US 20140186852A1

(19) **United States**

(12) **Patent Application Publication**

Van Eyk et al.

(10) **Pub. No.: US 2014/0186852 A1**

(43) **Pub. Date: Jul. 3, 2014**

(54) **BIOMARKERS FOR MYOCARDIAL ISCHEMIA**

(71) Applicant: **The Johns Hopkins University**, Baltimore, MD (US)

(72) Inventors: **Jennifer Van Eyk**, Baltimore, MD (US); **Simon Sheng**, Baltimore, MD (US); **Qin Fu**, Baltimore, MD (US)

(73) Assignee: **The Johns Hopkins University**, Baltimore, MD (US)

(21) Appl. No.: **13/953,226**

(22) Filed: **Jul. 29, 2013**

Related U.S. Application Data

(63) Continuation of application No. 12/994,034, filed on Sep. 15, 2011, now Pat. No. 8,497,078, filed as application No. PCT/US09/45168 on May 26, 2009.

(60) Provisional application No. 61/128,688, filed on May 23, 2008.

Publication Classification

(51) **Int. Cl.**

G01N 33/53	(2006.01)
G01N 33/68	(2006.01)
G01N 33/573	(2006.01)

(52) **U.S. Cl.**

CPC ***G01N 33/5308*** (2013.01); ***G01N 33/573*** (2013.01); ***G01N 33/6893*** (2013.01)

USPC **435/7.4**; 435/7.92; 435/23; 436/501

(57) **ABSTRACT**

This invention relates, e.g., to a method for determining if a subject has myocardial ischemia, comprising (a) providing a blood sample obtained from a subject suspected of having myocardial ischemia; (b) determining in the sample the amount of one or more of the following proteins: (i) Lumican and/or (ii) Extracellular matrix protein 1 and/or (iii) Carboxypeptidase N; and (c) comparing the amount(s) of the protein (s) to a baseline value that is indicative of the amount of the protein in a subject that does not have myocardial ischemia, wherein a statistically significantly increased amount of the protein(s) compared to the baseline value is indicative of myocardial ischemia. Other proteins indicative of myocardial ischemia are also described, as are methods for treating a subject based on a diagnostic procedure of the invention, and kits for carrying out a method of the invention.

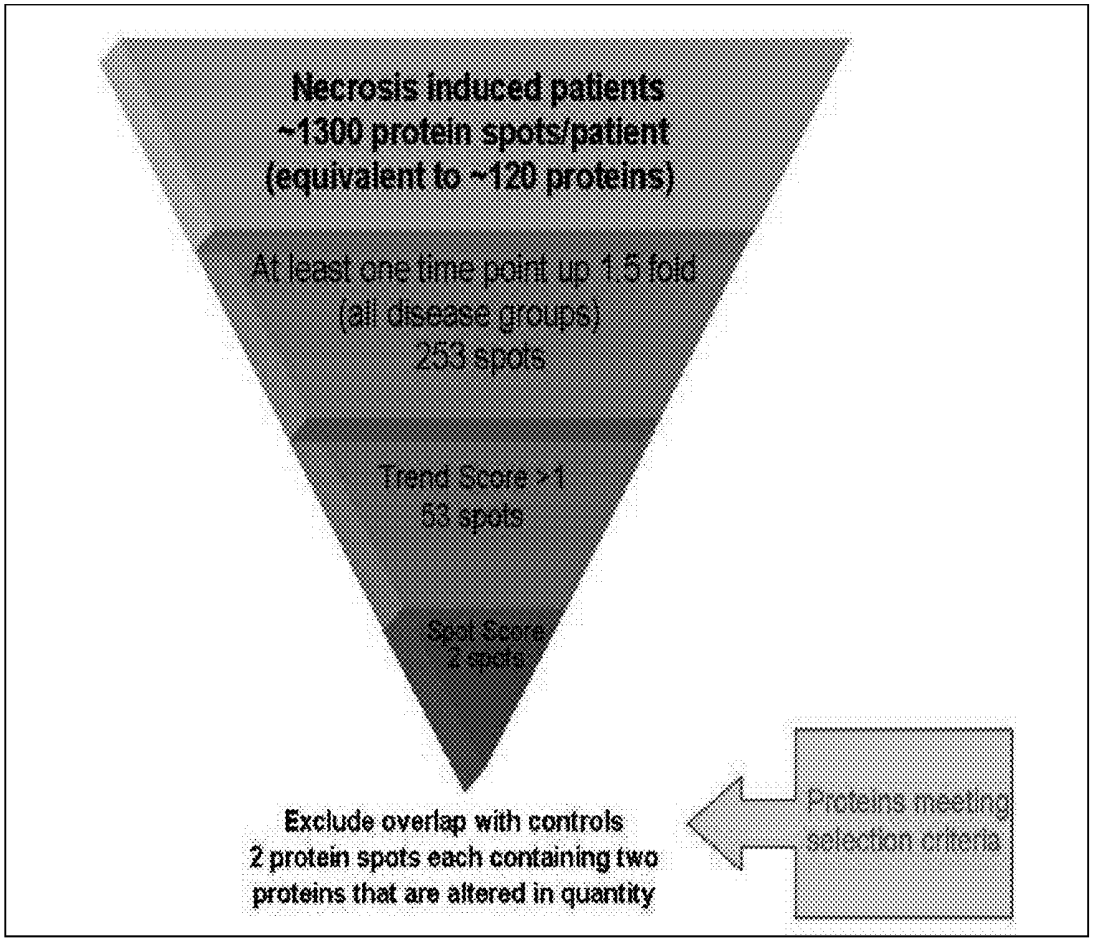
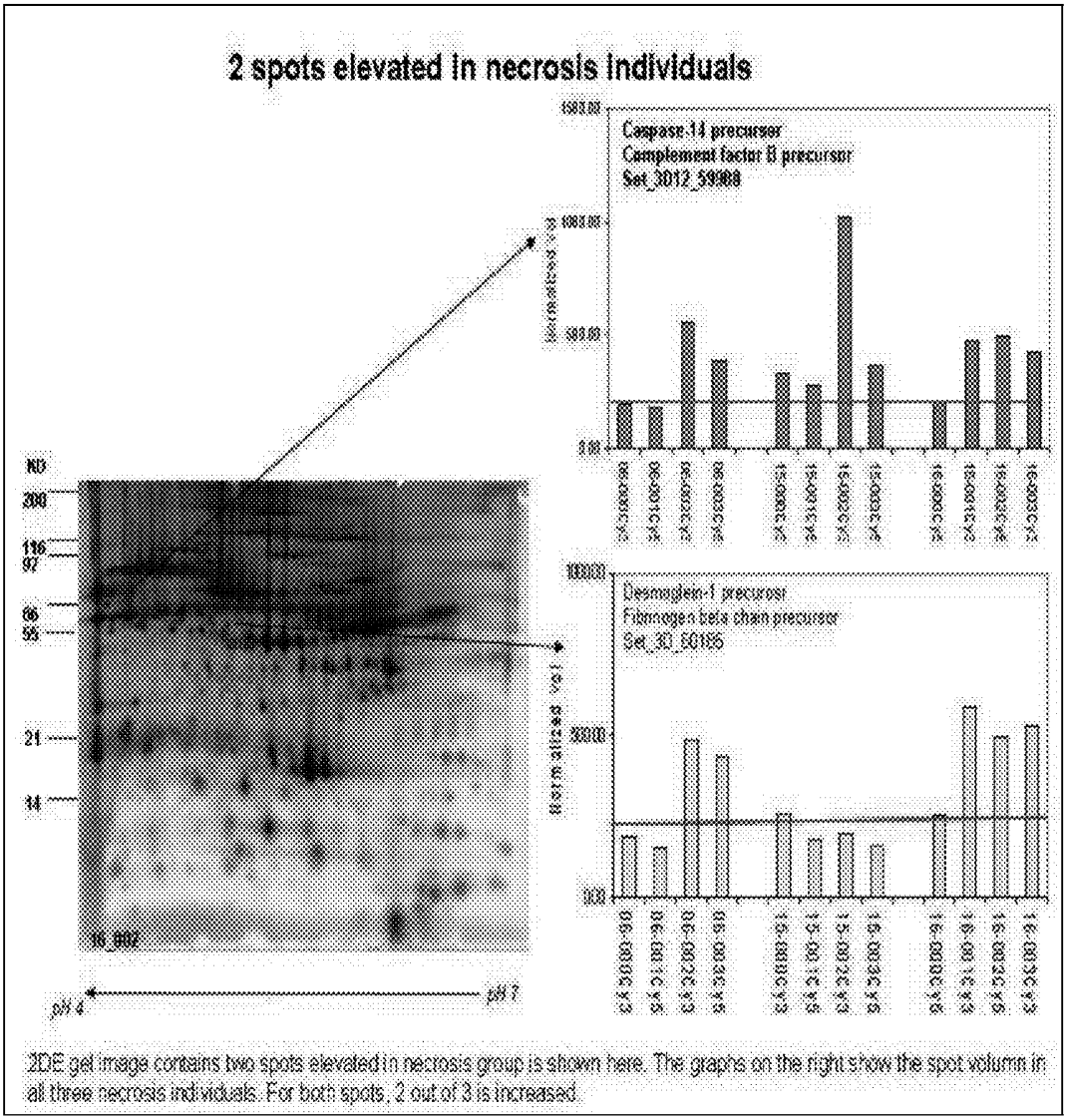

Necrosis induced patients
~1300 protein spots/patient
(equivalent to ~120 proteins)
At least one time point up 1.5 fold
(all disease groups)
253 spots
Trend Score >1
53 spots
Spot Score
2 spots
Exclude overlap with controls
2 protein spots each containing two
proteins that are altered in quantity
Proteins meeting
selection criteria

FIG. 1



2DE gel image contains two spots elevated in necrosis group is shown here. The graphs on the right show the spot volumn in all three necrosis individuals. For both spots, 2 out of 3 is increased.

FIG. 2

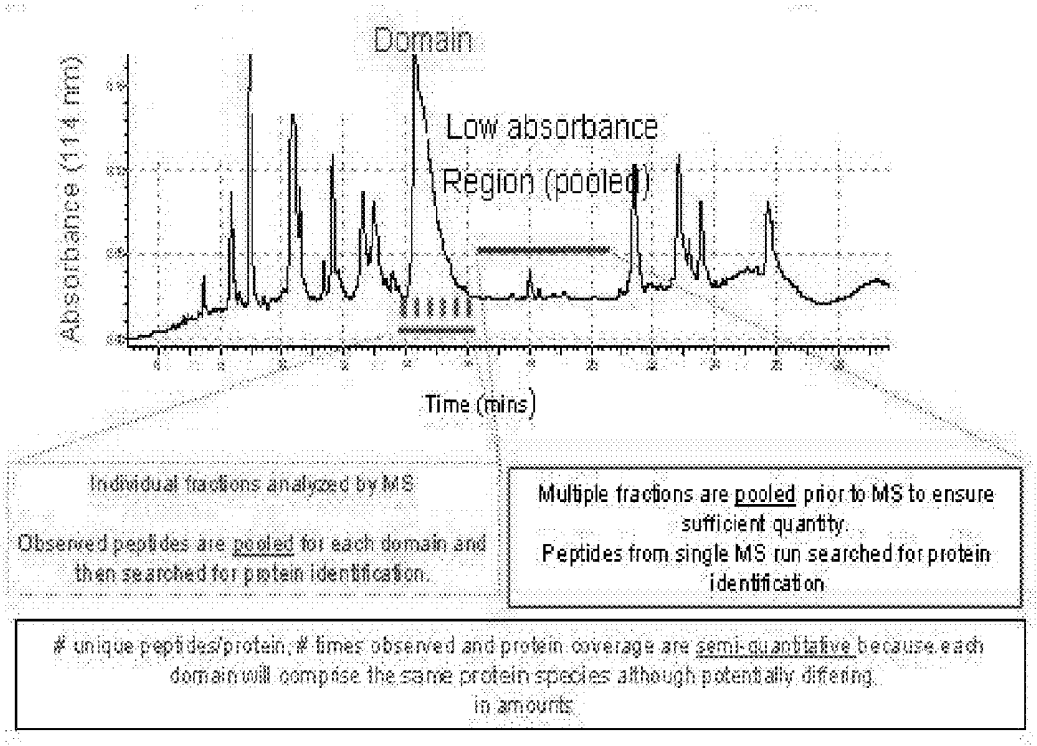
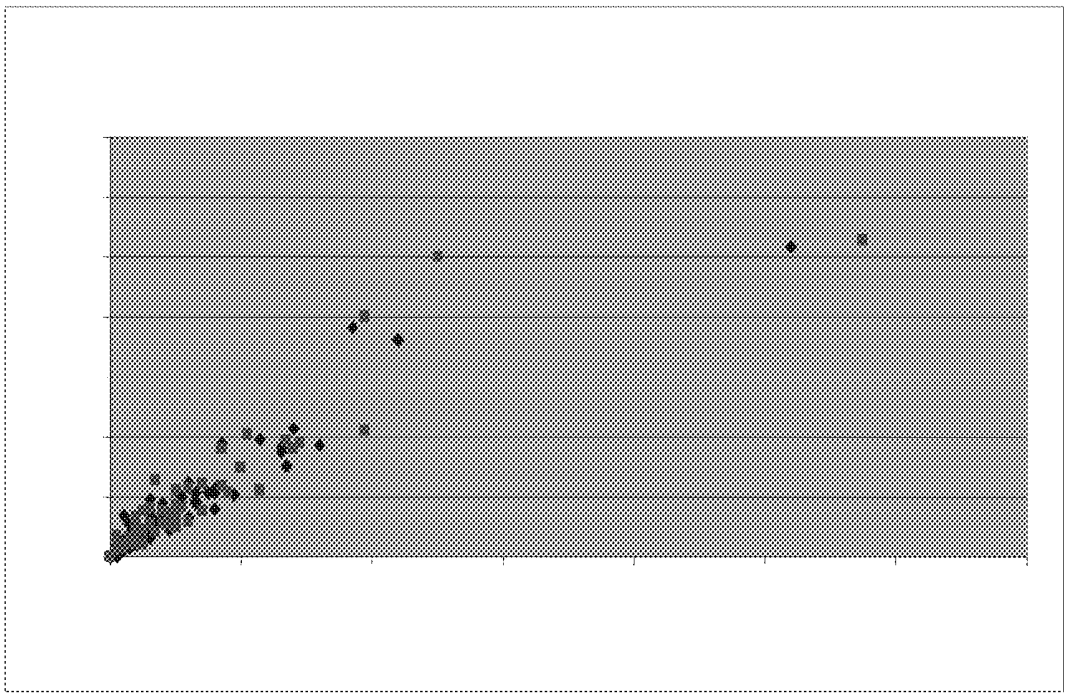

