His Asp Pro Cys Glu Arg Asp Pro Thr Asp Ala Leu Ser Tyr Met Thr
             20                  25                  30

Ile Gln Gln Lys Glu Asp Ile Thr His Ser Ala Gln His Ala Leu Arg
         35                  40                  45

Leu Ser Ala Phe Gly Gln Ile Tyr Lys Val Leu Glu Met Asp Pro Leu
     50                  55                  60

Pro Ser Ser Lys Pro Phe Gln Lys Tyr Ser Trp Ser Val Thr Asp Lys
 65                  70                  75                  80

Glu Gly Ala Gly Ser Ser Ala Leu Lys Arg Pro Phe Glu Asp Gly Leu
                 85                  90                  95

Gly Asp Asp Lys Asp Pro Asn Lys Lys Met Lys Arg Asn Leu Arg Lys
            100                 105                 110

Ile Leu Asp Ser Lys Ala Ile Asp Leu Met Asn Ala Leu Met Arg Leu
        115                 120                 125

Asn Gln Ile Arg Pro Gly Leu Gln Tyr Lys Leu Leu Ser Gln Ser Gly
    130                 135                 140

Pro Val His Ala Pro Val Phe Thr Met Ser Val Asp Val Asp Gly Thr
145                 150                 155                 160

Thr Tyr Glu Ala Ser Gly Pro Ser Lys Lys Thr Ala Lys Leu His Val
                165                 170                 175

Ala Val Lys Val Leu Gln Ala Met Gly Tyr Pro Thr Gly Phe Asp Ala
            180                 185                 190

Asp Ile Glu Cys Met Ser Ser Asp Glu Lys Ser Asp Asn Glu Ser Lys
        195                 200                 205

Asn Glu Thr Val Ser Ser Asn Ser Ser Asn Asn Thr Gly Asn Ser Thr
    210                 215                 220

Thr Glu Thr Ser Ser Thr Leu Glu Val Arg Thr Gln Gly Pro Ile Leu
225                 230                 235                 240
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```
Thr Ala Ser Gly Lys Asn Pro Val Met Glu Leu Asn Glu Lys Arg Arg
            245            250            255

Gly Leu Lys Tyr Glu Leu Ile Ser Glu Thr Gly Gly Ser His Asp Lys
         260            265            270

Arg Phe Val Met Glu Val Glu Val Asp Gly Gln Lys Phe Arg Gly Ala
      275            280            285

Gly Pro Asn Lys Lys Val Ala Lys Ala Ser Ala Ala Leu Ala Ala Leu
   290            295            300

Glu Lys Leu Phe Ser Gly Pro Asn Ala Ala Asn Asn Lys Lys Lys Lys
305            310            315            320

Ile Ile Pro Gln Ala Lys Gly Val Val Asn Thr Ala Val Ser Ala Ala
            325            330            335

Val Gln Ala Val Arg Gly Arg Gly Arg Gly Thr Leu Thr Arg Gly Ala
         340            345            350

Phe Val Gly Ala Thr Ala Ala Pro Gly Tyr Ile Ala Pro Gly Tyr Gly
      355            360            365

Thr Pro Tyr Gly Tyr Ser Thr Ala Ala Pro Ala Tyr Gly Leu Pro Lys
   370            375            380

Arg Met Val Leu Leu Pro Val Met Lys Phe Pro Thr Tyr Pro Val Pro
385            390            395            400

His Tyr Ser Phe Phe
            405


<210> SEQ ID NO 7
<211> LENGTH: 702
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1           5             10             15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
          20             25             30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
       35             40             45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
    50             55             60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65             70             75             80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
             85             90             95

Leu Val Ala Lys Cys Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
         100            105            110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
      115            120            125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
   130            135            140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145            150            155            160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
            165            170            175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
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```
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590
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```
Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655

Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Asp
        675                 680                 685

Phe Phe Thr Asp Cys Tyr Gly Tyr His Asp Phe Gly Ser Ser
    690                 695                 700


<210> SEQ ID NO 8
<211> LENGTH: 764
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
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                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655
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Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Gln
        675                 680                 685

Phe Ser Arg Pro Pro Pro Pro Ser Arg Pro Arg Cys Cys Val Val Arg
    690                 695                 700

Cys Ser Gly Ser Pro Cys Gly Pro Ser Cys Asp Pro Tyr Leu Ala Val
705                 710                 715                 720

Phe Gly Thr Pro Cys Leu Gln Trp Phe Val Ser Cys His Tyr Asn Phe
                725                 730                 735

Val Trp Val Glu Phe Leu Ser Phe Cys Ser Ser Val Ser Leu Cys Leu
            740                 745                 750

Phe Thr Leu Arg Val Ser Gly Asn Ser Val Cys Leu
        755                 760


<210> SEQ ID NO 9
<211> LENGTH: 702
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
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                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655
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Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Asp
        675                 680                 685

Phe Phe Thr Asp Cys Tyr Gly Tyr His Asp Phe Gly Ser Ser
    690                 695                 700


<210> SEQ ID NO 10
<211> LENGTH: 690
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
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305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655

Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Thr Gly
        675                 680                 685

Phe Val
    690

<210> SEQ ID NO 11
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<211> LENGTH: 894
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Cys Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
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    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655

Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Gln
        675                 680                 685

Phe Tyr Ser Asn Gly Gly His Ser Gly Asn Ala Ser Gly Gly Gly Gly
    690                 695                 700

Gly Gly Gly Gly Gly Ser Ser Gly Tyr Gly Ser Tyr Tyr Gln Gly Asp
705                 710                 715                 720

Asn Tyr Asn Ser Pro Val Pro Pro Lys His Ala Gly Lys Lys Gln Pro
                725                 730                 735

His Gly Gly Gln Gln Lys Pro Ser Tyr Gly Ser Gly Tyr Gln Ser His
            740                 745                 750

Gln Gly Gln Gln Gln Ser Tyr Asn Gln Ser Pro Tyr Ser Asn Tyr Gly
        755                 760                 765

Pro Pro Gln Gly Lys Gln Lys Gly Tyr Asn His Gly Gln Gly Ser Tyr
    770                 775                 780
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Ser Tyr Ser Asn Ser Tyr Asn Ser Pro Gly Gly Gly Gly Gly Ser Asp
785                 790                 795                 800

Tyr Asn Tyr Glu Ser Lys Phe Asn Tyr Ser Gly Ser Gly Gly Arg Ser
                805                 810                 815

Gly Gly Asn Ser Tyr Gly Ser Gly Gly Ala Ser Tyr Asn Pro Gly Ser
            820                 825                 830

His Gly Gly Tyr Gly Gly Gly Ser Gly Gly Gly Ser Ser Tyr Gln Gly
        835                 840                 845

Lys Gln Gly Gly Tyr Ser Gln Ser Asn Tyr Asn Ser Pro Gly Ser Gly
    850                 855                 860

Gln Asn Tyr Ser Gly Pro Pro Ser Ser Tyr Gln Ser Ser Gln Gly Gly
865                 870                 875                 880

Tyr Gly Arg Asn Ala Asp His Ser Met Asn Tyr Gln Tyr Arg
                885                 890


<210> SEQ ID NO 12
<211> LENGTH: 564
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr Glu Ile Leu Gln Ser Val
  1               5                  10                  15

Asp Asp Ala Ala Ile Val Ile Lys Asn Thr Lys Glu Pro Pro Leu Ser
             20                  25                  30

Leu Thr Ile His Leu Thr Ser Pro Val Val Arg Glu Glu Met Glu Lys
         35                  40                  45

Val Leu Ala Gly Glu Thr Leu Ser Val Asn Asp Pro Pro Asp Val Leu
     50                  55                  60

Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala Ser Leu Arg His Ala Lys
 65                  70                  75                  80

Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys Ser Cys Val Ile Val Ile
                 85                  90                  95

Arg Val Leu Arg Asp Leu Cys Thr Arg Val Pro Thr Trp Gly Pro Leu
            100                 105                 110

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

Asn Arg Pro Met Gly Ala Gly Glu Ala Leu Arg Arg Val Leu Glu Cys
    130                 135                 140

Leu Ala Ser Gly Ile Val Met Pro Asp Gly Ser Gly Ile Tyr Asp Pro
145                 150                 155                 160

Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly His Leu Asp Arg Gln Gln
                165                 170                 175

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

Phe Gly Gln Leu His Lys Val Leu Gly Met Asp Pro Leu Pro Ser Lys
        195                 200                 205

Met Pro Lys Lys Pro Lys Asn Glu Asn Pro Val Asp Tyr Thr Val Gln
    210                 215                 220

Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr Pro Met Lys Arg Pro Met
225                 230                 235                 240

Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser Lys Lys Lys Lys Lys Ile
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                245                 250                 255

Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro Gln Ala Met Asn Ala Leu
            260                 265                 270

Met Arg Leu Asn Gln Leu Lys Pro Gly Leu Gln Tyr Lys Leu Val Ser
        275                 280                 285

Gln Thr Gly Pro Val His Ala Pro Ile Phe Thr Met Ser Val Glu Val
    290                 295                 300

Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro Ser Lys Lys Thr Ala Lys
305                 310                 315                 320

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

Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu Asp Ser Ala Glu Glu Thr
            340                 345                 350