Domain
Low absorbance
Region (pooled)
Absorbance (114 nm)
Time (mins)
Individual fractions analyzed by MS
Observed peptides are pooled for each domain and then searched for protein identification.
Multiple fractions are pooled prior to MS to ensure sufficient quantity.
Peptides from single MS run searched for protein identification
unique peptides/protein, # times observed and protein coverage are semi-quantitative because each domain will comprise the same protein species although potentially differing in amounts

FIG. 3



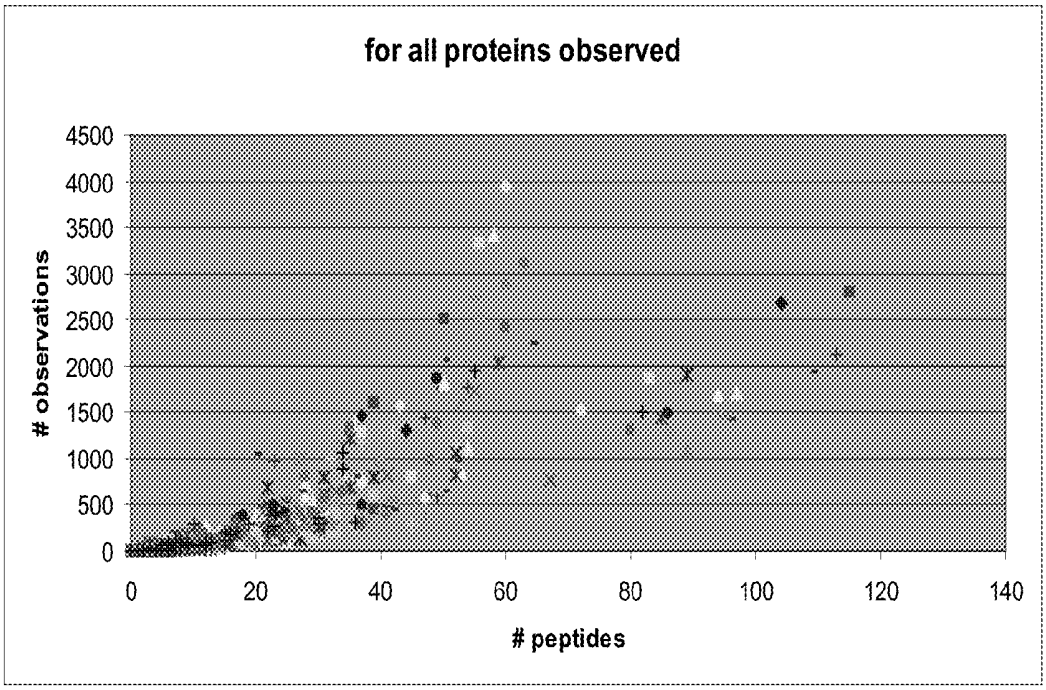

for all proteins observed
observations
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
20
40
60
80
100
120
140
peptides

FIG. 4

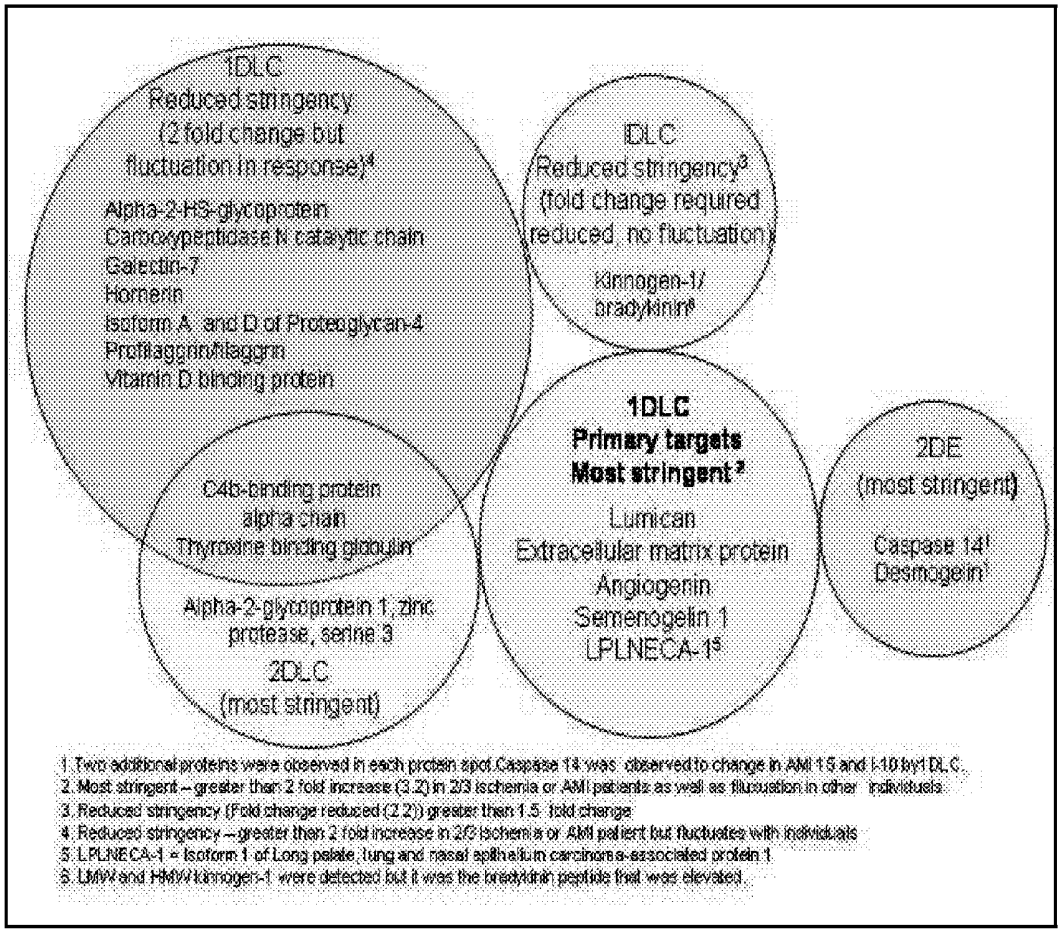

1DLC
Reduced stringency
(2 fold change but
fluctuation in response)[4]
Alpha-2-HS-glycoprotein
Carboxypeptidase N catalytic chain
Galectin-7
Hornerin
Isoform A and D of Proteoglycan-4
Profilaggrin/filaggrin
Vitamin D binding protein
C4b-binding protein
alpha chain
Thyroxine binding globulin
Alpha-2-glycoprotein 1, zinc
protease, serine 3
2DLC
(most stringent)
IDLC
Reduced stringency[3]
(fold change required
reduced, no fluctuation)
Kinnogen-1/
bradykinin[5]
1DLC
Primary targets
Most stringent [2]
Lumican
Extracellular matrix protein
Angiogenin
Semenogelin 1
LPLNECA-1[5]
2DE
(most stringent)
Caspase 14[1]
Desmoglein
1. Two additional proteins were observed in each protein spot.Caspase 14 was observed to change in AMI 1-5 and I-10 by1 DLC
2. Most stringent – greater than 2 fold increase (3.2) in 2/3 ischemia or AMI patients as well as fluctuation in other individuals
3. Reduced stringency (Fold change reduced (2.2)) greater than 1.5 fold change
4. Reduced stringency – greater than 2 fold increase in 2/3 ischemia or AMI patient but fluctuates with individuals
5. LPLNECA-1 = Isoform 1 of Long palate, lung and nasal epithelium carcinoma-associated protein 1
6. LMW and HMW kinnogen-1 were detected but it was the bradykinin peptide that was elevated

FIG. 5

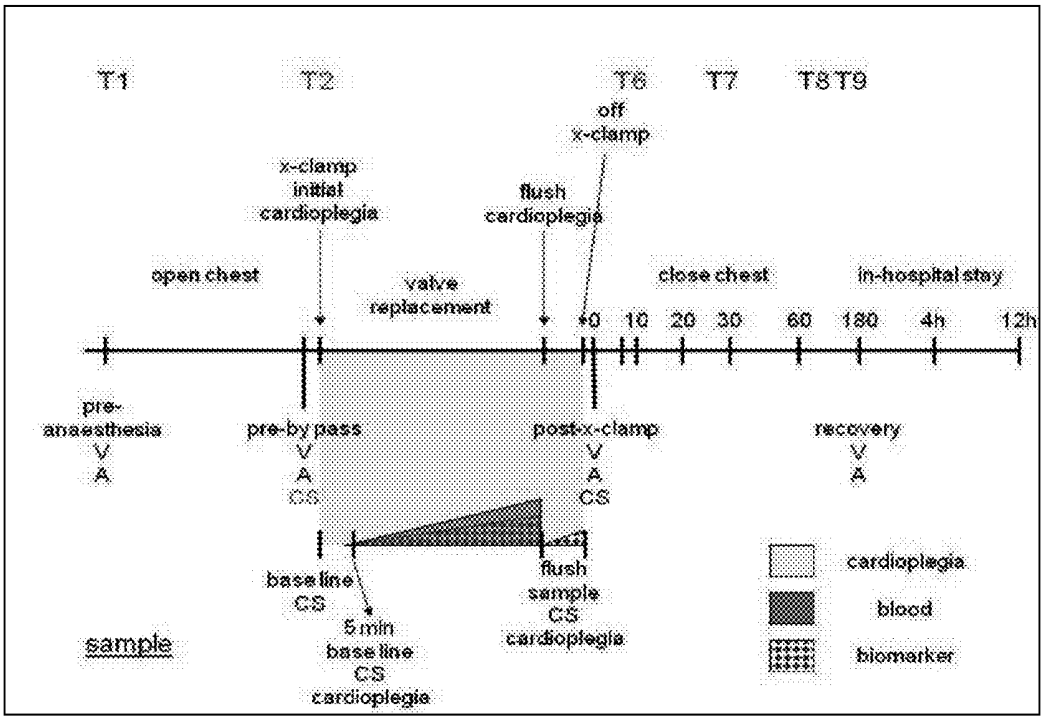

T1
T2
T6
T7
T8 T9
off
x-clamp
x-clamp
initial
cardioplegia
flush
cardioplegia
open chest
valve
replacement
close chest
in-hospital stay
0
10
20
30
60
180
4h
12h
pre-
anaesthesia
V
A
pre-by pass
V
A
CS
post-x-clamp
V
A
CS
recovery
V
A
baseline
CS
5 min
baseline
CS
cardioplegia
flush
sample
CS
cardioplegia
sample
cardioplegia
blood
biomarker

FIG. 6

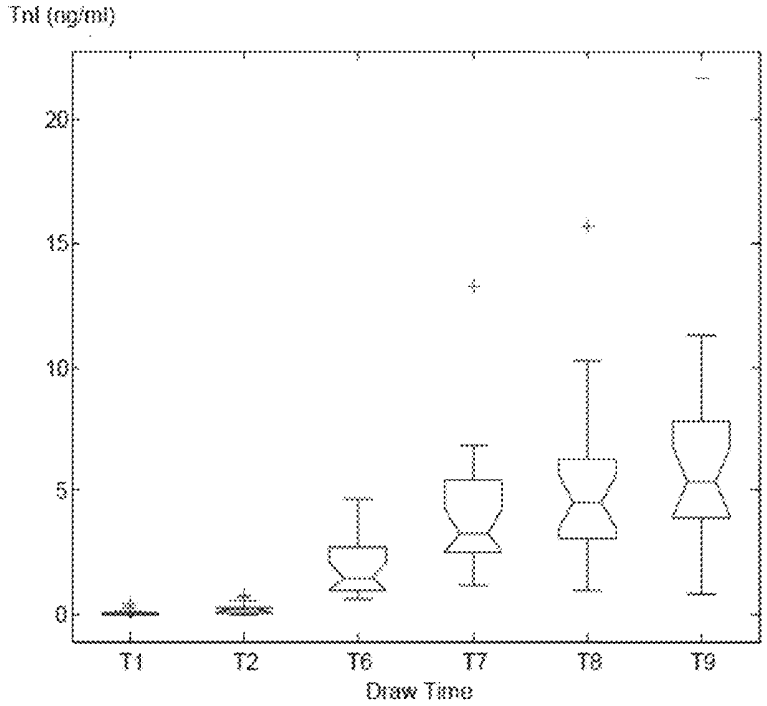

TnI (ng/ml)
20
15
10
5
0
T1
T2
T6
T7
T8
T9
Draw Time

FIG. 7

BIOMARKERS FOR MYOCARDIAL ISCHEMIA

[0001] This application claims the benefit of the filing date of provisional patent application 61/128,688, filed May 23, 2008, which is incorporated by reference in its entirety herein.

BACKGROUND INFORMATION

[0002] Coronary heart disease is the most common single cause of death in the western world, representing about 20% of all deaths. This is equivalent to about 2 million deaths in Europe per year or four people per minute. In the US, over 8 million people exhibit acute (chest pain) symptoms in the Emergency Department (ED) of hospitals, with 1.5 million individuals having confirmed acute coronary symptom (ACS) events, accounting for 500,000 short term deaths. In patients presenting to the emergency room with chest pain, fewer than 15% are ultimately diagnosed as having ischemia or acute myocardial infarction (MI). Currently, blood tests for the cardiac specific isoform of troponin I or troponin T (TnI or TnT, respectively) are generally used for the diagnosis of acute myocardial infarction (due to cardiac muscle (cell) death). Creatine kinase (CK) MB and myoglobin can also be used, but are considered to be less specific for cardiac injury. However, although these cardiac biomarkers can identify patients with even small amounts of myocardial necrosis, there is an earlier time point in which the heart is in ischemia but is not yet in necrosis, and the diagnosis of cardiac ischemia in the absence of necrosis cannot currently be made with accuracy.

[0003] It would be useful to be able to identify subjects in this diagnostic window (having non-necrotic ischemia). Such a diagnostic tool would be of great value for triage in the emergency department. For example, it would allow earlier intervention, including earlier perfusion, to allow increased salvage of the injured myocardium; and it would prevent unnecessary admittance to the hospital of patients with non-cardiac chest pain. Furthermore, such an assay could delay therapy in subjects who do not exhibit diagnostic electrocardiographic (ECG) changes, and could help to improve the accuracy of current provocative tests for ischemia, such as exercise stress testing. The sooner intervention can be carried out, the less cardiac damage will occur. Reduced damage is correlated with an increase in long term survival.

DESCRIPTION OF THE DRAWINGS

[0004] FIG. **1** shows a schematic representation of protein spot attrition due to stringent criteria, based on a cohort that underwent atrial pacing to induce demand on the heart such that the blood flow was inadequate, thereby potentially causing myocardial ischemia. Blood samples were drawn from the coronary sinuses of individuals subjected to atrial pacing. The change in lactate acid level was an indication of induced ischemia, while the detection of cTnI or cTnT was indicative of cardiac necrosis. Those subjects that did not exhibit any change in lacate acid level or cTnT/cTnT were considered controls.

[0005] FIG. **2** shows a 2DE gel image showing two spots that are elevated in necrosis individuals. Serum samples were initially depleted of immunoglobins (IgG) and albumin, then separated based on pI and MW using gel electrophorisis. The majority of the spots did not change in all of the individuals subjected to atrial pacing. The graphs on the right show the spot volume in all three necrosis individuals. For both spots, 2 out of 3 were increased for those individuals which had cTnI detected after atrial pacing in their coronary sinus blood samples.

[0006] FIG. **3** shows 1DLC fractions strategy used in MS analysis. Samples were depleted of immunoglobins (IgG, IgM and IgA) and albumin, then separated based on hydrophobicity (Reversed phase high performance liquid chromatography, RPLC, 1DLC). The number of unique peptides/protein observed, and the number of times observed and protein coverage are semi-quantitative, because each domain will comprise the same protein species, although potentially differing in amounts.

[0007] FIG. **4** shows the number of peptides observed vs. the number of spectra count for all individuals and all time points obtained by 1DLC (hydrophobicity, RPLC-MS run 1).

[0008] FIG. **5** schematically illustrates the overlap between the three different proteomic methods used: 2DE, 1DLC and 2DLC. For 2DLC, the serum samples were depleted of immunoglobins (IgG, IgM and IgA) and albumin, then separated based on chromatographic focusing (pH from 8.5 to 4.0) and reversed phase HPLC (1DLC). Fractions from areas found to be different in the 2DLC were analyzed by MS. Differences in spectral counting and or number of peptides observed were included as changed. Superscripts 1-6 refer to the following:

[0009] 1. Two additional proteins were observed in each protein spot. Caspase 14 was observed to change in AMI (individual) 15 and by 1 DLC for individuals (1-10) that underwent atrial pacing

[0010] 2. Most stringent—greater than 2 fold increase (3.2) in ⅔ ischemia or AMI patients as well as fluctuation in other individuals

[0011] 3. Reduced stringency (fold change reduced (2.2)) greater than 1.5 fold change

[0012] 4. Reduced stringency—greater than 2 fold increase in ⅔ ischemia or AMI patients but fluctuates with individuals

[0013] 5. LPLNECA-1=isoform 1 of Long palate, lung and nasal epithelium carcinoma-associated protein 1

[0014] 6. LMW and HMW kinnogen-1 were detected but it was the bradykinin peptide that was elevated

[0015] FIG. **6** shows schematically the collection during valve replacement. In this chorot, coronary sinus samples were obtained from individuals who underwent induced ischemia due to stopping of the heart (with cardioplegia) during valve replacement. Coronary sinus samples were obtained and depleted prior to being separated by 1DLC (as outlined above). Proteins found to be increased with ischemia in the majority of individuals were considered first teir. However, it must be recognized that lower abundant proteins may only be observed in a few patients due to inherent detection limits of this type of MS analysis. These proteins might be actually elevated in many patients and just not observed with this approach.

[0016] FIG. **7** shows a box plot of cTn1 at all time points for the individuals that under went valve replacement. Note that all individuals eventually had detectable cTnI/cTnT in their serum, indicating necrosis. However, at the time points at which de novo discovery was undertaken, none of the individuals had detectable cTnT or cTnI. This shows that all were ischemic at the time of study.

DESCRIPTION

[0017] The present inventors have identified a number of protein markers for cardiac (myocardial) ischemia, including non-necrotic cardiac (myocardial) ischemia.

[0018] Three different types of protein analysis were performed to identify these markers, in order to cover as broad a base as possible of proteome coverage, e.g. to allow the enhanced detection of isoforms and of post-translational modifications (PTM). These types of analysis were two-dimensional electrophoresis (2DE, separating proteins based on pI and molecular weight), two-dimensional liquid chromatography (2DLC, separating proteins based on pI and hydrophobicity) and one-dimensional liquid chromatography (1DLC, separating proteins based on hydrophobicity). Note that the starting pH differs between 2DLC and 1DLC: pH 8.5 and 2.3, respectively. Two different cohorts were analyzed—increased metabolic demand (cohort 1) and reduced supply (cohort 2).

[0019] In a first study, ischemia was induced in a first cohort of subjects by metabolic demand: subjects were stimulated by atrial pacing, which makes the heart beat faster and induces ischemia, as indicated by an increase in lactate, and potentially myocardial necrosis (based on detection of cTnI or cTnT in blood). In some cases, individuals did not exhibit any increase in lactate or detectable cTnI/cTnT. These latter individuals were considered controls. Multiple serum samples were obtained for each individual. Differences between baseline (prior to pacing) and those at peaking pacing and up to 60 minutes after were analyzed. Those proteins that were elevated compared to the baseline in the majority of ischemic or necroiss individuals (and not elevated in controls) were considered to be of interest.

[0020] This procedure mimics naturally occurring metabolic cardiac events, such as ministrokes, that might precede a full MI. Ischemia is a heterogeneous group of conditions, resulting from different underlying mechanisms, such as demand and supply limitation. We have "mimicked" these two conditions in the different cohorts used in the analysis. Thus, these cohorts are expected to reflect markers that are overexpressed in subjects suffering from ischemia resulting from a variety of such underlying mechanisms. Samples from demand (atrial pacing) were evaluated by 2DE, 2DLC and 1DLC.

[0021] In a second study, ischemia was induced in a second cohort by coronary blockage: subjects undergoing valve replacement surgery exhibited ischemia because of blood loss during the procedure. This procedure mimics naturally occurring events in which ischemia is induced by coronary blood vessel blockage. This cohort was evaluated only by 1DLC, the procedure which provided a comparison to the most useful results with the first cohort. Those proteins found to be altered in both cohorts are considered to be "tier one" markers, although strong hits in either cohort may also be considered to be prime candidate markers.

[0022] The results of the studies with these two cohorts are summarized in Table 13. Taken together, these studies show that three proteins are implicated as the most highly correlated markers (sometimes referred to herein as "first tier" markers, as they are observed to be elevated in both cohorts) for ischemia, regardless of the cause of the ischemia: Lumican; Extracellular matrix protein 1 (ECM-1); and Carboxypeptidase N (e.g., the catalytic chain).

[0023] Three markers in addition to Lumican, ECM-1 and Carboxypeptidase N are implicated as first tier markers for at least subjects similar to those in the first cohort: Angiogenin; Semenogelin (e.g., isoforms 1 and 2); and Long palate, lung and nasal epithelium carcinoma-associated protein 1 (LPLNECA-1) (e.g., isoform 1; isoforms 2-4 are also present, but the method of analysis employed in this study, although it supports isoform 1, cannot distinguish among the four isoforms, which are splice variants, so isoforms 2-4 cannot be ruled out due to sequence homology).

[0024] Ten markers in addition to Lumican, ECM-1 and Carboxypeptidase N are implicated as first tier markers for at least subjects similar to those in the second cohort: Peroxiredoxin isoform 2; S100 isoforms A7, A8 and A9 (other S100 isoforms were detected and not observed to be altered); Sortilin-related receptor; Catalase; Low density lipoprotein receptor related proteins 1 and 2; and Syntaxin 3.

[0025] In addition to these first tier markers, Table 13 lists some "second tier" markers which can also be used for identifying subjects similar to those in both cohorts I and II; in cohort I; or in cohort II. These include, e.g., Alpha-2-HS-glycoprotein; Galectin-7; Hornerin; Proteoglycan-4; Profilaggrin (also called Filaggrin); Vitamin D binding protein; C4b-binding protein alpha chain; Thyroxine binding globulin; Alpha-2-glycoprotein 1, zinc; protease, serine 3; Caspase 14; Desmogelin; Kininogen-1 (we observed the peptide for the intact protein, but our data cannot distinguish between changes to the LMW or HMW, which could also be present); Hepatocyte growth factor like protein; Hepatocyte growth factor activator; and Insulin like growth factor protein 6.

[0026] In some embodiments of the invention, it is desirable to distinguish between subjects whose ischemia is induced by metabolic causes (similar to the subjects of cohort I), and subjects whose ischemia is induced by coronary blood vessel blockage (similar to the subjects of cohort II), because different treatment methods can be used for the two classes of subjects. The markers of the invention can be used to make such distinctions.

[0027] This invention relates, e.g., to a method for determining if a subject has myocardial ischemia, comprising measuring in a sample from the subject the amount of at least one of the following proteins, compared to a baseline value:

[0028] a) Lumican and/or

[0029] b) Extracellular matrix protein 1 and/or

[0030] c) Carboxypeptidase N,

[0031] wherein a significant amount (e.g., at least a statistically significant amount) of over-expression of the protein (s) compared to the baseline value is indicative of myocardial ischemia (e.g., indicates that the subject has, or is likely to have, myocardial ischemia). The amount of expression may be determined for any combination of 1, 2, or all 3, of these proteins, and the determinations can be conducted simultaneously, or in any order.

[0032] Another aspect of the invention is a method for identifying subjects that have myocardial ischemia that is induced by a metabolic-induced ischemic event [due to a metabolic limitation, in which the heart is unable to meet metabolic need; (excessive) metabolic demand], comprising determining in the sample from the subject the amount, compared to a baseline value, of at least one of proteins a), b), c) above,

[0033] d) Angiogenin,

[0034] e) Semenogelin, and/or

[0035] f) Long palate, lung and nasal epithelium carcinoma-associated protein 1. The amount of expression may be

determined for any combination of 1, 2, 3, 4, 5, or 6 of these proteins, and the determinations can be conducted simultaneously, or in any order.

[0036] Another aspect of the invention is a method for identifying subjects that have myocardial ischemia that is induced by coronary blood vessel blockage, which limits the supply of blood, comprising determining in the sample from the subject the amount, compared to a baseline value, of at least one of proteins a), b), c) above,

[0037] g) Syntaxin,

[0038] h) Perioxiredoxin isoform 2,

[0039] i) S100 isoform A7,

[0040] j) S100 isoform A8,

[0041] k) S100 isoform A9,

[0042] l) Sortilin-related receptor

[0043] m) Catalase

[0044] n) Low density lipoprotein receptor related protein 1, and/or

[0045] o) Low density lipoprotein receptor related protein 2. The amount of expression may be determined for any combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 of these proteins, and the determinations can be conducted simultaneously, or in any order.

[0046] In addition to the proteins noted above, one of more of the "second tier" proteins indicated in Table 13 can also be measured. A skilled worker will recognize which of these markers are indicative of a cohort I-type of condition, and which are indicative of a cohort II-type of condition.

[0047] Another aspect of the invention is a method for determining if a subject has myocardial ischemia, comprising determining in a sample from the subject the amount, compared to a baseline value, of at least one (e.g., at least four) of at least proteins a)-p) as noted above. The amount of expression may be determined for any combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 of these proteins; and the determinations can be conducted simultaneously, or in any order.

[0048] In a method of the invention, a determination that increasing numbers of protein markers of the invention are overexpressed in a subject can further indicate that the subject has (or is likely to have) myocardial ischemia.

[0049] A method as above may further comprise measuring in the sample the amount of one or more other markers that have been reported to be diagnostic of cardiac necrosis, including cardiac specific isoforms of troponin I (TnI) and/or troponin T (TnT) (although CK-MB, myoglobin, have been used in the past, cTnI and cTnT are the current gold standards), wherein a significant increase (e.g., at least a statistically significant increase) of the one or more markers further is further indicative that the subject has myocardial ischemia.

[0050] As noted above, ischemia is a heterogeneous condition caused by a variety of underlying mechanisms. Even if a single marker of the invention is capable of detecting a subject having ischemia resulting from a particular mechanism, it is possible for some markers that the marker is also upregulated in a disease other than myocardial ischemia. In such a case, it would be desirable to screen for upregulation of at least one additional marker that is associated with ischemia caused by a different underlying mechanism. The column labeled "Function" in Table 13 shows that some of the markers of the invention can be divided into particular groups on the basis of their functions. A skilled worker, studying this table, could readily identify markers associated with different mechanisms. In one embodiment of the invention, markers associated with 2, 3, 4 or more underlying mechanisms can be tested together in an assay of the invention.

[0051] Another aspect of the method is a method for deciding how to treat a subject suspected of having myocardial ischemia, or a subject that is at high risk for having myocardial ischemia, comprising determining by a method as above if the subject has (or is likely to have) myocardial ischemia and, (1) if the subject is determined to have (or to be likely to have) myocardial ischemia, deciding to treat the subject aggressively [such as with angioplasty (mechanical widening in opening blood vessels), treating with an anti-thrombolysis agent or, if possible, with percutaneous coronary intervention (PCI, or TPA), or undergoing coronary bypass surgery to replace the injuried/blocked coronary artery], or (2) if the subject is determined not to have (or not to be likely to have) myocardial ischemia, deciding to treat the subject non-aggressively [such as with asprin and/or thrombolysis (e.g., TPA), with periodic monitoring to ensure no future MI events, or by recommending changes in life style. This method can be used to confirm that a subject does not have ischemia (especially if myocardial ischemia is not detectable by cTnI or cTnT elevation), and thus to allow the subject to be released from hospital care.]

[0052] Another aspect of the invention is a method for treating a subject suspected of having myocardial ischemia, or a subject that is at high risk for having myocardial ischemia, comprising determining by a method as above if the subject has (or is likely to have) myocardial ischemia and, (1) if the subject is determined to have (or to be likely to have) myocardial ischemia, treating the subject aggressively, as indicated above, or (2) if the subject is determined not to have (or not to be likely to have) myocardial ischemia, treating the subject non-aggressively, as indicated above.

[0053] Another aspect of the invention is a kit for detecting the presence of ischemia in a subject, comprising reagents for detecting the amounts of at least one (e.g., any combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 of at least proteins a)-o) as noted above.

[0054] This invention relates, e.g., to a method for determining if a subject has myocardial ischemia, comprising

[0055] (a) providing a sample obtained from a subject suspected of having myocardial ischemia;

[0056] (b) determining in the sample the amount of at least one of at least proteins a)-p) as noted above (e.g., any combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) of the proteins); and

[0057] (c) comparing the amount(s) of the protein(s) to a baseline value that is indicative of the amount of the protein in a subject that does not have myocardial ischemia, wherein an increased amount (e.g., a statistically significantly increased amount) of the protein(s) compared to the baseline value is indicative of myocardial ischemia.

[0058] In one embodiment of the invention, the amount(s) of the protein(s) is compared over time to the baseline value and/or to levels known to be associated with necrosis. The kinetic rise and fall of combinations of proteins is indicative of impending myocardial ischemia (or other cardio and vascular events, such as stroke. A method of the invention can also be used to determine risk in subjects (patients) with stable or unstable angina.