Glu Ala Lys Pro Ala Val Val Ala Pro Ala Pro Val Val Glu Ala Val
        355                 360                 365

Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp Ala Thr Ala Glu Asn Val
    370                 375                 380

Lys Gln Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro Val Met
385                 390                 395                 400

Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile Ser Glu
                405                 410                 415

Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu Val Asp
            420                 425                 430

Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala Lys Ala
        435                 440                 445

Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr Pro Leu
    450                 455                 460

Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val Arg Gly
465                 470                 475                 480

Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly Met Gly
                485                 490                 495

Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg Gly Arg
            500                 505                 510

Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly Phe Gly
        515                 520                 525

Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr Gly Ser
    530                 535                 540

Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Lys Cys Ala
545                 550                 555                 560

Phe Leu Ser Val


<210> SEQ ID NO 13
<211> LENGTH: 671
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
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         35                  40                  45

Ile His Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Cys Arg Gly Val Met Arg Ala Gly
                 85                  90                  95

Pro Gly Gly Gln Ser Ala Ser Tyr Ser Arg Gly Thr Trp Ile Trp Ser
            100                 105                 110

Trp Cys Cys Cys Val Arg Arg Ser Pro Gln Pro Ala Leu Leu Asp Lys
        115                 120                 125

Val Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys
    130                 135                 140

Tyr Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn
145                 150                 155                 160

Thr Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val
                165                 170                 175

Val Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val
            180                 185                 190

Asn Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Phe Ala Ala Leu
        195                 200                 205

Ala Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu
    210                 215                 220

Lys Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg
225                 230                 235                 240

Val Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys
                245                 250                 255

Glu Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala
            260                 265                 270

Leu Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp
        275                 280                 285

Gly Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile
    290                 295                 300

Gly His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln
305                 310                 315                 320

His Ala Leu Arg Leu Ala Ala Phe Gly Gln Leu His Lys Val Leu Gly
                325                 330                 335

Met Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn
            340                 345                 350

Pro Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile
        355                 360                 365

Thr Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro
    370                 375                 380

Ser Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro
385                 390                 395                 400

Pro Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly
                405                 410                 415

Leu Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile
            420                 425                 430

Phe Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly
        435                 440                 445
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Pro Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln
    450                 455                 460

Asp Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly
465                 470                 475                 480

Glu Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro
                485                 490                 495

Ala Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser
            500                 505                 510

Asp Ala Thr Ala Glu Asn Val Lys Gln Gln Gly Pro Ile Leu Thr Lys
        515                 520                 525

His Gly Lys Asn Pro Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu
    530                 535                 540

Lys Tyr Glu Leu Ile Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe
545                 550                 555                 560

Val Met Glu Val Glu Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser
                565                 570                 575

Asn Lys Lys Val Ala Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys
            580                 585                 590

Leu Phe Pro Asp Thr Pro Leu Ser Pro Leu Met Pro Thr Lys Arg Arg
        595                 600                 605

Glu Pro Gln Tyr Pro Ser Glu Gly Asp Arg Asn Leu Leu Leu Ser His
    610                 615                 620

Ile Thr Leu Ala Ser Ala Trp Glu Ala Pro Cys Thr Thr Lys Cys Pro
625                 630                 635                 640

His Pro Pro Thr Phe Glu Gly Gly Glu Glu Ala Gly Arg Ser Gly Asp
                645                 650                 655

Glu Gly Ala Gly Glu Asp Leu Val Ala Pro Thr Met Glu Ala Thr
            660                 665                 670


<210> SEQ ID NO 14
<211> LENGTH: 611
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                   10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
                 20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
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    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Val Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540
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Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly
    610


<210> SEQ ID NO 15
<211> LENGTH: 702
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Val Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
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        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Thr Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655

Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Asp
        675                 680                 685
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Phe Phe Thr Asp Cys Tyr Gly Tyr His Asp Phe Gly Ser Ser
    690                 695                 700


<210> SEQ ID NO 16
<211> LENGTH: 440
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                   10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
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            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly
        435                 440


<210> SEQ ID NO 17
<211> LENGTH: 345
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Leu Ala Ala Asn Pro Gly Lys Thr Pro Ile Ser Leu Leu Gln Glu
  1               5                  10                  15

Tyr Gly Thr Arg Ile Gly Lys Thr Pro Val Tyr Asp Leu Leu Lys Ala
             20                  25                  30

Glu Gly Gln Ala His Gln Pro Asn Phe Thr Phe Arg Val Thr Val Gly
         35                  40                  45

Asp Thr Ser Cys Thr Gly Gln Gly Pro Ser Lys Lys Ala Ala Lys His
     50                  55                  60

Lys Ala Ala Glu Val Ala Leu Lys His Leu Lys Gly Gly Ser Met Leu
 65                  70                  75                  80

Glu Pro Ala Leu Glu Asp Ser Ser Ser Phe Ser Pro Leu Asp Ser Ser
                 85                  90                  95

Leu Pro Glu Asp Ile Pro Val Phe Thr Ala Ala Ala Ala Ala Thr Pro
            100                 105                 110

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

Pro Val Ser Pro Gln Gln Ser Glu Cys Asn Pro Val Gly Ala Leu Gln
    130                 135                 140

Glu Leu Val Val Gln Lys Gly Trp Arg Leu Pro Glu Tyr Thr Val Thr
145                 150                 155                 160

Gln Glu Ser Gly Pro Ala His Arg Lys Glu Phe Thr Met Thr Cys Arg
                165                 170                 175

Val Glu Arg Phe Ile Glu Ile Gly Ser Gly Thr Ser Lys Lys Leu Ala
            180                 185                 190

Lys Arg Asn Ala Ala Ala Lys Met Leu Leu Arg Val His Thr Val Pro
        195                 200                 205

Leu Asp Ala Arg Asp Gly Asn Glu Val Glu Pro Asp Asp Asp His Phe
    210                 215                 220

Ser Ile Gly Val Gly Phe Arg Leu Asp Gly Leu Arg Asn Arg Gly Pro
225                 230                 235                 240

Gly Cys Thr Trp Asp Ser Leu Arg Asn Ser Val Gly Glu Lys Ile Leu
                245                 250                 255
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Ser Leu Arg Ser Cys Ser Leu Gly Ser Leu Gly Ala Leu Gly Pro Ala
            260                 265                 270

Cys Cys Arg Val Leu Ser Glu Leu Ser Glu Glu Gln Ala Phe His Val
        275                 280                 285

Ser Tyr Leu Asp Ile Glu Glu Leu Ser Leu Ser Gly Leu Cys Gln Cys
    290                 295                 300

Leu Val Glu Leu Ser Thr Gln Pro Ala Thr Val Cys His Gly Ser Ala
305                 310                 315                 320

Thr Thr Arg Glu Ala Ala Arg Gly Glu Ala Ala Arg Arg Ala Leu Gln
                325                 330                 335

Tyr Leu Lys Ile Met Ala Gly Ser Lys
            340                 345


<210> SEQ ID NO 18
<211> LENGTH: 313
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Met Ser Gln Ser Arg His Arg Ala Glu Ala Pro Pro Leu Glu Arg Glu
  1               5                  10                  15

Asp Ser Gly Thr Phe Ser Leu Gly Lys Met Ile Thr Ala Lys Pro Gly
             20                  25                  30

Lys Thr Pro Ile Gln Val Leu His Glu Tyr Gly Met Lys Thr Lys Asn
         35                  40                  45

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

Thr Phe Thr Phe Arg Val Thr Val Gly Asp Ile Thr Cys Thr Gly Glu
 65                  70                  75                  80

Gly Thr Ser Lys Lys Leu Ala Lys His Arg Ala Ala Glu Ala Ala Ile
                 85                  90                  95

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

Leu Met Pro Asp Pro Ser Lys Gln Pro Lys Asn Gln Leu Asn Pro Ile
        115                 120                 125

Gly Ser Leu Gln Glu Leu Ala Ile His His Gly Trp Arg Leu Pro Glu
    130                 135                 140

Tyr Thr Leu Ser Gln Glu Gly Gly Pro Ala His Lys Arg Glu Tyr Thr
145                 150                 155                 160

Thr Ile Cys Arg Leu Glu Ser Phe Met Glu Thr Gly Lys Gly Ala Ser
                165                 170                 175

Lys Lys Gln Ala Lys Arg Asn Ala Ala Glu Lys Phe Leu Ala Lys Phe
            180                 185                 190

Ser Asn Ile Ser Pro Glu Asn His Ile Ser Leu Thr Asn Val Val Gly
        195                 200                 205

His Ser Leu Gly Cys Thr Trp His Ser Leu Arg Asn Ser Pro Gly Glu
    210                 215                 220

Lys Ile Asn Leu Leu Lys Arg Ser Leu Leu Ser Ile Pro Asn Thr Asp
225                 230                 235                 240

Tyr Ile Gln Leu Leu Ser Glu Ile Ala Lys Glu Gln Gly Phe Asn Ile
                245                 250                 255

Thr Tyr Leu Asp Ile Asp Glu Leu Ser Ala Asn Gly Gln Tyr Gln Cys
            260                 265                 270
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Leu Ala Glu Leu Ser Thr Ser Pro Ile Thr Val Cys His Gly Ser Gly
        275                 280                 285

Ile Ser Cys Gly Asn Ala Gln Ser Asp Ala Ala His Asn Ala Leu Gln
    290                 295                 300