[0059] A sample which is "provided" can be obtained by the person (or machine) conducting the assay, or it can have been obtained by another, and transferred to the person (or machine) carrying out the assay.

[0060] By a "sample" (e.g. a test sample) from a subject meant a sample that might be expected to contain elevated levels of the protein markers of the invention in a subject having myocardial ischemia. Many suitable sample types will be evident to a skilled worker. In one embodiment of the invention, the sample is a blood sample, such as whole blood, plasma, or serum (plasma from which clotting factors have been removed). For example, peripheral, arterial or venous plasma or serum can be used. In another embodiment, the sample is urine, sweat, or another body fluid into which proteins are sometimes removed from the blood stream. In the case of urine, for example, the protein is likely to be broken down, so diagnostic fragments of the proteins of the invention can be screened for. In another embodiment, the sample is cardiac tissue, which is harvested, e.g., after a heart transplant or the insertion of a pacemaker or defibrillator. Methods for obtaining samples and preparing them for analysis (e.g., for detection of the amount of protein) are conventional and well-known in the art. Some suitable methods are described in the Examples herein or in the references cited therein.

[0061] A "subject," as used herein, includes any animal that has, or is suspected of having, myocaridal ischemia. Suitable subjects (patients) include laboratory animals (such as mouse, rat, rabbit, guinea pig or pig), farm animals, sporting animals (e.g. dogs or horses) and domestic animals or pets (such as a horse, dog or cat). Non-human primates and human patients are included. For example, human subjects who present with chest pain or other symptoms of cardiac distress, including, e.g. shortness of breath, nausea, vomiting, sweating, weakness, fatigue, or palpitations, can be evaluated by a method of the invention. About ¼ of MI are silent and without chest pain. Furthermore, patients who have been evaluated in an emergency room or in an ambulance or physician's office and then dismissed as not being ill according to current tests for infarction have an increased risk of having a heart attack in the next 24-48 hours; such patients can be monitored by a method of the invention to determine if and when they begin express markers of the invention, which indicates that, e.g., they are beginning to exhibit ischemia. Subjects can also be monitored by a method of the invention to improve the accuracy of current provocative tests for ischemia, such as exercise stress testing. An individual can be monitored by a method of the invention during exercise stress tests of Dobutamine stress tests to determine if the individual is at risk for ischemia; such monitoring can supplement or replace the test that is currently carried out. Athletes (e.g., humans, racing dogs or race horses) can be monitored during training to ascertain if they are exerting themselves too vigorously and are in danger of undergoing an MI.

[0062] In another embodiment of the invention, the method is used as a screen in order to identify a drug (or to improve a cardioplegic solution) that protects the heart from ischemia and necrosis. The detection of one or more of the proteins of the invention in blood (or media if cell culture is used) is indicative of ischemia, and the quantity of the protein(s) is indicative of the severity of the ischemia.

[0063] The properties and amino acid sequences of the proteins of the invention are well-known and can be determined routinely, as well as downloaded from various known databases. See, e.g., the database, International Protein Index (IPI) at the world wide web site, ebi.ac.uk/IPI/xrefs.html. A summary of some properties of some of the proteins discussed herein, including their IPI ID number and amino acid sequences, is provided in Examples II and IV. This information is accurate as of the date of filing of this application. However, some of this information, including the sequences, is routinely updated (e.g. to correct mistakes in the previous entries), so updated (corrected) information about the proteins is included in this application. Information provided in the IPI database is incorporated by reference in the present application.

[0064] Although much of the data presented in the Examples herein are directed to particular forms of proteins of interest (or peptides thereof), it will be evident to a skilled worker that a variety of forms of these proteins may be indicative of the presence of myocardial ischemia in a subject. For example, the protein may be an intact, full-length protein. If a protein undergoes processing naturally (e.g., is converted from a pre-pro-hormone to a pro-hormone to a fully processed hormone; the N-terminal methionine is cleaved off; the signal sequence is removed, often accompanied by a post-translational modification, such as acetylation; etc.), any of these forms of the protein are included in the invention. Furthermore, in some instances, a protein of the invention may be broken down or degraded (e.g., proteins that are found in the urine). In such a case, an investigator can determine the level of one or more of the fragments or degradation products. A "diagnostic protein fragment," as used herein, is a fragment that is unique to the protein being identified, as detected by the assay. For example, a diagnostic fragment is recognized specifically by an antibody used to detect the full-length protein. Certain isoforms or post translational modifications (PTM) may also be encompassed by the invention. For example, the inventors have obtained data indicating PTM for C4b binding proteins; protease, serine; 3 alpha-2-glycoprotein 1; and zinc caspase 14.

[0065] The proteins and combinations of proteins discussed herein are sometimes referred to herein as "proteins (or protein markers) of the invention."

[0066] A variety of tests that have been used to detect myocardial events (particularly late occurring events, such as necrotic myocardial ischemia). These include, e.g., determining the levels of cardiac specific isoform(s) of troponin I (TnI) and/or troponin T (TnT), CK-MB (Creatine Kinase-MB), or myoglobin, although only the former two are the current gold standard. CK MB and myoglobin are not cardiac-specific. However, none of these markers is completely satisfactory for the detection of myocardial ischemia. For example, they fail to detect early stages of heart disease, such as non-necrotic myocardial ischemia. The new markers described herein can be used in conjunction with these types of assays.

[0067] When the values of more than one protein are being analyzed, a statistical method such as multi-variant analysis or principal component analysis (PCA) is used which takes into account the levels of the various proteins (e.g., using a linear regression score). For verification, we will use either immunoassay or multiple reaction monitoring (MRM, a MS-based targeted method that quantifies peptides that are unique to the protein of interest) on individuals (control, ischemia and MI).

[0068] In some embodiments, it is desirable to express the results of an assay in terms of an increase (e.g., a statistically significant increase) in a value (or combination of values) compared to a baseline value.

[0069] A "significant" increase in a value, as used herein, can refer to a difference which is reproducible or statistically significant, as determined using statistical methods that are appropriate and well-known in the art, generally with a prob-

ability value of less than five percent chance of the change being due to random variation. In general, a statistically significant value is at least two standard deviations from the value in a "normal" healthy control subject. Suitable statistical tests will be evident to a skilled worker. For example, a significant increase in the amount of a protein compared to a baseline value can be about 50%, 2-fold, or more higher. A significantly elevated amount of a protein of the invention compared to a suitable baseline value, then, is indicative that a test subject has myocardial ischemia (indicates that the subject is likely to have myocardial ischemia). A subject is "likely" to have myocardial ischemia if the subject has levels of the marker protein(s) significantly above those of a healthy control or his own baseline (taken at an earlier time point). The extent of the increased levels correlates to the % chance. For example, the subject can have greater than about a 50% chance, e.g., greater than about 70%, 80% 90%, 95% or higher chance, of having the ischemia. In general, the presence of an elevated amount of a marker of the invention is a strong indication that the subject has ischemia.

[0070] As used herein, a "baseline value" generally refers to the level (amount) of a protein in a comparable sample (e.g., from the same type of tissue as the tested tissue, such as blood or serum), from a "normal" healthy subject that does not exhibit myocardial ischemia. If desired, a pool or population of the same tissues from normal subjects can be used, and the baseline value can be an average or mean of the measurements. Suitable baseline values can be determined by those of skill in the art without undue experimentation. Suitable baseline values may be available in a database compiled from the values and/or may be determined based on published data or on retrospective studies of patients' tissues, and other information as would be apparent to a person of ordinary skill implementing a method of the invention. Suitable baseline values may be selected using statistical tools that provide an appropriate confidence interval so that measured levels that fall outside the standard value can be accepted as being aberrant from a diagnostic perspective, and predictive of ischemia.

[0071] It is generally not practical in a clinical or research setting to use patient samples as sources for baseline controls. Therefore, one can use any of variety of reference values in which the same or a similar level of expression is found as in a subject that does not have myocardial ischemia.

[0072] It will be appreciated by those of skill in the art that a baseline or normal level need not be established for each assay as the assay is performed but rather, baseline or normal levels can be established by referring to a form of stored information regarding a previously determined baseline levels for a given protein or panel of proteins, such as a baseline level established by any of the above-described methods. Such a form of stored information can include, for example, a reference chart, listing or electronic file of population or individual data regarding "normal levels" (negative control) or positive controls; a medical chart for the patient recording data from previous evaluations; a receiver-operator characteristic (ROC) curve; or any other source of data regarding baseline levels that is useful for the patient to be diagnosed. In one embodiment of the invention, the amount of the proteins in a combination of proteins, compared to a baseline value, is expressed as a linear regression score, as described, e.g., in Irwin, in Neter, Kutner, Nachtsteim, Wasserman (1996) Applied Linear Statistical Models, 4^{th} edition, page 295.

[0073] In an embodiment in which the progress of a treatment is being monitored, a baseline value can be based on earlier measurements taken from the same subject, before the treatment was administered.

[0074] The amount of a protein can be measured using any suitable method. Some methods involve the use of antibodies, binding ligands, or mass spectrometry tagged peptides specific for a protein of interest. Antibodies suitable for use in assays of the invention are commercially available, or can be prepared routinely. Methods for preparing and using antibodies in assays for proteins of interest are conventional, and are described, e.g., in Green et al., Production of Polyclonal Antisera, in *Immunochemical Protocols* (Manson, ed.), (Humana Press 1992); Coligan et al., in *Current Protocols in Immunology*, Sec. 2.4.1 (1992); Kohler & Milstein (1975), *Nature* 256, 495; Coligan et al., sections 2.5.1-2.6.7; and Harlow et al., Antibodies: A Laboratory Manual, page 726 (Cold Spring Harbor Laboratory Pub. 1988).

[0075] Any of a variety of antibodies can be used in methods of the invention. Such antibodies include, e.g., polyclonal, monoclonal (mAbs), recombinant, humanized or partially humanized, single chain, Fab, and fragments thereof. The antibodies can be of any isotype, e.g., IgM, various IgG isotypes such as IgG_1' IgG_{2a}, etc., and they can be from any animal species that produces antibodies, including goat, rabbit, mouse, chicken or the like. The term, an antibody "specific for" a protein, means that the antibody recognizes a defined sequence of amino acids, or epitope in the protein. An antibody that is "specific for" a polypeptide refers to an antibody that binds selectively to the polypeptide and not generally to other polypeptides unintended for binding to the antibody. The parameters required to achieve such specificity can be determined routinely, using conventional methods in the art. Conditions that are effective for binding a protein to an antibody which is specific for it are well-known and conventional.

[0076] In one embodiment of the invention, antibodies specific for a (one or more) protein of the invention are immobilized on a surface (e.g., are reactive elements on an array, such as a microarray, or are on another surface, such as used for surface plasmon resonance (SPR)-based technology, such as Biacore), and proteins in the sample are detected by virtue of their ability to bind specifically to the antibodies. Alternatively, proteins in the sample can be immobilized on a surface, and detected by virtue of their ability to bind specifically to the antibodies. Methods of preparing the surfaces and performing the analyses, including conditions effective for specific binding, are conventional and well-known in the art.

[0077] Among the many types of suitable immunoassays are immunohistochemical staining, ELISA, Western blot (immunoblot), immunoprecipitation, radioimmuno assay (RIA), fluorescence-activated cell sorting (FACS), etc. Assays used in a method of the invention can be based on colorimetric readouts, fluorescent readouts, mass spectrometry, visual inspection, etc. Assays can be carried out, e.g., with suspension beads, or with arrays, in which antibodies or cell or blood samples are attached to a surface such as a glass slide or a chip.

[0078] In one embodiment, a tissue sample (e.g. a cardiac tissue sample) is stained with a suitable antibody in a conventional immunohistochemical assay for those proteins which are present in the myocardium. Note that it can be difficult to obtain human tissue unless an individual is undergoing sur-

gery or a routine biopsy (e.g. following heart transplantation), and such subjects are likely to be ischemic to some degree.

[0079] Mass spectrometry (MS) can also be used to determine the amount of a protein, using conventional methods. Some typical such methods are described in the Examples herein. Relative ratio between multiple samples can be determined using label free methods (as done in the present Examples), based on spectral count (and the number of unique peptides and the number of observation of each peptide). In the Examples herein, we used a LTQ-Orbitrap LC/MS/MS instrument to obtain the data. Alternatively, quantitative data can be obtained using multiple reaction monitoring (MRM), most often carried out using a triple quadripole mass spectrometer. In this case, peptides that are unique to a given protein are selected in the MS instrument and quantified. Absolute quantification can be obtained if a known labeled synthetic peptide is used. For detailed methods see, e.g., Qin Fu and J E Van Eyk, in Clinical Proteomics: from diagnostics to therapy (Van Eyk J E and Dunn M, eds), Wiley and Son Press; Current Protocols in Molecular Biology, Preparation of Proteins and Peptides for Mass Spectrometry Analysis in a Bottom-Up Proteomics Workflow, Gundry et al., chapter 10, 2009, in press)

[0080] In general, molecular biology methods referred to herein are well-known in the art and are described, e.g., in Sambrook et al., Molecular Cloning: A Laboratory Manual, current edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., and Ausubel et al., Current Protocols in Molecular Biology, John Wiley & sons, New York, N.Y.

[0081] A detection (diagnostic) method of the invention can be adapted for many uses. For example, it can be used to follow the progression of cardiac ischemia. In one embodiment of the invention, the detection is carried out both before (or at approximately the same time as), and after, the administration of a treatment, and the method is used to monitor the effectiveness of the treatment. A subject can be monitored in this way to determine the effectiveness for that subject of a particular drug regimen, or a drug or other treatment modality can be evaluated in a pre-clinical or clinical trial. If a treatment method is successful, the levels of the protein markers of the invention are expected to decrease.

[0082] A method of the invention can be used to suggest a suitable method of treatment for a subject. For example, if a subject is determined by a method of the invention to be likely to have myocardial ischemia, a decision can be made to treat the subject with an aggressive form of treatment; and, in one embodiment, the treatment is then administered. Suitable aggressive treatment modalities include, for example, angioplasty (mechanical widening to open blood vessels); treating with an anti-thrombolysis agent or, if possible, with percutaneous coronary intervention (PCI, or TPA); or undergoing coronary bypass surgery to replace the injuried/blocked coronary artery. Methods for carrying out such treatments are conventional and well-known. By contrast, if a subject is determined not to be likely to have myocardial ischemia, a decision can be made to adopt a less aggressive treatment regimen; and, in one embodiment, the subject is then treated with this less aggressive forms of treatment. Suitable less aggressive forms of treatment include, for example, treatment with asprin and/or agents that bring about thrombolysis (e.g., TPA); periodic monitoring to ensure no future MI events; or recommending changes in life style. A subject that does not have myocardial ischemia is thus spared the unpleasant side-effects associated with the unnecessary, more aggressive forms of treatment. By "treated" is meant that an effective amount of a drug or other anti-heart disease procedure is administered to the subject. An "effective" amount of an agent refers to an amount that elicits a detectable response (e.g. of a therapeutic response) in the subject.

[0083] One aspect of the invention is a kit for detecting whether a subject is likely to have myocardial ischemia, comprising one or more agents for detecting the amount of a protein of the invention. As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. For example, "a" protein of the invention, as used above, includes 2, 3, 4, 5 or more of the proteins. In addition, other markers for ischemia (e.g., as discussed elsewhere herein) can also be present in a kit. If mass spectrometry is to be used to measure protein levels, the following reagents can be included in the kit: known amounts of a labeled (e.g. stable isotope) peptide (synthetic or recombinant) standard for each peptide to be assessed, separately or combined into a single mixture containing all peptides; optionally, a different peptide standard for assessing reproducibility of the assay; and/or, optionally, dilutent and trypsin for preparation of the sample. If an antibody-based method is to be used to measure protein levels, the agents in the kit can encompass antibodies specific for the proteins. The kit may also include additional agents suitable for detecting, measuring and/or quantitating the amount of protein, including conventional analytes for creation of standard curves. Among other uses, kits of the invention can be used in experimental applications. A skilled worker will recognize components of kits suitable for carrying out a method of the invention.

[0084] Optionally, a kit of the invention may comprise instructions for performing the method. Optional elements of a kit of the invention include suitable buffers, containers, or packaging materials. The reagents of the kit may be in containers in which the reagents are stable, e.g., in lyophilized form or stabilized liquids. The reagents may also be in single use form, e.g., for the performance of an assay for a single subject. In one embodiment of the invention, the kit is a "home chest pain test kit," that can be used to test blood, urine, or other body fluids for the presence (and/or level) of protein markers of the invention. Thus, a patient who has been released from an Emergency Department (ED) or a cardiac ward, but who is at risk over the next about 48 hours, can take the test over time at home and, if the test produces positive results, return to the ED.

[0085] In the foregoing and in the following examples, all temperatures are set forth in uncorrected degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

EXAMPLES

Example I

Identification of Novel Cardiac Biomarkers that are Rapidly Released into the Coronary Sinus in Response to Cardiac Ischemia, Even in the Absence of Detectable Myocyte Necrosis

A. Overview of the Studies

[0086] Rapid atrial pacing has been reported to produce reversible and controlled myocardial ischemia, as measured by a coronary sinus lactate concentration that rises above arterial lactate concentration, in approximately ⅔ of patients

with fixed epicardial coronary artery disease (>70% diameter stenosis in at least one coronary artery). (Dehmer et al. (1983) *Am Heart J* 106, 114-24; Markham et al. (1983) *Am J Cardiol* 51, 1589-94). Therefore, in the experiments shown in this Example, atrial pacing was used as the human demand ischemia model.

[0087] In the studies shown in this Example, three types of protein analysis were conducted to identify protein markers of the invention. There is normally less than 40% overlap (e.g., 3-5) in the proteins observed between the different types of analysis platforms. This is because every protein is intrinsically different with respect to its pI, hydrophobicity and mass. Furthermore, post translational modifications (PTM) alter the intrinsic nature of the protein and thus may display quite different separation or enrichment characteristics. As such, the choice of technology or group of technologies should be dictated by the characteristics of the proteins targeted by the experimental question. In the case of biomarker discovery (and based on the lessons learnt from the biomarker, cTnI), multiple protein separation strategies should (and do) increase proteome coverage.

[0088] The present inventors and collaborators have found that the combination of intact protein separation technologies of 2DE (two-dimensional electrophoresis), 2DLC (two-dimensional liquid chromatography) and 1DLC (one-dimensional liquid chromatography) increases the proteome coverage while allowing enhanced detection of isoforms and PTM. 2DE of serum (and plasma) was optimized for separation by using pH 4-7 and 10% Bis-Tris gel (Graham et al. (20050) *Proteomics* 5 2309-14; Fu et al. (2005) *Proteomics* 5, 2656-64), as were the liquid chromatography methods. The combination of chemical depletion and optimized 2DE conditions can achieve good reproducibility (~20% CV) (Fu et al. (supra)). Liquid chromatography (LC) separates proteins based on one or more of their intrinsic properties: mass (size exclusion), isoelectric point (pI, chromatographic focusing or ion exchange), hydrophobicity (reversed phase) or affinity chromatography (bio-specificity). Our laboratory has optimized 2DLC combining chromatographic focusing and reversed phase HPLC with the commercial Beckman Coulter instrument, the Two-Dimensional Protein Fractionation (PF2D) system (McDonald et al. (2006) *Mol Cell Proteomics* 5, 2392-411; Sheng et al. (2006) *Mol Cell Proteomics* 5, 26-34; Stasna et al. Protein separation: Liquid chromatography, In "Proteomic and Genomic Analysis of Cardiovascular Disease" (eds. Van Eyk J E and Dunn M) 2008 Wiley and Son Press, page 241). Briefly, samples are loaded onto the first dimension column (ion exchange column) at pH 8.5 in presence of urea and detergent and separated based on pI by decreasing the pH to 4.0 (Graham et al. (2006) (supra). Proteins that are bound tightly to the column or have a pI below 4.0 are eluted using 1M salt. We found that including 20% isopropanol in the buffers can eliminate "artificial" binding of a subset of proteins to the first dimension. Fractions are collected throughout the chromatographic separation and each fraction is subsequently separated by reversed phase chromatography using a linear gradient composed of aqueous trifloroacetic acid (TFA), pH 2.3 and TFA/acetronitrile, pH 2.3. The second dimension elution profile is monitored at 214 nm (peptide bonds) and is semi-quantitative. On average, fractions contain 1-100 proteins in each peak (McDonald et al. (2006); Graham et al. (2006) (both supra)). These samples can be further analyzed by electrophoresis (ME or 2DE) or analyzed directly by mass spectrometry (MS). If so, due to the complexity of the reversed phase fractions they must undergo further online LC separation prior to MS. An overview outlining the process is summarized in Fu et al. (2008) (supra).

B. Cohort Information for Atria Pacing Human Model—Cohort I

1. Research Design

[0089] Patients >20 years old with stable exertional angina referred for cardiac catheterization were recruited Exclusion criteria were atrial fibrillation, valvular heart disease, prior coronary artery bypass surgery, depressed left ventricular systolic function, acute coronary syndrome, and/or left bundle branch block. As well, patients were excluded if they reported angina within 48 hours of the catheterization. 19 individuals were recruited. The study was approved by the Institutional Review Boards of UT Southwestern and Parkland Hospital. All patients have signed written informed consent.

[0090] A 7 or 8 Fr Gorlin catheter was advanced to the coronary sinus from the right brachial vein. Coronary sinus, peripheral arterial, and peripheral venous serum samples were obtained prior to start of the atrial pacing. The left atrium was paced at 20 beats/minute above the resting heart rate and this was increased every 3 minutes by 20 beats/minute until one of the following occurs: chest pain, AV block, or a heart rate of 160 beats/minutes is achieved. The patient was maximally paced at this rate for 3 minutes. At the end of the three-minute period, repeat blood samples were collected from the coronary sinus and peripheral artery. Repeat sampling from the coronary sinus was performed at 30 and 60 minutes after pacing termination.

TABLE 1

Timing line for serum sample collection

Location	Baseline	Immediate post-pacing	30 minutes post-pacing	60 minutes post-pacing
Coronary Sinus	X	X	X	X

[0091] Blood was immediately placed on ice and was transported to the processing center within 30 minutes of collection. Samples were centrifuged, serum (and plasma) separated, and specimens aliquoted into 100 μL tubes using an automated micropipette system. No samples were at room temperature for longer than 10 minutes. The longest duration between sample collection and freezing was less than one hour. Lactate and cardiac troponin T (TnT) was measured in heparinized plasma a (see table 2)

2. Cohort and Experimental Group Designation

[0092] The cohort was designated based on the following criteria:

[0093] 1) Cases (n=19) Significant coronary artery disease (at least one vessel with a diameter stenosis ≥70%) and coronary sinus lactate>arterial lactate after pacing (data not shown).

[0094] 2) Controls are individuals with no or little change in lactate pre vs. post.

[0095] 3) Moderate or severe ischemia: individuals with increase in lactate and are cTnT negative.

[0096] 4) Necrosis designation was for individuals with increase in lactate and are cTnT positive.

[0097] 5)

TABLE 2

coronary sinus values

PATIENT	age	csLpre	csLpost	TnT-cs0	TnT-cs1	TnT-cs2	TnT-cs3	Definition
1	50	0.4	0.7	<0.01	<0.01	<0.01	<0.01	ml
2	40	0.8	0.6	<0.01	<0.01	<0.01	<0.01	C
3	60	0.7	0.7	<0.01	<0.01	<0.01	<0.01	C
4	56	0.8	1	<0.01	<0.01	<0.01	<0.01	ml
5	63	0.8	0.9	<0.01	<0.01	<0.01	<0.01	C
6	51	0.7	0.7	<0.01	<0.01	0.016	0.029	N
7	51	0.4	1.2	<0.01	<0.01	<0.01	<0.01	sl
8	52	0.3	0.4	<0.01	<0.01	<0.01	<0.01	C
9	45	0.6	0.6	<0.01	<0.01	NA	NA	C
10	56	0.7	1.3	<0.01	<0.01	<0.01	<0.01	sl
11	50	0.5	0.9	<0.01	<0.01	<0.01	<0.01	sl
12	47	0.3	0.5	<0.01	<0.01	<0.01	<0.01	ml
13	57	1.1	0.9	<0.01	<0.01	NA	NA	excluded
14	62	0.9	1	<0.01	<0.01	<0.01	<0.01	excluded
15	43	0.3	0.8	<0.01	<0.01	0.026	0.109	N
16	52	1.22	1.48	<0.01	<0.01	<0.01	0.041	N
17	47	COAG	0.28	<0.01	<0.01	<0.01	<0.01	excluded
18	47	0.23	0.46	<0.01	<0.01	<0.01	<0.01	ml
19	53	0.17	0.16					C

Pre and post define samples taken at baseline and after maximum pacing

Definition defines, control (c) as no change in lactate and TnT negative, ischemia (I) as increase in lactate and TnT negative and differentiated in to moderate (mI) or severe (sI); necrosis (n) TnT positive and excluded for LC analysis (but included for 2DE).

C. 2-Dimensional Gel Electrophoresis Analysis

1. 2DE Cohort

[0098] All patients and all time points were analyzed.

2. 2DE Methods

[0099] Serum was depleted of IgG using protein G affinity chromatography and depleted of albumin using our in-house affinity/chemical depletion method (Fu et al. (2005) (supra). Protein concentration was determined using BCA assay (Pierce) for each depleted sample. 50 ug of each time point (baseline time point 1, 2 and 3) per individual was labeled with one of the three Cy dyes (Applied Biosystems Inc.). As well, a pool sample was created from equal amounts of each time point of a single patient sample. For each individual, equal amount of two labeled sample (two time points) were mixed with the pool sample and then separated simultaneously using optimized pH 4-7 gel, followed by 10% Bis-Tris SDS PAGE. The gels were then imaged on a fluorescent gel imager at the Cy3, Cy5 and Cy2 wavelengths. Subsequently, the gels were stained with silver to allow visualization for spot picking. Gel images were analyzed by Ludesi Inc (.http://www.ludesi.com/). Gels were aligned, spots matched and quantified. For example, gel images were prepared for an individual that became ischemic or underwent necrosis with pacing. Comparisons were made between baseline and the other subsequent time points for each individual. To avoid a nondetected (zero) value 0.1 was added to all values.

3. Selection Criteria.

[0100] Selection criteria for 2DE was based on analysis of all individual in each group (induced ischemia and induced necrosis) and are as follows:

[0101] i) Equal or greater than 1.5 fold increase compared to time point 0 (baseline).

[0102] ii) The spot volume was above (100 units) to allow protein identification by mass spectrometry.

[0103] iii) The spot was resolved.

[0104] iv) The change in the profile remains above baseline once elevated.

[0105] v) A changed in 3 out of the 3 or 2 out of the 3 individuals in a designated group (induced ischemia or induced necrosis) at any time point.

4. Results for 2DE

[0106] Approximately 1200 protein spots were resolved on each 2DE gel. Due to stringent criteria for cut offs, most protein spots were deemed not to change or biological variability was too great to be significant (FIG. **1**, see breakdown). Caspase 14 and complement factor B (isoform 1) increased specifically in patients with necrosis while fibrinogen beta chain and desmoglein-1 increased in patients with severe ischemia and necrosis (table 3).

TABLE 3

summary of changes detected by 2DE

Protein name	observed at baseline	control	large ischemia	moderate ischemia	necrosis
Caspase-14	yes	1 out of 5	1 out of 3	0 out of 4	2 out of 3
Isoform 1 of Complement factor B	yes	1 out of 5	1 out of 3	0 out of 4	2 out of 3
Fibrinogen beta chain	yes	2 out of 5	1 out of 3	2 out of 4	2 out of 3
Desmoglein-1	yes	2 out of 5	1 out of 3	2 out of 4	2 out of 3

[0107] The majority of proteins observed by 2DE, high abundant soluble proteins, do not change with induced ischemia or necrosis. Without wishing to be bound by any particular mechanism, Caspase 14 (IPI00013885) is proposed to be involved in the death receptor and granzyme B apoptotic pathways. It may act as a downstream signal transducer of cell death. Desmoglein-1 (IPI00025753) is a component of the cell desmosome junctions which are distinct plasma membrane domains. It has a single transmembrane domain. Desmosomes are the most common type of intercellular junction in vertebrate epithelial cells but found in other cell types. This protein is part of a complex comprising plakophilin 1, plakophilin 2, desmoplakin, desmoglein 1, desmoglein 4, plakoglobin and corneodesmosin. Other proteins of the desmosome complex as well as caspase 14 are found by 1DLC and 2DLC in a few individuals.

[0108] Information sheets summarizing some of the properties of these and other proteins discussed herein are provided as Example II.

D. 1DLC Work Flow

1. 1DLC Cohort

[0109] Each individual time sample outlined below (table 4) was analyzed using reversed phase HPLC. The control group samples were selected based on having similar prelacate concentrations compared to the two disease groups.