Tyr Leu Lys Ile Ile Ala Glu Arg Lys
305                 310


<210> SEQ ID NO 19
<211> LENGTH: 741
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Met Asp Ile Glu Asp Glu Glu Asn Met Ser Ser Ser Ser Thr Asp Val
  1               5                  10                  15

Lys Glu Asn Arg Asn Leu Asp Asn Val Ser Pro Lys Asp Gly Ser Thr
             20                  25                  30

Pro Gly Pro Gly Glu Gly Ser Gln Leu Ser Asn Gly Gly Gly Gly Gly
         35                  40                  45

Pro Gly Arg Lys Arg Pro Leu Glu Glu Gly Ser Asn Gly His Ser Lys
     50                  55                  60

Tyr Arg Leu Lys Lys Arg Arg Lys Thr Pro Gly Pro Val Leu Pro Lys
 65                  70                  75                  80

Asn Ala Leu Met Gln Leu Asn Glu Ile Lys Pro Gly Leu Gln Tyr Thr
                 85                  90                  95

Leu Leu Ser Gln Thr Gly Pro Val His Ala Pro Leu Phe Val Met Ser
            100                 105                 110

Val Glu Val Asn Gly Gln Val Phe Glu Gly Ser Gly Pro Thr Lys Lys
        115                 120                 125

Lys Ala Lys Leu His Ala Ala Glu Lys Ala Leu Arg Ser Phe Val Gln
    130                 135                 140

Phe Pro Asn Ala Ser Glu Ala His Leu Ala Met Gly Arg Thr Leu Ser
145                 150                 155                 160

Val Asn Thr Asp Phe Thr Ser Asp Gln Ala Asp Phe Pro Asp Thr Leu
                165                 170                 175

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

Gly Ser Asn Gly Asp Asp Ser Phe Ser Ser Ser Gly Asp Leu Ser Leu
        195                 200                 205

Ser Ala Ser Pro Val Pro Ala Ser Leu Ala Gln Pro Pro Leu Pro Val
    210                 215                 220

Leu Pro Pro Phe Pro Pro Pro Ser Gly Lys Asn Pro Val Met Ile Leu
225                 230                 235                 240

Asn Glu Leu Arg Pro Gly Leu Lys Tyr Asp Phe Leu Ser Glu Ser Gly
                245                 250                 255

Glu Ser His Ala Lys Ser Phe Val Met Ser Val Val Val Asp Gly Gln
            260                 265                 270

Phe Phe Glu Gly Ser Gly Arg Asn Lys Lys Leu Ala Lys Ala Arg Ala
        275                 280                 285

Ala Gln Ser Ala Leu Ala Ala Ile Phe Asn Leu His Leu Asp Gln Thr
    290                 295                 300

Pro Ser Arg Gln Pro Ile Pro Ser Glu Gly Leu Gln Leu His Leu Pro
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305                 310                 315                 320

Gln Val Leu Ala Asp Ala Val Ser Arg Leu Val Leu Gly Lys Phe Gly
                325                 330                 335

Asp Leu Thr Asp Asn Phe Ser Ser Pro His Ala Arg Arg Lys Val Leu
            340                 345                 350

Ala Gly Val Val Met Thr Thr Gly Thr Asp Val Lys Asp Ala Lys Val
        355                 360                 365

Ile Ser Val Ser Thr Gly Thr Lys Cys Ile Asn Gly Glu Tyr Met Ser
    370                 375                 380

Asp Arg Gly Leu Ala Leu Asn Asp Cys His Ala Glu Ile Ile Ser Arg
385                 390                 395                 400

Arg Ser Leu Leu Arg Phe Leu Tyr Thr Gln Leu Glu Leu Tyr Leu Asn
                405                 410                 415

Asn Lys Asp Asp Gln Lys Arg Ser Ile Phe Gln Lys Ser Glu Arg Gly
            420                 425                 430

Gly Phe Arg Leu Lys Glu Asn Val Gln Phe His Leu Tyr Ile Ser Thr
        435                 440                 445

Ser Pro Cys Gly Asp Ala Arg Ile Phe Ser Pro His Glu Pro Ile Leu
    450                 455                 460

Glu Gly Ser Arg Ser Tyr Thr Gln Ala Gly Val Gln Trp Cys Asn His
465                 470                 475                 480

Gly Ser Leu Gln Pro Arg Pro Pro Gly Leu Leu Ser Asp Pro Ser Thr
                485                 490                 495

Ser Thr Phe Gln Gly Ala Gly Thr Thr Glu Pro Ala Asp Arg His Pro
            500                 505                 510

Asn Arg Lys Ala Arg Gly Gln Leu Arg Thr Lys Ile Glu Ser Gly Glu
        515                 520                 525

Gly Thr Ile Pro Val Arg Ser Asn Ala Ser Ile Gln Thr Trp Asp Gly
    530                 535                 540

Val Leu Gln Gly Glu Arg Leu Leu Thr Met Ser Cys Ser Asp Lys Ile
545                 550                 555                 560

Ala Arg Trp Asn Val Val Gly Ile Gln Gly Ser Leu Leu Ser Ile Phe
                565                 570                 575

Val Glu Pro Ile Tyr Phe Ser Ser Ile Ile Leu Gly Ser Leu Tyr His
            580                 585                 590

Gly Asp His Leu Ser Arg Ala Met Tyr Gln Arg Ile Ser Asn Ile Glu
        595                 600                 605

Asp Leu Pro Pro Leu Tyr Thr Leu Asn Lys Pro Leu Leu Ser Gly Ile
    610                 615                 620

Ser Asn Ala Glu Ala Arg Gln Pro Gly Lys Ala Pro Asn Phe Ser Val
625                 630                 635                 640

Asn Trp Thr Val Gly Asp Ser Ala Ile Glu Val Ile Asn Ala Thr Thr
                645                 650                 655

Gly Lys Asp Glu Leu Gly Arg Ala Ser Arg Leu Cys Lys His Ala Leu
            660                 665                 670

Tyr Cys Arg Trp Met Arg Val His Gly Lys Val Pro Ser His Leu Leu
        675                 680                 685

Arg Ser Lys Ile Thr Lys Pro Asn Val Tyr His Glu Ser Lys Leu Ala
    690                 695                 700

Ala Lys Glu Tyr Gln Ala Ala Lys Ala Arg Leu Phe Thr Ala Phe Ile
705                 710                 715                 720
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Lys Ala Gly Leu Gly Ala Trp Val Glu Lys Pro Thr Glu Gln Asp Gln
                725                 730                 735

Phe Ser Leu Thr Pro
            740


<210> SEQ ID NO 20
<211> LENGTH: 1225
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Asn Pro Arg Gln Gly Tyr Ser Leu Ser Gly Tyr Tyr Thr His Pro
  1               5                  10                  15

Phe Gln Gly Tyr Glu His Arg Gln Leu Arg Tyr Gln Gln Pro Gly Pro
             20                  25                  30

Gly Ser Ser Pro Ser Ser Phe Leu Leu Lys Gln Ile Glu Phe Leu Lys
         35                  40                  45

Gly Gln Leu Pro Glu Ala Pro Val Ile Gly Lys Gln Thr Pro Ser Leu
     50                  55                  60

Pro Pro Ser Leu Pro Gly Leu Arg Pro Arg Phe Pro Val Leu Leu Ala
 65                  70                  75                  80

Ser Ser Thr Arg Gly Arg Gln Val Asp Ile Arg Gly Val Pro Arg Gly
                 85                  90                  95

Val His Leu Gly Ser Gln Gly Leu Gln Arg Gly Phe Gln His Pro Ser
            100                 105                 110

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

His Phe Gln Glu Leu Ser Ile Tyr Gln Asp Gln Glu Gln Arg Ile Leu
    130                 135                 140

Lys Phe Leu Glu Glu Leu Gly Glu Gly Lys Ala Thr Thr Ala His Asp
145                 150                 155                 160

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

Tyr Ser Leu Ala Lys Lys Gly Lys Leu Gln Lys Glu Ala Gly Thr Pro
            180                 185                 190

Pro Leu Trp Lys Ile Ala Val Ser Thr Gln Ala Trp Asn Gln His Ser
        195                 200                 205

Gly Val Val Arg Pro Asp Gly His Ser Gln Gly Ala Pro Asn Ser Asp
    210                 215                 220

Pro Ser Leu Glu Pro Glu Asp Arg Asn Ser Thr Ser Val Ser Glu Asp
225                 230                 235                 240

Leu Leu Glu Pro Phe Ile Ala Val Ser Ala Gln Ala Trp Asn Gln His
                245                 250                 255

Ser Gly Val Val Arg Pro Asp Ser His Ser Gln Gly Ser Pro Asn Ser
            260                 265                 270

Asp Pro Gly Leu Glu Pro Glu Asp Ser Asn Ser Thr Ser Ala Leu Glu
        275                 280                 285

Asp Pro Leu Glu Phe Leu Asp Met Ala Glu Ile Lys Glu Lys Ile Cys
    290                 295                 300

Asp Tyr Leu Phe Asn Val Ser Asp Ser Ser Ala Leu Asn Leu Ala Lys
305                 310                 315                 320