TABLE 4

1DLC		
Group designation	Patient numbers	Time points
control	3, 5	0 and 1
ischemia	7, 10, 11	0, 1, 2, 3
necrosis	6, 15, 16	0, 1, 3

2. 1DLC Method

[0110] Serum was depleted using an affinity chromatography comprised of IgY antibodies specific for all forms of immunoglobins (IgG, IgA and IgM) and then depleted of albumin using our in-house affinity/chemical depletion method. This was done in order to reduce background of the chromatogram. Protein concentration was determined using BCA assay (Pierce) for each depleted sample. Samples were analyzed on the same 1DLC columns. 50 ug of each sample was run (in duplicate) using our optimized gradient. One set was used for mass spectrometric analysis; the other set was stored at −80° C. Fractions were collected into 96-well plates, stored at −80° C. until analyzed. Protein standard was run every morning to ensure good, consistent and reproducible performance of HPLC system. Extensive washing was carried out between runs to eliminate possible cross-over contamination. Chromatographic images were compared and regions/domains with acceptable intensities from each experimental sample were selected or combined (FIG. **5**). Total 650 fractions (26 fractions per sample) were dried down, neutralized, and digested with trypsin. 50% of the digested sample was applied to the LC LTQ-Orbitrap MS.

[0111] For LC-MS/MS experiments on the LTQ-Orbitrap (ThermoFinnigan, San Jose, Calif.), peptides were dissolved in 6 μl resuspension buffer (4% acetonitrile in water with 0.1% formic acid). Samples (3 μl) were loaded onto a 75 um×10 cm BioBasic C18 column (New Objective, Woburn, Mass.). Peptides were eluted into an LTQ-Orbitrap (ThermoFinnigan, San Jose, Calif.) using an Agilent 1200 nano-LC system (Agilent, Santa Clara, Calif.). The HPLC gradient was 5% to 60% B (90% acetonitrile/water in 0.1% Formic acid) over 30 or 60 min depended on sample complexity. The mass spectrometer was operated in data-dependent mode in which every FT-MS scan (survey 350-2000 Da) was followed by MS/MS scans of the 5 most abundant ions.

[0112] All mass spectrometry data was analyzed according to a pipeline established and already used in our laboratory, designed to meet stringent criteria from the proteomics community. Data from the LTQ-Orbitrap was searched against the IPI databases where possible, using Sorcerer Sequest (Sagen, San Jose, Calif.). Search results were validated and analyzed using Scaffold (Proteome Systems, Portland, Oreg.). Protein identifications based upon a single peptide observation were handled carefully through manual inspection of the tandem MS (MS/MS) spectra, BLAST searching of the sequence to ensure it matches only the reported protein, requiring a minimum of 8 amino acids and a peptide probability score of >0.9.

[0113] Data analysis was based on the following: peptide redundancy removed, protein name redundancy removed, the number of unique peptides and number of observation for each peptide regardless of charge state (2+. 3+ or 4+) were determined for each protein. The protein was proposed to have a potential PTM if it was identified in multiple non-sequential domain/fractions. This was noted and all data regardless of the fraction was included for quantitation of the protein.

[0114] Data reanalysis was carried out using a version of the published algorithm for spectral counting (Old et al. (2005) *Molecular and Cellular Proteomics* 4.10, 1487-502) that added a 1.25 correction factor value to all numbers, in order to eliminate any zero values (non detectable values). The algorithm $R_p=\text{Log}_{10}$ (Px+1.25)/(P0+1.25)+Log_{10} (TP0−P0+1.25)/(TPx−Px+1.25)) and $R_{sc}=\text{Log}_{10}$) (SCx+1.25)/(SC0+SCx+1.25)+Log_{10}) (TSC0−SC0+1.25)/(TSCx−SCx+1.25), where R_p is the Log_{10} ratio of number of unique peptides between time points 0 and x, R_{sc} is the Log_{10} ratio of spectral counts between time points 0 and x, P0 or Px is the number of unique peptides or at baseline (0) or another time point (x) for the specific protein of interest. TP0 or TPx is the number of all unique peptides for the complete data set for that individual at that specific time point (0 or x). SC0 and SCx are the spectral counts at time points 0 and x for the protein. TSC0 and TSCx are the total number of spectral counts in the experiment at time points 0 and x. There is a linear correlation between number of peptides observed and the spectra count (under 70 peptides/protein). However, for very abundant protein with 100's of peptides and observations the relationship is more non-linear. A cut off of 0.3 (2 fold) was used to indicate a change.

3. Duplicate MS Analysis

[0115] Two independent MS analyses were done on each LC fraction. In both cases, LC fractions were stored (−80° C.) following an independent LC separation of the intact proteins. Image analysis was carried out between the various LC runs to match the fractions as closely as possible. However, the fractions analyzed were not completely identical due to variation in the LC run and exact timing of the fraction collection. The stored fractions were dried down, neutralized and digested with trypsin. The digested sample was applied to the LC LTQ-Orbitrap MS and number of peptides and spectra count were determined (table 5). The total number of peptide and counts for each time points is shown in table 6. This is taken into account when calculating change.

TABLE 5

MS replicate on frozen intact protein sample
cohort I, two protein LC runs, separated digestion and MS run

	sample: AMI-15-003 (F = fraction number)					
	# peptides	# peptides	# peptides	# peptides	# peptides	# peptides
Protein name	F1 + 2 + 3 + 4-duplicate	F1 + 2 + 3 + 4-original	F15 + 16-duplicate	F15 + 16-original	F25-original	F25-duplicate
alpha-1 antiproteinase	1	2	20	25	16	16
alpha1-antichymotrypsin	0	0	1	8	7	6
alpha-1-microglobulin/bikunin	0	0	2	0	0	0
Alpha-2-macroglobulin	0	0	7	2	32	31
alpha-2-plasmin inhibitor	0	0	0	0	0	2
Angiotensinogen	0	0	0	0	2	13
Apolipoprotein A-I	2	0	9	7	13	15
apolipoprotein A-IV	0	0	5	4	2	10
Apolipoprotein C-I	0	0	2	3	0	0
apolipoprotein E	0	0	0	0	2	8
Beta2- Glycoprotein	0	2	0	0	0	0
B-factor, properdin	0	0	15	19	2	8
C9 complement protein	0	0	8	2	0	1
carboxypeptidase N	0	0	6	0	0	0
caspase 14	2	0	0	0	0	0
cathelicidin antimicrobial peptide	0	0	2	0	0	0
coagulation factor II (thrombin)	0	0	4	3	0	0
coagulation factor XIII B subunit	2	3	0	0	0	0
complement component 1, s	0	0	0	2	0	0
complement component 2	0	0	0	0	3	2
complement component 3	2	2	33	14	71	81
complement component 4 binding protein, alpha chain	0	0	3	0	0	0
complement component 5	0	0	0	0	0	5
complement component 7	0	0	3	5	0	0
complement component 8, alpha	0	0	3	3	0	0
complement component 8, gamma	0	0	3	6	0	0
complement component C4A	0	0	32	19	16	29
complement component C6	0	0	3	2	0	0
complement component C8 beta chain	0	0	1	9	0	0
complement factor H	17	20	9	7	1	3
complement factor I	0	0	4	0	0	0
dermcidin	2	2	0	0	0	0
filaggrin 2	1	0	0	0	0	0
gelsolin	0	0	13	3	0	5
hemopexin	0	0	5	2	0	0
histidine-rich glycoprotein	0	0	3	0	0	0
hornerin	2	0	0	0	0	0
hyaluronan binding protein 2	0	0	0	3	0	0
Insulin-like growth factor-binding protein 3	4	4	0	0	0	0
Inter-alpha-trypsin inhibitor heavy chain H1	0	0	9	6	6	9
Inter-alpha-trypsin inhibitor heavy chain H2	0	0	8	3	6	15
Inter-alpha-trypsin inhibitor heavy chain H3	0	0	6	0	0	0
Inter-alpha-trypsin inhibitor heavy chain H4	0	0	10	2	0	4
kallikrein B, plasma (Fletcher factor) 1	0	0	0	4	0	0
kininogen-1	0	0	1	2	0	0
leucine-rich alpha-2-glycoprotein 1	0	0	5	0	0	0
lumican	0	0	4	5	0	0
pigment epithelium-derived factor precursor (PEDF)	0	0	0	0	10	0
plasma protease (C1) inhibitor	0	0	0	0	0	3
amyloid P	0	0	6	2	0	0
profilaggrin	0	1	0	0	0	0
S100 calcium-binding protein A7	3	4	0	0	0	0
S100 calcium-binding protein A8	1	2	0	0	0	1
S100 calcium-binding protein A9	1	2	0	0	0	1
transferrin	0	0	13	18	7	10
transthyretin	0	0	6	6	0	0
vitronectin	0	0	2	2	0	0

TABLE 6

total number of peptide and spectra count in MS run 1 and 2

	run 1	run 1	run 1	run 1	run 1	run 1	run 2	run 2	run 2
	peptides	counts	peptides	counts	peptides	counts	peptides	counts	peptides
sample	time point 0	TP 0	TP 1	TP 1	TP 2	TP 2	TP 0	TP 0	TP 1
A-15	976	10694	820	10527	767	9761	530	3005	770
A-16	715	9250	737	8615	682	7908	728	4724	709

	run 1	run 1	run 1	run 1	run 1	run 1	run 1	run 1	run 2
	time point 0	TP 0	TP 1	TP 1	TP 2	TP 2	TP 3	TP 3	TP 0
1-7	794	10673	788	10661	806	10806	828	10529	652
1-10	763	12629	810	11952	873	12868	894	12353	693
1-11	997	10783	830	11027	645	15836	830	10666	661

		run 2	run 2	run 2
		counts	peptides	counts
	sample	TP 1	TP 2	TP 2
	A-15	4702	802	4621
	A-16	4962	695	4683

	run 2	run 2	run 2	run 2	run 2	run 2	run 2
	TP 0	TP 1	TP 1	TP 2	TP 2	TP 3	TP 3
1-7	3880	654	3338	621	4338	715	3370
1-10	3398	589	3486	489	2904	746	3493
1-11	4501	604	4012	603	3865	595	3791

4. Criteria Selection for 1DLC

[0116] Selection criteria for 1DLC was based on analysis of all individuals in each group (induced necrosis or induced ischemia) and are as follows:

[0117] i) Changes in the number of unique peptides or the number of time each peptide was observed regardless of charge state (2+. 3+ or 4+) were compared to the equivalent protein (if observed) at time point 0. Changes are based on R_p or R_{sc} values of 0.30 or greater. The fold changes associated with these R values depend on the number of observations and range from 1:4 ratio (R=0.36 before total observation correction, 4 fold change) to a 300:600 (R=0.3001 before total observation correction, 2 fold change). The total observation correction will shift the R value depending on the different in size of the 2 sample groups and the proportion of observations for a the protein of interest relative to the entire sample. A 10% difference in sample size between the compared samples could increase or decrease the R value by 0.045ii)

[0118] ii) Changes in 2 out of the 3 or 3 out of the 3 individuals in a designated group (induced ischemia or induced necrosis) at any time point.

5. Results

[0119] Although the number of unique peptides observed between MS run 1 and 2 were similar, the number of peptide observations was reduced in the second run (Table 6). This did not overly affect the number of proteins observed except for the lower abundant proteins. There were 25 different serum samples analyzed, giving raise to 650 fractions being analyzed per MS analysis (1300 total MS runs). This resulted in, for both MS runs, over 41,000 unique peptides being identified, with these peptides observed over 410,600 times. Table 7 outlines the proteins that met the criteria above and whether they were observed to change by 2DLC.

[0120] An additional level of stringency was added in which the variation within an individual was taken into account. The first tier proteins are found consistently to remain elevated. These are highlighted in bold type. Those proteins with variation between patients or time points were ranked as second tier. Bradykinin peptide was also included (rather than kininogen, the parent protein which had a weaker correlation) based on reducing the fold change required to 1.5 fold. It was the only additional protein that met this weaker criterion. For details regarding the proteins see Example II.

TABLE 7

summary of protein changes observed by 1DLC

protein name	accession	up in ischemia 2 or 3 of 3	up in necrosis 2 or 3 of 3	Protein change detected by 2DLC
Alpha-2-HS-glycoprotein precursor	IPI00022431	yes		
Angiogenin	IPI00008554	yes		
Carboxypeptidase N catalytic chain	IPI00010295	yes		
Extracellular matrix protein 1	IPI00645849	yes		
Galectin-7	IPI00219221	yes		
Hornerin	IPI00398625	yes		

TABLE 7-continued

summary of protein changes observed by 1DLC

protein name	accession	up in ischemia 2 or 3 of 3	up in necrosis 2 or 3 of 3	Protein change detected by 2DLC
Isoform 1 of Long palate, lung and nasal epithelium carcinoma-associated protein 1	IPI00291410	yes		
Isoform 2 of Semenogelin-1	IPI00414684	yes		
Lumican	IPI00020986		yes	
Profilaggrin	IPI00654788	yes		
Thyroxine-binding globulin	IPI00292946	yes		yes
Vitamin D-binding protein	IPI00555812	yes		
Isoform LMW of Kininogen-1 (specifically bradykinin)	IPI00215894		yes	
C4b-binding protein alpha chain	IPI00021727	yes		yes
Proteoglycan-4 (isoforms A and D)	IPI00655676/	yes		

E. 2-Dimensional Liquid Chromatography

1. 2DLC Cohort

[0121] Since 2DLC requires 2 mg of protein or greater for each analysis and the quantity of sample for the atria pacing cohort was limited so pooling was required for each group as outlined in table 8.

TABLE 8

2DLC pool

Group designation	Patient numbers pooled	Time points analyzed
control	3, 19, 9	0 (2 mg protein)
	3, 19	3 (2 mg protein)
ischemia	7, 10, 11	0 (2 mg protein)
	7, 10, 11	1 (2 mg protein)
	7, 10, 11	2 and 3 (equal amounts) (2 mg protein)
necrosis	15, 16	0 and 1 (equal amounts) (1.9 mg protein)
	15, 16	2 and 3 (equal amounts) (1.9 mg protein)

2. 2DLC Method

[0122] Serum was depleted using an affinity chromatography comprised of IgY antibodies specific for 3 major forms of immunoglobins (IgG, IgA and IgM) and then depleted of albumin using our in-house affinity/chemical depletion method. This was done in order to reduce background of the chromatogram. Protein concentration was determined using BCA assay (Pierce). Samples were analyzed on the same set of first and second dimension columns. 2 mg of sample from each time point were sequentially injected on the HPCF first dimension column, followed by HPRF second dimension separation. Fractions were collected into 96-well plates and stored at −80 C until analyzed. Extensive washing was carried out between runs to eliminate possible cross-over contamination.

[0123] Chromatographic images were compared and the same regions/domains from multiple-pH fractions were combined based on profile and previous identification. Fractions from high salt wash were analyzed individually without pooling. Total 315 fractions from 7 time points were dried down, neutralized, and digested with trypsin. 50% of the digested sample was applied to the LC LTQ-Orbitrap MS.