Asn Ile Gly Leu Thr Lys Ala Arg Asp Ile Asn Ala Val Leu Ile Asp
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                325                 330                 335

Met Glu Arg Gln Gly Asp Val Tyr Arg Gln Gly Thr Thr Pro Pro Ile
            340                 345                 350

Trp His Leu Thr Asp Lys Lys Arg Glu Arg Met Gln Ile Lys Arg Asn
        355                 360                 365

Thr Asn Ser Val Pro Glu Thr Ala Pro Ala Ala Ile Pro Glu Thr Arg
    370                 375                 380

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

Asn Asn Met Val Thr Thr Glu Lys Val Glu Asn Gly Gln Glu Pro Val
                405                 410                 415

Lys Leu Glu Asn Arg Gln Glu Ala Arg Pro Glu Pro Ala Arg Leu Lys
            420                 425                 430

Pro Pro Val His Tyr Asn Gly Pro Ser Lys Ala Gly Tyr Val Asp Phe
        435                 440                 445

Glu Asn Gly Gln Trp Ala Thr Asp Asp Ile Pro Asp Asp Leu Asn Ser
    450                 455                 460

Ile Arg Ala Ala Pro Gly Glu Phe Arg Ala Ile Met Glu Met Pro Ser
465                 470                 475                 480

Phe Tyr Ser His Gly Leu Pro Arg Cys Ser Pro Tyr Lys Lys Leu Thr
                485                 490                 495

Glu Cys Gln Leu Lys Asn Pro Ile Ser Gly Leu Leu Glu Tyr Ala Gln
            500                 505                 510

Phe Ala Ser Gln Thr Cys Glu Phe Asn Met Ile Glu Gln Ser Gly Pro
        515                 520                 525

Pro His Glu Pro Arg Phe Lys Phe Gln Val Val Ile Asn Gly Arg Glu
    530                 535                 540

Phe Pro Pro Ala Glu Ala Gly Ser Lys Lys Val Ala Lys Gln Asp Ala
545                 550                 555                 560

Ala Met Lys Ala Met Thr Ile Leu Leu Glu Glu Ala Lys Ala Lys Asp
                565                 570                 575

Ser Gly Lys Ser Glu Glu Ser Ser His Tyr Ser Thr Glu Lys Glu Ser
            580                 585                 590

Glu Lys Thr Ala Glu Ser Gln Thr Pro Thr Pro Ser Ala Thr Ser Phe
        595                 600                 605

Phe Ser Gly Lys Ser Pro Val Thr Thr Leu Leu Glu Cys Met His Lys
    610                 615                 620

Leu Gly Asn Ser Cys Glu Phe Arg Leu Leu Ser Lys Glu Gly Pro Ala
625                 630                 635                 640

His Glu Pro Lys Phe Gln Tyr Cys Val Ala Val Gly Ala Gln Thr Phe
                645                 650                 655

Pro Ser Val Ser Ala Pro Ser Lys Lys Val Ala Lys Gln Met Ala Ala
            660                 665                 670

Glu Glu Ala Met Lys Ala Leu His Gly Glu Ala Thr Asn Ser Met Ala
        675                 680                 685

Ser Asp Asn Gln Pro Glu Gly Met Ile Ser Glu Ser Leu Asp Asn Leu
    690                 695                 700

Glu Ser Met Met Pro Asn Lys Val Arg Lys Ile Gly Glu Leu Val Arg
705                 710                 715                 720

Tyr Leu Asn Thr Asn Pro Val Gly Gly Leu Leu Glu Tyr Ala Arg Ser
                725                 730                 735
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His Gly Phe Ala Ala Glu Phe Lys Leu Val Asp Gln Ser Gly Pro Pro
            740                 745                 750

His Glu Pro Lys Phe Val Tyr Gln Ala Lys Val Gly Gly Arg Trp Phe
        755                 760                 765

Pro Ala Val Cys Ala His Ser Lys Lys Gln Gly Lys Gln Glu Ala Ala
    770                 775                 780

Asp Ala Ala Leu Arg Val Leu Ile Gly Glu Asn Glu Lys Ala Glu Arg
785                 790                 795                 800

Met Gly Phe Thr Glu Val Thr Pro Val Thr Gly Ala Ser Leu Arg Arg
                805                 810                 815

Thr Met Leu Leu Leu Ser Arg Ser Pro Glu Ala Gln Pro Lys Thr Leu
            820                 825                 830

Pro Leu Thr Gly Ser Thr Phe His Asp Gln Ile Ala Met Leu Ser His
        835                 840                 845

Arg Cys Phe Asn Thr Leu Thr Asn Ser Phe Gln Pro Ser Leu Leu Gly
    850                 855                 860

Arg Lys Ile Leu Ala Ala Ile Ile Met Lys Lys Asp Ser Glu Asp Met
865                 870                 875                 880

Gly Val Val Val Ser Leu Gly Thr Gly Asn Arg Cys Val Lys Gly Asp
                885                 890                 895

Ser Leu Ser Leu Lys Gly Glu Thr Val Asn Asp Cys His Ala Glu Ile
            900                 905                 910

Ile Ser Arg Arg Gly Phe Ile Arg Phe Leu Tyr Ser Glu Leu Met Lys
        915                 920                 925

Tyr Asn Ser Gln Thr Ala Lys Asp Ser Ile Phe Glu Pro Ala Lys Gly
    930                 935                 940

Gly Glu Lys Leu Gln Ile Lys Lys Thr Val Ser Phe His Leu Tyr Ile
945                 950                 955                 960

Ser Thr Ala Pro Cys Gly Asp Gly Ala Leu Phe Asp Lys Ser Cys Ser
                965                 970                 975

Asp Arg Ala Met Glu Ser Thr Glu Ser Arg His Tyr Pro Val Phe Glu
            980                 985                 990

Asn Pro Lys Gln Gly Lys Leu Arg Thr Lys Val Glu Asn Gly Glu Gly
        995                 1000                1005

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

Arg Leu Gly Glu Arg Leu Arg Thr Met Ser Cys Ser Asp Lys Ile Leu
1025                1030                1035                1040

Arg Trp Asn Val Leu Gly Leu Gln Gly Ala Leu Leu Thr His Phe Leu
                1045                1050                1055

Gln Pro Ile Tyr Leu Lys Ser Val Thr Leu Gly Tyr Leu Phe Ser Gln
            1060                1065                1070

Gly His Leu Thr Arg Ala Ile Cys Cys Arg Val Thr Arg Asp Gly Ser
        1075                1080                1085

Ala Phe Glu Asp Gly Leu Arg His Pro Phe Ile Val Asn His Pro Lys
    1090                1095                1100

Val Gly Arg Val Ser Ile Tyr Asp Ser Lys Arg Gln Ser Gly Lys Thr
1105                1110                1115                1120

Lys Glu Thr Ser Val Asn Trp Cys Leu Ala Asp Gly Tyr Asp Leu Glu
                1125                1130                1135
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Ile Leu Asp Gly Thr Arg Gly Thr Val Asp Gly Pro Arg Asn Glu Leu
            1140                1145                1150

Ser Arg Val Ser Lys Lys Asn Ile Phe Leu Leu Phe Lys Lys Leu Cys
        1155                1160                1165

Ser Phe Arg Tyr Arg Arg Asp Leu Leu Arg Leu Ser Tyr Gly Glu Ala
    1170                1175                1180

Lys Lys Ala Ala Arg Asp Tyr Glu Thr Ala Lys Asn Tyr Phe Lys Lys
1185                1190                1195                1200

Gly Leu Lys Asp Met Gly Tyr Gly Asn Trp Ile Ser Lys Pro Gln Glu
                1205                1210                1215

Glu Lys Asn Phe Tyr Leu Cys Pro Val
            1220                1225


<210> SEQ ID NO 21
<211> LENGTH: 702
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270
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Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

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

Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655

Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670
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Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Asp
        675                 680                 685

Phe Phe Thr Asp Cys Tyr Gly Tyr His Asp Phe Gly Ser Ser
    690                 695                 700


<210> SEQ ID NO 22
<211> LENGTH: 764
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Arg Pro Met Arg Ile Phe Val Asn Asp Asp Arg His Val Met Ala
  1               5                  10                  15

Lys His Ser Ser Val Tyr Pro Thr Gln Glu Glu Leu Glu Ala Val Gln
             20                  25                  30

Asn Met Val Ser His Thr Glu Arg Ala Leu Lys Ala Val Ser Asp Trp
         35                  40                  45

Ile Asp Glu Gln Glu Lys Gly Ser Ser Glu Gln Ala Glu Ser Asp Asn
     50                  55                  60

Met Asp Val Pro Pro Glu Asp Asp Ser Lys Glu Gly Ala Gly Glu Gln
 65                  70                  75                  80

Lys Thr Glu His Met Thr Arg Thr Leu Arg Gly Val Met Arg Val Gly
                 85                  90                  95

Leu Val Ala Lys Gly Leu Leu Leu Lys Gly Asp Leu Asp Leu Glu Leu
            100                 105                 110

Val Leu Leu Cys Lys Glu Lys Pro Thr Thr Ala Leu Leu Asp Lys Val
        115                 120                 125

Ala Asp Asn Leu Ala Ile Gln Leu Ala Ala Val Thr Glu Asp Lys Tyr
    130                 135                 140