[0124] For LC-MS/MS experiments on the LTQ-Orbitrap (ThermoFinnigan, San Jose, Calif.), peptides from the digestion of LC fraction were resuspended in 6 μA resuspension buffer (4% acetonitrile in water with 0.1% formic acid). Samples (3 μl) were loaded onto a 75 um×10 cm BioBasic C18 column (New Objective, Woburn, Mass.). Peptides were eluted into an LTQ-Orbitrap (ThermoFinnigan, San Jose, Calif.) using an Agilent 1200 nano-LC system (Agilent, Santa Clara, Calif.). The HPLC gradient was 5% to 60% B (90% acetonitrile/water in 0.1% Formic acid) over 30 or 60 min dependent on sample complexity. The mass spectrometer was operated in data-dependent mode in which every FT-MS scan (survey 350-2000 Da) was followed by MS/MS scans of the 5 most abundant ions.

[0125] All mass spectrometry data was analyzed according to the pipeline established and already used in the Van Eyk laboratory, designed to meet stringent criteria from the proteomics community. Data from the LTQ-Orbitrap was searched against the IPI databases where possible, using Sorcerer Sequest (Sagen, San Jose, Calif.). Search results were validated and analyzed using Scaffold (Proteome Systems, Portland, Oreg.). Protein identifications based upon a single peptide observation were handled carefully through manual inspection of the tandem MS (MS/MS) spectra, BLAST searching of the sequence to ensure it matches only the reported protein, requiring a minimum of 8 amino acids and a peptide probability score of >0.9.

[0126] Data analysis flow was based on the following: peptide redundancy removed, protein name redundancy removed, the number of unique peptides and number of observation for each peptide regardless of charge state were determined for each protein and, in the cases where the protein was observed in multiple domains as an indicator of potential PTM this was noted and all data for the protein was included for quantitation.

[0127] The number of unique peptides and total number of counts (number of times each peptide is observed) were dependently used to semi-quantify each protein that was observed. To deal with proteins which peptides were only observed at some but not all time points (resulting in no information) a correction factor of 1.25 was used in all R value calculations with a R>0.3 as indicative of change. See 1DLC for more detail.

3. Criteria Selection for 2DLC

A) Individual in Each Group (Induced Necrosis or Induced Ischemia)

[0128] i) Changes in the number of unique peptides or the number of times each peptide was observed regardless of charge state (+2. +3 or +4) were compared to the equivalent protein (if observed) at time point 0. All proteins only seen in time points after baseline were included.

[0129] ii) Changes in 3 out of the 3 or 2 out of the 3 individuals in a designated group (induced ischemia or induced necrosis) at any time point.

B) Group

[0130] i) proteins that met the above criteria for either induced ischemia or induced necrosis that did not change in all of the control (non ischemic) samples at any time point.

4. 2DLC Results

[0131] Over 7500 specta were analyzed per pooled sample and thus, over 52,5000 spectra in total. Spectra were removed based on poor quality and each mass was assigned to a single peptide sequence resulting in ~5500 spectra remaining. The number of the proteins that met the criteria are listed below in table 9. See Example II for detailed protein information.

TABLE 9

protein observed changed by 2DLC

Protein name	IPI accession number	increased in Ischemia	increased in necrosis	potential PTM in any sample	present at baseline	Ischemia T1/T0	Ischemia T2/T0	present at baseline	necrosis T1/T0	Control present at baseline	Control_ T1/T0
Protease, serine, 3	IPI00748381	yes	yes	no	0	0	>	0	>	0	0
C4b-binding protein alpha chain	IPI00021727	yes	yes	yes	yes	0	>	yes	>	yes	=
Alpha-2-glycoprotein 1, zinc (no)	IPI00166729	yes	yes	yes	0	>	>	0	>	0	0
Thyroxine-binding globulin precursor	IPI00292946	no	yes	no	yes	0	0	0	>	0	0

Criteria was that both number of peptide and number of count must increased

increased in ischemia = if protein is increases over baseline in the POOLED sample comprising severe ischemia patients. Ischemia was based on increase in lactate over time and no detectable cTnT

increased in necrosis = if protein is increases over baseline in the POOLED sample comprising necrosis patients analyzed. Necrosis was based on detectable cTnT (at time point 2 and or 3)

PTM = protein found in multiple fractions in any of the pooled sample.

Note,

if sequential maybe reflect not PTM but rather large quantity of protein eluting over multiple fractions

yes = present at baseline

0 not detected,

> greater than baseline

< less than baseline

= equal to baseline

yes - detected at baseline

control pool: all T0 = baseline from 13, 19, 9; T1 = time point 1 for 13, 19 and 9

ischemia pool: T0 = baseline from 7, 10, 11; T1 = time point 1 from 7, 10, 11; T2 = time point 2 and 3 from 7, 10, 11

necrosis pool: T0 = baseline and time point 1 for 16, 15; T2 = time points 2 and 3 of patient 16 and 15

Interestingly, two proteins, junction plakoglobin, desmoplakin, that are part of the desmonsomal protein complex were detected in a few patients but not enough to make it meet the criteria. Desmoglein-1, the other protein of the same complex was found elevated in necrosis individual with 2DE.

name	IPI #	Increase in ischemia	Increase in necrosis	Potential PTM	Ischemia TP1	Ischemia TP2	Ischemia TP3
Junction plakoglobin (catenin gamma isoform 1)	IPI00554711	yes	no	no	0	>	0
DPII isoform (most likely also DPI) Desmoplakin	IPI00217182 (IPI0013933)	yes	no	no	0	>	0

F. Final Summary of all Protein Changes with Three Methods of Proteomic Analysis

[0132] Coronary sinus serum samples were analyzed from patients undergoing atrial pacing. Patients were designated into control, ischemia or necrosis groups based on the presence of cTnT at any time point (necrosis group) and an increase in lactate during the pacing protocol (ischemia and necrosis groups). Depleted samples were analyzed for all patients and all time points by 2DE. Depleted samples for 3 patients that were control, ischemia or necrosis were analyzed at multiple time points by 1DLC. Pooling of these individuals (2 or 3) from control, necrosis and ischemia were required for analyzed by 2DLC due to the amount of protein required for this technology. Proteins selection criteria for each method and MS-based quantitation for each method are described above.

[0133] The following proteins have been selected as primary or secondary targets based on the robustness of their changes with ischemia and or necrosis and known biological functions. The overlap is schematically shown in FIG. **5**. Detailed information about each target is located in Example II.

Primary Targets

Lumican

[0134] Extracellular matrix protein 1

Angiogenin

[0135] Semenogelin (all isoforms 1 and 2)

Long palate, lung and nasal epithelium carcinoma-associated protein 1 (all isoforms, 1 and 2)

Secondary Targets

Alpha-2-HS-glycoprotein

[0136] Carboxypeptidase N (all subunits including catalytic chain)

Galectin-7

Hornerin

Proteoglycan-4 (Isoform A and D)

Profilaggrin (Filaggrin)

[0137] Vitamin D binding protein

C4b-binding protein alpha chain

Thyroxine binding globulin

Alpha-2-glycoprotein 1, zinc

protease, serine 3

Caspase 14

Desmogelin

[0138] Kininogen-1 (LMW and HMW and bradykinin)

Example II

Summary of Some of the Properties of Proteins Discussed with Regard to Cohort I

A. Vitamin D-Binding Protein

[0139] Name: Vitamin D-binding protein

IPI ID: IPI00555812

[0140] UniProtKB/Swiss-Prot entry ID: P02774, Q16309, Q16310

Length: 474 aa, molecular weight: 52964 Da (of precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0141] FUNCTION: Multifunctional protein found in plasma, ascitic fluid, cerebrospinal fluid, and urine and on the surface of many cell types. In plasma, it carries the vitamin D sterols and prevents polymerization of actin by binding its monomers. DBP associates with membrane-bound immunoglobulin on the surface of B-lymphocytes and with IgG Fc receptor on the membranes of T-lymphocytes.

[0142] SUBCELLULAR LOCATION: Secreted.

[0143] POLYMORPHISM: Over 80 variants of human DBP have been identified. The three most common alleles are called GC*1F, GC*1S, and GC*2. The sequence shown is that of the GC*2 allele

2. Sequence

[0144]

(SEQ ID NO: 1)

*MKRVLVLLLA*VAFGHALERGRDYEKNKVCKEFSHLGKEDFTSLSLVLY

SRKFPSGTFEQVSQLVKEVVSLTEACCAEGADPDCYDTRTSALSAKSCE

SNSPFPVHPGTAECCTKEGLERKLCMAALKHQPQEFPTYVEPTNDEICE

AFRKDPKEYANQFMWEYSTNYGQAPLSLLVSYTKSYLSMVGSCCTSASP

TVCFLKERLQLKHLSLLTTLSNRVCSQYAAYGEKKSRLSNLIKLAQKVP

TADLEDVLPLAEDITNILSKCCESASEDCMAKELPEHTVKLCDNLSTKN

SKFEDCCQEKTAMDVFVCTYFMPAAQLPELPDVELPTNKDVCDPGNTKV

MDKYTFELSRRTHLPEVFLSKVLEPTLKSLGECCDVEDSTTCFNAKGPL

LKKELSSFIDKGQELCADYSENTFTEYKKKLAERLKAKLPDATPKELAK

LVNKRSDFASNCCSINSPPLYCDSEIDAELKNIL

1-16 Leader Sequence.

[0145] Peptides used in the MS analysis described in this application are indicated by highlighting (shading) in the protein sequences shown herein. A skilled worker can use peptides for some of the proteins which have been described previously by others who have performed MS on those proteins. The sequences of peptides is dependent on the particu-

lar type of MS used. For example, the peptides for MALDI can be different from those in ESI. The studies performed herein were ESI.

3. Alternative Names:

[0146] DBP, Group-specific component, Gc-globulin, VDB

4. Additional Information on Function

[0147] Serum vitamin D3-binding protein (Gc protein) is the precursor for the principal macrophage activating factor (MAF).

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0153] FUNCTION: Major thyroid hormone transport protein in serum.

[0154] SUBCELLULAR LOCATION: Secreted.

[0155] TISSUE SPECIFICITY: Expressed by the liver and secreted in plasma.

[0156] DISEASE: Defects in SERPINA7 are a cause of TBG deficiency [MIM:314200]. Mutations in the SERPINA7 gene can result as a whole spectrum of deficiencies, characterized by either reduced or increased TBG levels in the serum. Patients show, respectively, reduced or elevated protein-bound iodine but are euthyroid.

2. Sequence

[0157]

(SEQ ID NO: 2)

*MSPFLYLVLLVLGLHATIHC*ASPEGKVTACHSSQPNATLYKMSSINADFAFNLYRRFTVE

TPDKNIFFSPVSISAALVMLSFGACCSTQTEIVETLGFNLTDTPMVEIQHGEFQHLICSLN

FPKKELELQIGNALFIGKHLKPLAKFLNDVKTLYETEVFSTGDFSNISAAKQEINSHVEMQ

TKGKVVGLIQDLKPNTIMVLVNYIHFKAQWANPFDPSKTEDSSSFLIDKTTTVQVPMMHQ

MEQYYHLVDMELNCTVLQMDYSKNALALFVLPKEGQMESVEAAMSSKTLKKWNRLLQKGW

VDLFVPKFSISATYDLGATLLKMGIQHAYSENADFSGLTEDNGLKLSNAAHKAVLHIGEK

GTEAAAVPEVELSDQPENTFLHPIIQIDRSFMLLILERSTRSILFLGKVVNPTEA

1-20 Signal Sequence

3. Alternative Names:

[0158] T4-binding globulin, Serpin A7

4. Summary

[0159] Thyroxine-binding globulin binds with high-affinity to the thyroid hormone. It is proposed to be a biomarker for senescence and aging. Chronic treatment with perindopril, an angiotensin I-converting enzyme inhibitor used in cardiac and renal disease, enhanced thyroxine-binding capacity and possibility the protein level itself. In a study on ACS, thyroxine binding globulin was measured in those with acute myocardial infarction after 14 days and there was no change compared to control. It has not been studied in myocardial ischemia or events leading up to MI.

C. Lumican

Name: Lumican

IPI ID: IPI00020986

[0160] UniProtKB/Swiss-Prot entry ID:
Length: 338 aa, molecular weight: 38429 Da, (of precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0161] SUBUNIT Binds to laminin (By similarity).

[0162] SUBCELLULAR LOCATION Secreted, extracellular space, extracellular matrix (By similarity).

[0148] Gc protein was deglycosylated by serum alpha-N-acetylgalactosaminidase (Nagalase)

[0149] The level of Gc globulin is reduced in patients with fulminate hepatic failure, septic shock and trauma. Furthermore, low levels of Gc globulin in patients with fulminant hepatic failure and multiple trauma have been found to correlate with the morbidity and mortality of patients. It has not been studied in heart disease.

5. Summary

[0150] Assays are available for total Vitamin D binding protein and for the amount of protein which is either free or bound to actin. This protein is known to be diagnostic for several diseases. It seems to be change with cellular injury and decrease with long term chronic disease. Clinical studies and animal models have shown that Gc-globulin has an important role in the clearance of procoagulant actin from the circulation after its release during cell necrosis and tissue injury but it is not known if it is in the heart.

B. Thyroxine-Binding Globulin

[0151] Name: Thyroxine-binding globulin precursor

IPI ID: IPI00292946

[0152] UniProtKB/Swiss-Prot entry ID: P05543
Length: 415 aa, molecular weight: 46325 Da (precursor)

2. Sequence

[0163]

(SEQ ID NO: 3)

*MSLSAFTLFLALIGGTSG*QYYDYDFPLSIYGQSSPNCAPECNCPESYPSAMYCDELKLKS

VPMVPPGIKYLYLRNNQIDHIDEKAFENVTDLQWLILDHNLLENSKIKGRVFSKLKQLKK

LHINHNNLTESVGPLPKSLEDLQLTHNKITKLGSFEGLVNLTFIHLQHNRLKEDAVSAAF

KGLKSLEYLDLSFNQIARLPSGLPVSLLTLYLDNNKISNIPDEYFKRFNALQYLRLSHNE

LADSGIPGNSFNVSSLVELDLSYNKLKNIPTVNENLENYYLEVNQLEKFDIKSFCKILGP

LSYSKIKHLRLDGNRISETSLPPDMYECLRVANEVTLN

1-18 Signal Sequence

3. Alternative Names:

(Keratan Sulfate Proteoglycan Lumican) (KSPG Lumican).

4. Summary

[0164] Protein involved in injury response in a number of tissues and is a secreted protein. In a study on the lumican in fibrosis with chronic ischemic and reperfused rat heart (which is not the acute myocardial infaction model, but rather would induce heart failure), the level of lumican mRNA increased, peaking at the fourth week. The protein level was not investigated. This protein is also known to inhibits cell adhesion and neurite outgrowth and be involved in wound healing of the cornea. It plays an important role in cell migration and proliferation during embryonic development, tissue repair, and tumor growth. It has not been studied in the context of myocardial ischemia or events leading up to MI.