Glu Ile Leu Gln Ser Val Asp Asp Ala Ala Ile Val Ile Lys Asn Thr
145                 150                 155                 160

Lys Glu Pro Pro Leu Ser Leu Thr Ile His Leu Thr Ser Pro Val Val
                165                 170                 175

Arg Glu Glu Met Glu Lys Val Leu Ala Gly Glu Thr Leu Ser Val Asn
            180                 185                 190

Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys Leu Ala Ala Leu Ala
        195                 200                 205

Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg Ala Asn Gly Leu Lys
    210                 215                 220

Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp Leu Cys Thr Arg Val
225                 230                 235                 240

Pro Thr Trp Gly Pro Leu Arg Gly Trp Pro Leu Glu Leu Leu Cys Glu
                245                 250                 255

Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala Gly Glu Ala Leu
            260                 265                 270

Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val Met Pro Asp Gly
        275                 280                 285

Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr Asp Ala Ile Gly
    290                 295                 300

His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln His
305                 310                 315                 320

Ala Leu Arg Leu Ala Ala Phe Gly Gln Leu His Lys Val Leu Gly Met
                325                 330                 335
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Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn Pro
            340                 345                 350

Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr Tyr Ala Ile Thr
        355                 360                 365

Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu Lys Ser Pro Ser
    370                 375                 380

Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro Pro
385                 390                 395                 400

Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly Leu
                405                 410                 415

Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile Phe
            420                 425                 430

Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly Pro
        435                 440                 445

Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln Asp
    450                 455                 460

Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser Ser Lys Gly Glu
465                 470                 475                 480

Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro Ala
                485                 490                 495

Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser Asp
            500                 505                 510

Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn Pro
        515                 520                 525

Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu Ile
    530                 535                 540

Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val Glu
545                 550                 555                 560

Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val Ala
                565                 570                 575

Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp Thr
            580                 585                 590

Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro Val
        595                 600                 605

Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe Gly
    610                 615                 620

Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu Arg
625                 630                 635                 640

Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg Gly
                645                 650                 655

Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly Tyr
            660                 665                 670

Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser Gln
        675                 680                 685

Phe Ser Arg Pro Pro Pro Pro Ser Arg Pro Arg Cys Cys Val Val Arg
    690                 695                 700

Cys Ser Gly Ser Pro Cys Gly Pro Ser Cys Asp Pro Tyr Leu Ala Val
705                 710                 715                 720

Phe Gly Thr Pro Cys Leu Gln Trp Phe Val Ser Cys His Tyr Asn Phe
                725                 730                 735
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Val Trp Val Glu Phe Leu Ser Phe Cys Ser Ser Val Ser Leu Cys Leu
            740                 745                 750

Phe Thr Leu Arg Val Ser Gly Asn Ser Val Cys Leu
        755                 760


<210> SEQ ID NO 23
<211> LENGTH: 591
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Gly His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln Ser Ala Gln
  1               5                  10                  15

His Ala Leu Arg Leu Ala Ala Phe Gly Gln Leu His Lys Val Leu Gly
             20                  25                  30

Met Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys Asn Glu Asn
         35                  40                  45

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

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

Ser Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys Ala Glu Pro
                 85                  90                  95

Pro Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu Lys Pro Gly
            100                 105                 110

Leu Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His Ala Pro Ile
        115                 120                 125

Phe Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu Ala Ser Gly
    130                 135                 140

Pro Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys Val Leu Gln
145                 150                 155                 160

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

Glu Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val Val Ala Pro
            180                 185                 190

Ala Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala Phe Pro Ser
        195                 200                 205

Asp Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His Gly Lys Asn
    210                 215                 220

Pro Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys Tyr Glu Leu
225                 230                 235                 240

Ile Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val Met Glu Val
                245                 250                 255

Glu Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn Lys Lys Val
            260                 265                 270

Ala Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu Phe Pro Asp
        275                 280                 285

Thr Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala Pro Val Pro
    290                 295                 300

Val Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn Pro Gly Phe
305                 310                 315                 320

Gly Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro Pro Asn Leu
                325                 330                 335
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Arg Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly Arg Gly Arg
            340                 345                 350

Gly Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala Gly Ala Gly
        355                 360                 365

Tyr Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala Gly Tyr Ser
    370                 375                 380

Gln Phe Tyr Ser Asn Gly Gly His Ser Gly Asn Ala Ser Gly Gly Gly
385                 390                 395                 400

Gly Gly Gly Gly Gly Gly Ser Ser Gly Tyr Gly Ser Tyr Tyr Gln Gly
                405                 410                 415

Asp Asn Tyr Asn Ser Pro Val Pro Pro Lys His Ala Gly Lys Lys Gln
            420                 425                 430

Pro His Gly Gly Gln Gln Lys Pro Ser Tyr Gly Ser Gly Tyr Gln Ser
        435                 440                 445

His Gln Gly Gln Gln Gln Ser Tyr Asn Gln Ser Leu Tyr Ser Asn Tyr
    450                 455                 460

Gly Pro Pro Gln Gly Lys Gln Lys Gly Tyr Asn His Gly Gln Gly Ser
465                 470                 475                 480

Tyr Ser Tyr Ser Asn Ser Tyr Asn Ser Pro Gly Gly Gly Gly Gly Ser
                485                 490                 495

Asp Tyr Asn Tyr Glu Ser Lys Phe Asn Tyr Ser Gly Ser Gly Gly Arg
            500                 505                 510

Ser Gly Gly Asn Ser Tyr Gly Ser Gly Gly Ala Ser Tyr Asn Pro Gly
        515                 520                 525

Ser His Gly Gly Tyr Gly Gly Gly Ser Gly Gly Gly Ser Ser Tyr Gln
    530                 535                 540

Gly Lys Gln Gly Gly Tyr Ser Gln Ser Asn Tyr Asn Ser Pro Gly Ser
545                 550                 555                 560

Gly Gln Asn Tyr Ser Gly Pro Pro Ser Ser Tyr Gln Ser Ser Gln Gly
                565                 570                 575

Gly Tyr Gly Arg Asn Ala Asp His Ser Met Asn Tyr Gln Tyr Arg
            580                 585                 590


<210> SEQ ID NO 24
<211> LENGTH: 514
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Thr Leu Ser Val Asn Asp Pro Pro Asp Val Leu Asp Arg Gln Lys Cys
  1               5                  10                  15

Leu Ala Ala Leu Ala Ser Leu Arg His Ala Lys Trp Phe Gln Ala Arg
             20                  25                  30

Ala Asn Gly Leu Lys Ser Cys Val Ile Val Ile Arg Val Leu Arg Asp
         35                  40                  45

Leu Cys Thr Arg Val Pro Thr Gly Pro Leu Arg Gly Trp Pro Leu Glu
     50                  55                  60

Leu Leu Cys Glu Lys Ser Ile Gly Thr Ala Asn Arg Pro Met Gly Ala
 65                  70                  75                  80

Gly Glu Ala Leu Arg Arg Val Leu Glu Cys Leu Ala Ser Gly Ile Val
                 85                  90                  95

Met Pro Asp Gly Ser Gly Ile Tyr Asp Pro Cys Glu Lys Glu Ala Thr
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            100                 105                 110

Asp Ala Ile Gly His Leu Asp Arg Gln Gln Arg Glu Asp Ile Thr Gln
        115                 120                 125

Ser Ala Gln His Ala Leu Arg Leu Ala Ala Phe Gly Gln Leu His Lys
    130                 135                 140

Val Leu Gly Met Asp Pro Leu Pro Ser Lys Met Pro Lys Lys Pro Lys
145                 150                 155                 160

Asn Glu Asn Pro Val Asp Tyr Thr Val Gln Ile Pro Pro Ser Thr Thr
                165                 170                 175

Tyr Ala Ile Thr Pro Met Lys Arg Pro Met Glu Glu Asp Gly Glu Glu
            180                 185                 190

Lys Ser Pro Ser Lys Lys Lys Lys Lys Ile Gln Lys Lys Glu Glu Lys
        195                 200                 205

Ala Glu Pro Pro Gln Ala Met Asn Ala Leu Met Arg Leu Asn Gln Leu
    210                 215                 220

Lys Pro Gly Leu Gln Tyr Lys Leu Val Ser Gln Thr Gly Pro Val His
225                 230                 235                 240

Ala Pro Ile Phe Thr Met Ser Val Glu Val Asp Gly Asn Ser Phe Glu
                245                 250                 255

Ala Ser Gly Pro Ser Lys Lys Thr Ala Lys Leu His Val Ala Val Lys
            260                 265                 270

Val Leu Gln Asp Met Gly Leu Pro Thr Gly Ala Glu Gly Arg Asp Ser
        275                 280                 285

Ser Lys Gly Glu Asp Ser Ala Glu Glu Thr Glu Ala Lys Pro Ala Val
    290                 295                 300

Val Ala Pro Ala Pro Val Val Glu Ala Val Ser Thr Pro Ser Ala Ala
305                 310                 315                 320

Phe Pro Ser Asp Ala Thr Ala Glu Gln Gly Pro Ile Leu Thr Lys His
                325                 330                 335

Gly Lys Asn Pro Val Met Glu Leu Asn Glu Lys Arg Arg Gly Leu Lys
            340                 345                 350

Tyr Glu Leu Ile Ser Glu Thr Gly Gly Ser His Asp Lys Arg Phe Val
        355                 360                 365

Met Glu Val Glu Val Asp Gly Gln Lys Phe Gln Gly Ala Gly Ser Asn
    370                 375                 380

Lys Lys Val Ala Lys Ala Tyr Ala Ala Leu Ala Ala Leu Glu Lys Leu
385                 390                 395                 400

Phe Pro Asp Thr Pro Leu Ala Leu Asp Ala Asn Lys Lys Lys Arg Ala
                405                 410                 415

Pro Val Pro Val Arg Gly Gly Pro Lys Phe Ala Ala Lys Pro His Asn
            420                 425                 430

Pro Gly Phe Gly Met Gly Gly Pro Met His Asn Glu Val Pro Pro Pro
        435                 440                 445

Pro Asn Leu Arg Gly Arg Gly Arg Gly Gly Ser Ile Arg Gly Arg Gly
    450                 455                 460

Arg Gly Arg Gly Phe Gly Gly Ala Asn His Gly Gly Tyr Met Asn Ala
465                 470                 475                 480

Gly Ala Gly Tyr Gly Ser Tyr Gly Tyr Gly Gly Asn Ser Ala Thr Ala
                485                 490                 495

Gly Tyr Ser Asp Phe Phe Thr Asp Cys Tyr Gly Tyr His Asp Phe Gly
            500                 505                 510
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Ser Ser


<210> SEQ ID NO 25
<211> LENGTH: 422
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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

Val Ala Lys Pro Gly Pro Val Lys Thr Leu Thr Arg Lys Lys Asn Lys
             20                  25                  30

Lys Lys Lys Arg Phe Trp Lys Ser Lys Ala Arg Glu Val Ser Lys Lys
         35                  40                  45

Pro Ala Ser Gly Pro Gly Ala Val Val Arg Pro Pro Lys Ala Pro Glu
     50                  55                  60

Asp Phe Ser Gln Asn Trp Lys Ala Leu Gln Glu Trp Leu Leu Lys Gln
 65                  70                  75                  80

Lys Ser Gln Ala Pro Glu Lys Pro Leu Val Ile Ser Gln Met Gly Ser
                 85                  90                  95

Lys Lys Lys Pro Lys Ile Ile Gln Gln Asn Lys Lys Glu Thr Ser Pro
            100                 105                 110

Gln Val Lys Gly Glu Glu Met Pro Ala Gly Lys Asp Gln Glu Ala Ser
        115                 120                 125

Arg Gly Ser Val Pro Ser Gly Ser Lys Met Asp Arg Arg Ala Pro Val
    130                 135                 140

Pro Arg Thr Lys Ala Ser Gly Thr Glu His Asn Lys Lys Gly Thr Lys
145                 150                 155                 160

Glu Arg Thr Asn Gly Asp Ile Val Pro Glu Arg Gly Asp Ile Glu His
                165                 170                 175

Lys Lys Arg Lys Ala Lys Glu Ala Ala Pro Ala Pro Pro Thr Glu Glu
            180                 185                 190

Asp Ile Trp Phe Asp Asp Val Asp Pro Ala Asp Ile Glu Ala Ala Ile
        195                 200                 205

Gly Pro Glu Ala Ala Lys Ile Ala Arg Lys Gln Leu Gly Gln Ser Glu
    210                 215                 220

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

Thr Arg Ala Leu Ala Leu Asp Cys Glu Met Val Gly Val Gly Pro Lys
                245                 250                 255

Gly Glu Glu Ser Met Ala Ala Arg Val Ser Ile Val Asn Gln Tyr Gly
            260                 265                 270

Lys Cys Val Tyr Asp Lys Tyr Val Lys Pro Thr Glu Pro Val Thr Asp
        275                 280                 285

Tyr Arg Thr Ala Val Ser Gly Ile Arg Pro Glu Asn Leu Lys Gln Gly
    290                 295                 300

Glu Glu Leu Glu Val Val Gln Lys Glu Val Ala Glu Met Leu Lys Gly
305                 310                 315                 320

Arg Ile Leu Val Gly His Ala Leu His Asn Asp Leu Lys Val Leu Phe
                325                 330                 335

Leu Asp His Pro Lys Lys Lys Ile Arg Asp Thr Gln Lys Tyr Lys Pro
            340                 345                 350
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Phe Lys Ser Gln Val Lys Ser Gly Arg Pro Ser Leu Arg Leu Leu Ser
        355                 360                 365

Glu Lys Ile Leu Gly Leu Gln Val Gln Gln Ala Glu His Cys Ser Ile
    370                 375                 380

Gln Asp Ala Gln Ala Ala Met Arg Leu Tyr Val Met Val Lys Lys Glu
385                 390                 395                 400

Trp Glu Ser Met Ala Arg Asp Arg Arg Pro Leu Leu Thr Ala Pro Asp
                405                 410                 415

His Cys Ser Asp Asp Ala
            420


<210> SEQ ID NO 26
<211> LENGTH: 422
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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

Val Ala Lys Pro Gly Pro Val Lys Thr Leu Thr Arg Lys Lys Asn Lys
             20                  25                  30

Lys Lys Lys Arg Phe Trp Lys Ser Lys Ala Arg Glu Val Ser Lys Lys
         35                  40                  45

Pro Ala Ser Gly Pro Gly Ala Val Val Arg Pro Pro Lys Ala Pro Glu
     50                  55                  60

Asp Phe Ser Gln Asn Trp Lys Ala Leu Gln Glu Trp Leu Leu Lys Gln
 65                  70                  75                  80

Lys Ser Gln Ala Pro Glu Lys Pro Leu Val Ile Ser Gln Met Gly Ser
                 85                  90                  95

Lys Lys Lys Pro Lys Ile Ile Gln Gln Asn Lys Lys Glu Thr Ser Pro
            100                 105                 110

Gln Val Lys Gly Glu Glu Met Pro Ala Gly Lys Asp Gln Glu Ala Ser
        115                 120                 125

Arg Gly Ser Val Pro Ser Gly Ser Lys Met Asp Arg Arg Ala Pro Val
    130                 135                 140

Pro Arg Thr Lys Ala Ser Gly Thr Glu His Asn Lys Lys Gly Thr Lys
145                 150                 155                 160

Glu Arg Thr Asn Gly Asp Ile Val Pro Glu Arg Gly Asp Ile Glu His
                165                 170                 175

Lys Lys Arg Lys Ala Lys Glu Ala Ala Pro Ala Pro Pro Thr Glu Glu
            180                 185                 190

Asp Ile Trp Phe Asp Asp Val Asp Pro Pro Asp Ile Glu Ala Ala Ile
        195                 200                 205

Gly Pro Glu Ala Ala Lys Ile Ala Arg Lys Gln Leu Gly Gln Ser Glu
    210                 215                 220

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

Thr Arg Ala Leu Ala Leu Asp Cys Glu Met Val Gly Val Gly Pro Lys
                245                 250                 255

Gly Glu Glu Ser Met Ala Ala Arg Val Ser Ile Val Asn Gln Tyr Gly
            260                 265                 270

Lys Cys Val Tyr Asp Lys Tyr Val Lys Pro Thr Glu Pro Val Thr Asp
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        275                 280                 285

Tyr Arg Thr Ala Val Ser Gly Ile Arg Pro Glu Asn Leu Lys Gln Gly
    290                 295                 300

Glu Glu Leu Glu Val Val Gln Lys Glu Val Ala Glu Met Leu Lys Gly
305                 310                 315                 320

Arg Ile Leu Val Gly His Ala Leu His Asn Asp Leu Lys Val Leu Phe
                325                 330                 335

Leu Asp His Pro Lys Lys Lys Ile Arg Asp Thr Gln Lys Tyr Lys Pro
            340                 345                 350

Phe Lys Ser Gln Val Lys Ser Gly Arg Pro Ser Leu Arg Leu Leu Ser
        355                 360                 365

Glu Lys Ile Leu Gly Leu Gln Val Gln Gln Ala Glu His Cys Ser Ile
    370                 375                 380

Gln Asp Ala Gln Ala Ala Met Arg Leu Tyr Val Met Val Lys Lys Glu
385                 390                 395                 400

Trp Glu Ser Met Ala Arg Asp Arg Arg Pro Leu Leu Thr Ala Pro Asp
                405                 410                 415

His Cys Ser Asp Asp Ala
            420


<210> SEQ ID NO 27
<211> LENGTH: 422
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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

Val Ala Lys Pro Gly Pro Val Lys Thr Leu Thr Arg Lys Lys Asn Lys
             20                  25                  30

Lys Lys Lys Arg Phe Trp Lys Ser Lys Ala Arg Glu Val Ser Lys Lys
         35                  40                  45

Pro Ala Ser Gly Pro Gly Ala Val Val Arg Pro Pro Lys Ala Pro Glu
     50                  55                  60

Asp Phe Ser Gln Asn Trp Lys Ala Leu Gln Glu Trp Leu Leu Lys Gln
 65                  70                  75                  80

Lys Ser Gln Ala Pro Glu Lys Pro Leu Val Ile Ser Gln Met Gly Ser
                 85                  90                  95

Lys Lys Lys Pro Lys Ile Ile Gln Gln Asn Lys Lys Glu Thr Ser Pro
            100                 105                 110

Gln Val Lys Gly Glu Glu Met Pro Ala Gly Lys Asp Gln Glu Ala Ser
        115                 120                 125

Arg Gly Ser Val Pro Ser Gly Ser Lys Met Asp Arg Arg Ala Pro Val
    130                 135                 140

Pro Arg Thr Lys Ala Ser Gly Thr Glu His Asn Lys Lys Gly Thr Lys
145                 150                 155                 160

Glu Arg Thr Asn Gly Asp Ile Val Pro Glu Arg Gly Asp Ile Glu His
                165                 170                 175

Lys Lys Arg Lys Ala Lys Glu Ala Ala Pro Ala Pro Pro Thr Glu Glu
            180                 185                 190

Asp Ile Trp Phe Asp Asp Val Asp Pro Pro Asp Ile Glu Ala Ala Ile
        195                 200                 205
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```
Gly Pro Glu Ala Ala Lys Ile Ala Arg Lys Gln Leu Gly Gln Ser Glu
    210                 215                 220

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

Thr Arg Ala Leu Ala Leu Asp Cys Glu Met Val Gly Val Gly Pro Lys
                245                 250                 255

Gly Glu Glu Ser Met Ala Ala Arg Val Ser Ile Val Asn Gln Tyr Gly
            260                 265                 270

Lys Cys Val Tyr Asp Lys Tyr Val Lys Pro Thr Glu Pro Val Thr Asp
        275                 280                 285

Tyr Arg Thr Ala Val Ser Gly Ile Arg Pro Glu Asn Leu Lys Gln Gly
    290                 295                 300

Glu Glu Leu Glu Val Val Gln Lys Glu Val Ala Glu Met Leu Lys Gly
305                 310                 315                 320

Arg Ile Leu Val Gly His Ala Leu His Asn Asp Leu Lys Val Leu Phe
                325                 330                 335

Leu Asp His Pro Lys Lys Lys Ile Arg Asp Thr Gln Lys Tyr Lys Pro
            340                 345                 350

Phe Lys Ser Gln Val Lys Ser Gly Arg Pro Ser Leu Arg Leu Leu Ser
        355                 360                 365

Glu Lys Ile Leu Gly Leu Gln Val Gln Gln Ala Glu His Cys Ser Ile
    370                 375                 380

Gln Asp Ala Gln Ala Ala Met Arg Leu Tyr Val Met Val Lys Lys Glu
385                 390                 395                 400

Trp Glu Ser Met Ala Arg Asp Arg Arg Pro Leu Leu Thr Ala Pro Asp
                405                 410                 415

His Cys Ser Asp Asp Ala
            420


<210> SEQ ID NO 28
<211> LENGTH: 422
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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

Val Ala Lys Pro Gly Pro Val Lys Thr Leu Thr Arg Lys Lys Asn Lys
             20                  25                  30

Lys Lys Lys Arg Phe Trp Lys Ser Lys Ala Arg Glu Val Ser Lys Lys
         35                  40                  45

Pro Ala Ser Gly Pro Gly Ala Val Val Arg Pro Pro Lys Ala Pro Glu
     50                  55                  60

Asp Phe Ser Gln Asn Trp Lys Ala Leu Gln Glu Trp Leu Leu Lys Gln
 65                  70                  75                  80

Lys Ser Gln Ala Pro Glu Lys Pro Leu Val Ile Ser Gln Met Gly Ser
                 85                  90                  95

Lys Lys Lys Pro Lys Ile Ile Gln Gln Asn Lys Lys Glu Thr Ser Pro
            100                 105                 110

Gln Val Lys Gly Glu Glu Met Pro Ala Gly Lys Asp Gln Glu Ala Ser
        115                 120                 125

Arg Gly Ser Val Pro Ser Gly Ser Lys Met Asp Arg Arg Ala Pro Val
    130                 135                 140
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Pro Arg Thr Lys Ala Ser Gly Thr Glu His Asn Lys Lys Gly Thr Lys
145                 150                 155                 160

Glu Arg Thr Asn Gly Asp Ile Val Pro Glu Arg Gly Asp Ile Glu His
                165                 170                 175

Lys Lys Arg Lys Ala Lys Glu Ala Ala Pro Ala Pro Pro Thr Glu Glu
            180                 185                 190

Asp Ile Trp Phe Asp Asp Val Asp Pro Ala Asp Ile Glu Ala Ala Ile
        195                 200                 205

Gly Pro Glu Ala Ala Lys Ile Ala Arg Lys Gln Leu Gly Gln Ser Glu
    210                 215                 220

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

Thr Arg Ala Leu Ala Leu Asp Cys Glu Met Val Gly Val Gly Pro Lys
                245                 250                 255

Gly Glu Glu Ser Met Ala Ala Arg Val Ser Ile Val Asn Gln Tyr Gly
            260                 265                 270

Lys Cys Val Tyr Asp Lys Tyr Val Lys Pro Thr Glu Pro Val Thr Asp
        275                 280                 285

Tyr Arg Thr Ala Val Ser Gly Ile Arg Pro Glu Asn Leu Lys Gln Gly
    290                 295                 300

Glu Glu Leu Glu Val Val Gln Lys Glu Val Ala Glu Met Leu Lys Gly
305                 310                 315                 320

Arg Ile Leu Val Gly His Ala Leu His Asn Asp Leu Lys Val Leu Phe
                325                 330                 335

Leu Asp His Pro Lys Lys Lys Ile Arg Asp Thr Gln Lys Tyr Lys Pro
            340                 345                 350

Phe Lys Ser Gln Val Lys Ser Gly Arg Pro Ser Leu Arg Leu Leu Ser
        355                 360                 365

Glu Lys Ile Leu Gly Leu Gln Val Gln Gln Ala Glu His Cys Ser Ile
    370                 375                 380

Gln Asp Ala Gln Ala Ala Met Arg Leu Tyr Val Met Val Lys Lys Glu
385                 390                 395                 400

Trp Glu Ser Met Ala Arg Asp Arg Arg Pro Leu Leu Thr Ala Pro Asp
                405                 410                 415

His Cys Ser Asp Asp Ala
            420


<210> SEQ ID NO 29
<211> LENGTH: 353
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Met Ser Thr Leu Leu Leu Asn Leu Asp Phe Gly Glu Pro Pro Pro Lys
  1               5                  10                  15

Lys Ala Leu Glu Gly Asn Ala Lys His Arg Asn Phe Val Lys Lys Arg
             20                  25                  30

Arg Leu Leu Glu Arg Arg Gly Phe Leu Ser Lys Lys Asn Gln Pro Pro
         35                  40                  45

Ser Lys Ala Pro Lys Leu His Ser Glu Pro Ser Lys Lys Gly Glu Thr
     50                  55                  60

Pro Thr Val Asp Gly Thr Trp Lys Thr Pro Ser Phe Pro Lys Lys Lys
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 65                  70                  75                  80

Thr Ala Ala Ser Ser Asn Gly Ser Gly Gln Pro Leu Asp Lys Lys Ala
                 85                  90                  95

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

Ala Ala Lys Val Asp Leu Leu Gly Glu Phe Gln Ser Ala Leu Pro Lys
        115                 120                 125

Ile Asn Ser His Pro Thr Arg Ser Gln Lys Lys Ser Ser Gln Lys Lys
    130                 135                 140

Ser Ser Lys Lys Asn His Pro Gln Lys Asn Ala Pro Gln Asn Ser Thr
145                 150                 155                 160

Gln Ala His Ser Glu Asn Lys Cys Ser Gly Ala Ser Gln Lys Leu Pro
                165                 170                 175

Arg Lys Met Val Ala Ile Asp Cys Glu Met Val Gly Thr Gly Pro Lys
            180                 185                 190

Gly His Val Ser Ser Leu Ala Arg Cys Ser Ile Val Asn Tyr Asn Gly
        195                 200                 205

Asp Val Leu Tyr Asp Glu Tyr Ile Leu Pro Pro Cys His Ile Val Asp
    210                 215                 220

Tyr Arg Thr Arg Trp Ser Gly Ile Arg Lys Gln His Met Val Asn Ala
225                 230                 235                 240

Thr Pro Phe Lys Ile Ala Arg Gly Gln Ile Leu Lys Ile Leu Thr Gly
                245                 250                 255

Lys Ile Val Val Gly His Ala Ile His Asn Asp Phe Lys Ala Leu Gln
            260                 265                 270

Tyr Phe His Pro Lys Ser Leu Thr Arg Asp Thr Ser His Ile Pro Pro
        275                 280                 285

Leu Asn Arg Lys Ala Asp Cys Pro Glu Asn Ala Thr Met Ser Leu Lys
    290                 295                 300

His Leu Thr Lys Lys Leu Leu Asn Arg Asp Ile Gln Val Gly Lys Ser
305                 310                 315                 320

Gly His Ser Ser Val Glu Asp Ala Gln Ala Thr Met Glu Leu Tyr Lys
                325                 330                 335

Leu Val Glu Val Glu Trp Glu Glu His Leu Ala Arg Asn Pro Pro Thr
            340                 345                 350

Asp


<210> SEQ ID NO 30
<211> LENGTH: 208
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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

Ser Ile Val Ser Tyr His Gly Asp Val Leu Tyr Asp Lys Tyr Ile Arg
             20                  25                  30

Pro Glu Met Pro Ile Ala Asp Tyr Arg Thr Arg Trp Ser Gly Ile Thr
         35                  40                  45

Arg Gln His Met Arg Lys Ala Val Pro Phe Gln Val Ala Gln Lys Glu
     50                  55                  60

Ile Leu Lys Leu Leu Lys Gly Lys Val Val Val Gly His Ala Leu His
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 65                  70                  75                  80

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

Asp Thr Thr Tyr Val Pro Asn Phe Leu Ser Glu Pro Gly Leu His Thr
            100                 105                 110

Arg Ala Arg Val Ser Leu Lys Asp Leu Ala Leu Gln Leu Leu His Lys
        115                 120                 125

Lys Ile Gln Val Gly Gln His Gly His Ser Ser Val Glu Asp Ala Thr
    130                 135                 140

Thr Ala Met Glu Leu Tyr Arg Leu Val Glu Val Gln Trp Glu Gln Gln
145                 150                 155                 160

Glu Ala Arg Ser Leu Trp Thr Cys Pro Glu Asp Arg Glu Pro Asp Ser
                 165                 170                 175

Ser Thr Asp Met Glu Gln Tyr Met Glu Asp Gln Tyr Trp Pro Asp Asp
            180                 185                 190

Leu Ala His Gly Ser Arg Gly Gly Ala Arg Glu Ala Gln Asp Arg Arg
        195                 200                 205


<210> SEQ ID NO 31
<211> LENGTH: 476
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(476)
<223> OTHER INFORMATION: n = a, c, t, g, any, unknown, or other

<400> SEQUENCE: 31

tctggctcac ctggaggaag aggtccacga caaggtggtt gcccgggacc tggttggagc      60

catgttgagc ccactgccgc agccacgccc ctctgccccc caggtgctgg cccaccccgt     120

tcttttggag cagancaagc aactccagtt cttccaggac gtcagtgact ggctggagaa     180

ggagtccgag caggagcccc tggtgagggc actggaggcg ggaggctgcg cagtggtccg     240

ggacaactgg cacgagcaca tctccatgcc gctgcagaca gatctgagaa agttccggtc     300

ctataagggg acatcagtgc gagacctgct ccgtgctgtg aggaacaaga agcaccacta     360

cagggagctc ccagttgagg tgcgacaggc attcggccaa gtccctgatg gcttcgtcca     420

gtacttcaca aaccgctttc caanggctgc tcntcaaang caccgagcca tgagga         476
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1. A method of examining efficacy of treatment with a nucleotide or a nucleoside in a given subject comprising:

(a) measuring the amount of expression or activity of at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4 in a blood or tissue sample previously taken from the subject;

(b) administering the nucleotide or the nucleoside into a tissue of the subject or a tissue taken from the subject followed by measuring the amount of expression or activity of the same protein as that measured in (a) in blood or treated tissue after 3-48 hours from administration; and

(c) comparing the measurement obtained in step (a) with that obtained in step (b) and evaluating the change in the amount of expression or the activity of the protein.

2. A method of examining efficacy of treatment with a nucleotide or a nucleoside in a given subject comprising:

(a) measuring the amount of expression or activity of at least one protein among those each having amino acid sequences of SEQ ID NO: 5-30 in a blood or tissue sample previously taken from the subject;

(b) administering the nucleotide or the nucleoside into a tissue of the subject or a tissue taken from the subject followed by measuring the amount of expression or activity of the same protein as that measured in (a) in blood or treated tissue after 3-48 hours from administration; and

(c) comparing the measurement obtained in step (a) with that obtained in step (b) and evaluating the change in the amount of expression or the activity of the protein.

3. The method of claim 1 or **2**, wherein the nucleotide or nucleoside exerts antitumor or antivirus activity at least when entered into a cell and is used in the form of a complex with a carrier effective to transfer the same into a cell.

4. The method of claim 3, wherein the carrier is cationic liposome carrier.

5. The method of claim 4, wherein the cationic liposome carrier is a cationic liposome carrier comprising as basic essential components 2-O-(2-diethylaminoethyl)carbamoyl-1,3-O-dioleoyl glycerol and a phospholipid in the ratio of 1:3 to 2:1 (the glycerol derivative:the phospholipid) by weight; Lipofectin® (a cationic liposome carrier comprising as basic essential components N-[1-(2,3-dioleyloxy)propyl]-n,n,n-trimethylammonium chloride (DOTMA) and dioleoyl phosphatidylethanolamine (DOPE) in the ratio of 1:1 by weight), Lipofectamine® (a cationic liposome carrier comprising as basic essential components 2,3-dioleyloxy-N-[2-(sperminecarboxamido) ethyl]-N,N-dimethyl-1-propanammonium trifluoroacetate (DOSPA) and dioleoyl phosphatidylethanolamine (DOPE) in the ratio of 3:1 by weight), Cellfectin® (a cationic liposome carrier comprising as basic essential components N, N^{I}, N^{II}, N^{III}-tetramethyl-N, N^{I}, N^{II}, N^{III}-tetrapalmitylspermine (TMTPS) and dioleoyl phosphatidylethanolamine (DOPE) in the ratio of 1:1.5 by weight), or DMRIE-C® (a cationic liposome carrier comprising as basic essential components 1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DMRIE) and cholesterol in the molar ratio of 1:1).

6. The method of claim 1 or **2**, wherein the nucleotide or the nucleoside is a homopolymer•homopolymer double-stranded RNA, homopolymer•copolymer double-stranded RNA, copolymer single-stranded RNA, 5-Fluorouracil, or cytosine arabinoside.

7. The method of claim 6, wherein the homopolymer•homopolymer double-stranded RNA is selected from the group consisting of polyinosinic acid•polycytidylic acid, polyinosinic acid•poly(5-bromocytidylic acid), polyinosinic acid•poly(2-thiocytidylic acid), poly(7-deazainosinic acid)•polycytidylic acid, poly(7-deazainosinic acid)•poly(5-bromocytidylic acid), poly(2'-azidoinosinic acid)•polycytidylic acid, polyinosinic acid•poly(cytidine-5'-thiophosphoric acid), and polyinosinic acid poly(1-vinylcytidylic acid).

8. The method of claim 6, wherein the homopolymer• copolymer double-stranded RNA is polyinosinic acid•poly(cytidylic acid, uridylic acid) or polyinosinic acid•poly(cytidylic acid, 4-thiouridylic acid).

9. The method of claim 6, wherein the copolymer single-stranded RNA is poly(adenylic acid, uridylic acid).

10. A method of examining efficacy of treatment with a complex of polyinosinic acid•polycytidylic acid of average chain length between 100 bp and 500 bp with a cationic liposome carrier which comprises as basic essential components 2-O-(2-diethylaminoethyl)carbamoyl-1,3-O-dioleoyl glycerol and a phospholipid in the ratio of 1:3 to 2:1 (the glycerol derivative:the phospholipid) by weight in a given subject comprising:

(a) measuring the amount of expression or activity of at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4 in a blood or tissue sample previously taken from the subject;

(b) administering the nucleotide or the nucleoside into a tissue of the subject or a tissue taken from the subject followed by measuring the amount of expression or activity of the same protein as that measured in (a) in blood or treated tissue after 3-48 hours from administration; and

(c) comparing the measurement obtained in step (a) with that obtained in step (b) and evaluating the change in the amount of expression or the activity of the protein.

11. A method of screening for agents potentially having antitumor or antivirus activity comprising examining a test compound for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4.

12. A method of screening for agents potentially having antitumor or antivirus activity comprising examining a test compound for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 5-30.

13. A method of investigating the mechanism of action of an antitumor or antivirus agent in vivo comprising examining the antitumor or antivirus agent for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 1-4.

14. A method of investigating the mechanism of action of an antitumor or antivirus agent in vivo comprising examining the antitumor or antivirus agent for ability to bind to at least one protein among those each having amino acid sequences of SEQ ID NO: 5-30.

* * * * *

专利名称(译)	检查用核酸治疗功效的方法		
公开(公告)号	US20030125285A1	公开(公告)日	2003-07-03
申请号	US10/233553	申请日	2002-09-04
[标]申请(专利权)人(译)	平林和子 矢野JUNICHI		
申请(专利权)人(译)	平林和子 矢野JUNICHI		
当前申请(专利权)人(译)	平林和子 矢野JUNICHI		
[标]发明人	HIRABAYASHI KAZUKO YANO JUNICHI		
发明人	HIRABAYASHI, KAZUKO YANO, JUNICHI		
IPC分类号	A61P35/00 C07K14/47 C12Q1/68 G01N33/50 A61K48/00 G01N33/53 A61K31/7076 A61K31/7072		
CPC分类号	C07K14/47 G01N33/5023 C12Q2600/158 C12Q1/6883 A61P31/12 A61P35/00		
优先权	2001267385 2001-09-04 JP		
外部链接	Espacenet USPTO		

摘要(译)

本发明提供了一种检测个体患者预先用具有抗肿瘤或抗病毒活性的核苷酸或核苷治疗效果的方法，该方法主要涉及定制治疗，筛选可能具有抗肿瘤或抗病毒的药剂的方法。活性和研究抗肿瘤或抗病毒剂在体内作用机制的方法。

Fig. 1