D. Galectin-7

Name: Galectin-7

IPI ID: IPI00219221

[0165] UniProtKB/Swiss-Prot entry ID:

Length: 136 aa, molecular weight: 15075 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0166] FUNCTION Could be involved in cell-cell and/or cell-matrix interactions necessary for normal growth control. Pro-apoptotic protein that functions intracellularly upstream of JNK activation and cytochrome c release.

[0167] SUBCELLULAR LOCATION Cytoplasm. Nucleus. Secreted (Potential). Note=May be secreted by a non-classical secretory pathway.

[0168] TISSUE SPECIFICITY Mainly in stratified squamous epithelium.

2. Sequence

[0169]

(SEQ ID NO: 4)

*MS*NVPHKSSLPEGIRPGTVLRIRGLVPPNASRFHVNLLCGEEQGSDAALHFNPRLDTSEV

VFNSKEQGSWGREERGPGVPFQRGQPFEVLIIASDDGFKAVVGDAQYHHFRHRLPLARVR

LVEVGGDVQLDSVRIF

Initial Met is Removed

3. Alternative Names:

[0170] Galectin-7 (Gal-7) (HKL-14) (PI7) (p53-induced gene 1 protein).

Homologous 100% to Q6IB87_HUMAN LGALS7 protein (HCG1776519) (HCG42850)

[LGALS7]

Note on Sequence:

[0171] Note only 36% homology with galectin 3 which is known to be involved in cancer.

4. Additional Information on Function

[0172] The literature suggests that galectin 7 is involved in apoptosis. It is most likely is secreted and forms dimers. Galectin 7 is an emerging marker involved in the epidermal development of pluristratified epithelia and in epidermal cell migration. It is elevated in wound healing. It has not been studied in the context of myocardial ischemia or events leading up to MI.

E. Extracellular Matrix Protein 1

[0173] Name: Extracellular matrix protein 1

IPI ID: IPI00645849

[0174] UniProtKB/Swiss-Prot entry ID: Q5T5G4
Length: 567 AA (includes signal sequence)
Molecular weight: 63563 Da (includes signal sequence)

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0175] FUNCTION: Not known

[0176] SUBCELLULAR LOCATION: Secreted, extracellular space.

[0177] DISEASE: Defects in ECM1 are the cause of lipoid proteinosis (LiP); also known as lipoid proteinosis of Urbach and Wiethe or hyalinosis cutis et mucosae. LiP is a rare autosomal recessive disorder characterized by generalized thickening of skin, mucosae and certain viscera. Classical features include beaded eyelid papules and laryngeal infiltration leading to hoarseness. Histologically, there is widespread deposition of hyaline material and disruption/reduplication of basement membrane.

2. Sequence Information from 1DLC

(SEQ ID NO: 5)

*MGTTARAALVLTYLAVASA*ASPGGPTATGQRQLRPEHFQEVGYAAPPSPPLSRSLPMDHPD

SSQHGPPFEGQSGKEGRGPRPHSQPWLGERVGCSHIPPSIVQPPPSQEATPLQQEKLLPAQ

LPAEKEVGPPLPQEAVPLQKELPSLQHPNEQKEGTPAPFGDQSHPEPESWNAAQHCQQDRS

QGGWGHRLDGFPPGRPSPDNLNQICLPNRQHVVYGPWNLPQSSYSHLTRQGETLNFLEIGY

SRCCHCRSHTNRLECAKLVWEEAMSRFCEAEFSVKTRPHWCCTRQGEARFSCFQEEAFQPH

YQLRACPSHQPDISSGLELPFPPGVPTLDNIKNICHLRRFRSVPRNLPATDPLQRELLALI

QLEREFQRCCRQGNNHTCTWKAWEDTLDKYCDREYAVKTHHHLCCRHPPSPTRDECFARRA

PYPNYDRDILTIDIGRVTPNLMGHLCGNQRVLTKHKHIPGLIHNMTARCCDLPFPEQACCA

EEEKLTFINDLCGPRRNIWRDPALCCYLSPGDEQVNCFNINYLRNVALVSGDTENAKGQGE

QGSTGGTNISSTSEPKEE

3. Alternative Names:

[0178] Secretory component p85; Q5T5G5, Q8IZ60, Q5T5G6, Q16610

Note on Sequence:

[0179] Signal sequence 1-19 is removed in the mature protein.

4. Summary

[0180] Mutations of this protein result in lipoid proteinosis, a rare recessive disorder of the skin and mucosae. It binds perlecan, MMP9 and fibulin in the skin. It can inhibit MMP9. Auto antibodies to this protein occur with lichen sclerosus. Neither disease is common and so specificity to ischemia is likely. It has not been studied in the context of myocardial ischemia or events leading up to MI.

F. Semenogelin 1

Name: Semenogelin 1

[0181] IPI ID: IPI00414684 (Semenogelin-2 precursor IPI00025415)
UniProtKB/Swiss-Prot entry ID: P04279, Q6X4I9, Q6Y809, Q6Y822, Q6Y823, Q86U64, Q96QM3
Length: 402 aa, molecular weight: 45322 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0182] FUNCTION Predominant protein in semen. It participates in the formation of a gel matrix entrapping the accessory gland secretions and ejaculated spermatozoa. Fragments of semenogelin and/or fragments of the related proteins may contribute to the activation of progressive sperm movements as the gel-forming proteins are fragmented by KLK3/PSA.

[0183] FUNCTION Alpha-inhibin-92 and alpha-inhibin-31, derived from the proteolytic degradation of semenogelin, inhibit the secretion of pituitary follicle-stimulating hormone.

[0184] SUBUNIT Occurs in disulfide-linked complexes which may also contain two less abundant 71- and 76-kDa semenogelin-related polypeptides.

[0185] SUBCELLULAR LOCATION Secreted.

[0186] Event=Alternative splicing; Named isoforms=2;

[0187] Name=1;

[0188] ALTERNATIVE PRODUCTS IsoId=P04279-1; Sequence=Displayed;

[0189] Name=2;

[0190] IsoId=P04279-2; Sequence=VSP_004385;

[0191] Note=No experimental confirmation available;

[0192] TISSUE SPECIFICITY Seminal vesicle. However references show it is also present in other tissues including skeletal muscle

2. Sequence

[0193]

(SEQ ID NO: 6)

MKPNIIFVLSLLLILEKQAAVMGQKGGSKGRLPSEFSQFFHGQKGQHYSGQKGKQQTESK

GSFSIQYTYHVDANDHDQSRKSQQYDLNALHKTTKSQRHLGGSQQLLHNKQEGRDHDKSK

GHFHRVVIHHKGGKAHRGTQNPSQDQGNSPSGKGISSQYSNTEERLWVHGLSKEQTSVSG

AQKGRKQGGSQSSYYLQTEELVANKQQRETKNSHQNKGHYQNVVEVREEHSSKVQTSLCP

AHQDKLQHGSKDIFSTGDELLVYNKNQHQTKNLNQDQQHGRKANKISYQSSSTEERRLHY

GENGVQKDVSQRSIYSQTEKLVAGKSQIQAPNPKQEPWHGENAKGESGQSTNREQDLLSH

EQKGRHQHGSHGGLDIVIIEQEDDSDRHLAQHLNNDRNPLFT

1-23 Signal Sequence

3. Alternative Names:

SEMG

4. Summary

[0194] SGI isoform is found in skeletal muscle as well as epithelial cells. Isoform expression is tissue specific and SGI isoform is found in skeletal muscle as well as epithelial cells. The peptides produced by cleavage of semenogelin I, the predominant human semen coagulum protein, had high levels of antibacterial activity. It has not been studied in the context of myocardial ischemia or events leading up to MI.

G. Isoform 1 of Long Palate, Lung and Nasal Epithelium Carcinoma-Associated Protein 1

[0195] Name: Isoform 1 of Long palate, lung and nasal epithelium carcinoma-associated protein 1

IPI ID: IPI00291410,

[0196] UniProtKB/Swiss-Prot entry ID: Q8TDL5-1 Length: 484 aa, molecular weight: 52442 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0197] FUNCTION May play a role in innate immunity in mouth, nose and lungs.

[0198] SUBCELLULAR LOCATION Secreted (By similarity).

[0199] Event=Alternative splicing; Named isoforms=2;

[0200] Name=1;

[0201] IsoId=Q8TDL5-1; Sequence=Displayed;

[0202] ALTERNATIVE PRODUCTS Name=2;

[0203] IsoId=Q8TDL5-2; Sequence=VSP_015285, VSP_015286,

[0204] VSP 015287,

[0205] VSP 015288;

[0206] Note=No experimental confirmation available;

[0207] TISSUE SPECIFICITY Detected in trachea, nasal septal epithelium and lung. 0 hits

2. Sequence

[0208]

(SEQ ID NO: 7)

*MAGPWTFTLLCGLLAATLIQ*ATLSPTAVLILGPKVIKEKLTQELKDHNATSILQQLPLLS

AMREKPAGGIPVLGSLVNTVLKHIIWLKVITANILQLQVKPSANDQELLVKIPLDMVAGF

NTPLVKTIVEFHMTTEAWATIRMDTSASGPTRLVLSDCATSHGSLRIQLLHKLSFLVNAL

AKQVMNLLVPSLPNLVKNQLCPVIEASFNGMYADLLQLVKVPISLSIDRLEFDLLYPAIK

GDTIQLYLGAKLLDSQGKVTKWFNNSAASLTMPTLDNIPFSLIVSQDVVKAAVAAVLSPE

EFMVLLDSVLPESAHRLKSSIGLINEKAADKLGSTQIVKILTQDTPEFFIDQGHAKVAQL

-continued

IVLEVPPSSEALRPLPTLGIEASSEAQEYTKGDQLILNLNNISSDRIQLMNSGIGWFQPD

VLKNITEIIHSILLPNQNGKLRSGVPVSLSVKALGFEAAESSLTKDALVLTPASWKPSS

PVSQ

1-21 potential signal sequence. Isoform 2 is truncated at N-terminus. Also have insert (underlined) which has no peptides. Therefore, cannot distinguish between isoform one and two

3. Alternative Names:

[0209] C20orf114

[0217] DEVELOPMENTAL STAGE: Low level expression in the developing fetus, increased in the neonate, and maximal in the adult

[0218] SIMILARITY: Belongs to the pancreatic ribonuclease family.

[0219] It is uncertain whether Met-1 or Met-3 is the initiator.

2. Sequence Information from 1DLC

(SEQ ID NO: 8)

MVMGLGVLLL VFVLGLGLTP PTLAQDNSRY THFLTQHYDA KPQGRDDRYC ESIMRRRGLT

SPCKDINTFI HGNKRSIKAI CENKNGNPHR ENLRISKSSF QVTTCKLHGG SPWPPCQYRA

TAGFRNVVVA CENGLPVHLD QSIFRRP

4. Summary

[0210] Little is known about this protein or its shorter isoform (2). It has not been studied in the context of myocardial ischemia or events leading up to MI.

H. Angiogenin

[0211] Name: Angiogenin, precursor

IPI ID: IPI00008554

[0212] UniProtKB/Swiss-Prot entry ID: P03950

Length: 147 AA [This is the length of the unprocessed precursor]

Molecular weight: 42051 Da [This is the MW of the unprocessed precursor

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0213] FUNCTION: May function as a tRNA-specific ribonuclease that binds to actin on the surface of endothelial cells; once bound, angiogenin is endocytosed and translocated to the nucleus, thereby promoting the endothelial invasiveness necessary for blood vessel formation. Angiogenin induces vascularization of normal and malignant tissues. Abolishes protein synthesis by specifically hydrolyzing cellular tRNAs.

[0214] INTERACTIONS: May bind alpha-actinin P35609

[0215] SUBCELLULAR LOCATION: Secreted

[0216] TISSUE SPECIFICITY: Expressed predominantly in the liver.

Multiple Peptides

[0220] 3. Alternative Names:

[0221] RNASE5, Ribonuclease A family, 5, RNASE4 protein, ANG protein Q53×86, Q6P5T2

Note on Sequence:

[0222] Most likely have either intact molecule or the mature processed form.

[0223] Signal peptide residues 1-24

Additional Information on Function

[0224] Angiogenin is a normal constituent of the circulation and contained in a vasculature that rarely undergoes proliferation, but in some physiological and pathological conditions its levels increase in blood, promoting neovascularization. This is a potentially important physiological protein involved in angiogenesis.

4. Summary

[0225] Interestingly, this protein may play a role in angiogenesis. Recently it has been potentially linked to poor outcome in ACS patients, which is a chronic condition that can result from many different etiologies. Plasma angiogenin levels was increased in ACS also with ischemic brain damage. However, it has not been studied in the context of myocardial ischemia or events leading up to MI.

I. C4b-Binding Protein

Name: C4b-binding protein (alpha chain)r

IPI ID: IPI00021727

[0226] UniProtKB/Swiss-Prot entry ID: P04003

Length: 597 AA [This is the length of the unprocessed precursor]

Molecular weight: 67033 Da [This is the MW of the unprocessed precursor]

DNA, limiting DNA release and inhibiting complement activation L A. Trouw et al., JEM, 2005, 201, 1937-1948)

2. Sequence

[0235]

(SEQ ID NO: 9)

MHPPKTPSGA LHRKRKMAAW PFSRLWKVSD PILFQMTLIA ALLPAVLGNC GPPPTLSFAA

PMDITLTETR FKTGTTLKYT CLPGYVRSHS TQTLTCNSDG EWVYNTFCIY KRCRHPGELR

NGQVEIKTDL SFGSQIEFSC SEGFFLIGST TSRCEVQDRG VGWSHPLPQC EIVKCKPPPD

IRNGRHSGEE NFYAYGFSVT YSCDPRFSLL FHASISCTVE NETIGVWRPS PPTCEKITCR

KPDVSHGEMV SGFGPIYNYK DTIVFKCQKG FVLRGSSVIH CDADSKWNPS PPACEPNSCI

NLPDIPHASW ETYPRPTKED VYVVGTVLRY RCHPGYKPTT DEPTTVICQK NLRWTPYQGC

EALCCPEPKL NNGEITQKRK SRPANHCVYF YGDEISFSCH ETSRFSAICQ GDGTWSPRTP

SCGDICNFPP KIAHGHYKQS SSYSFFKEEI IYECDKGYIL VGQAKLSCSY SHWSAPAPQC

KALCRKPELV NGRLSVDKDQ YVEPENVTIQ CDSGYGVVGP QSITCSGNRT WYPEVPKCEW

ETPEGCEQVL TGKRLMQCLP NPEDVKMALE VYKLSLEIEQ LELQRDSARQ STLDKEL

Green both 1DLC and 2DLC
Glue only 2DLC

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0227] FUNCTION: Controls the classical pathway of complement activation. It binds as a cofactor to C3b/C4b inactivator (C3bINA), which then hydrolyzes the complement fragment C4b. It also accelerates the degradation of the C4bC2a complex (C3 convertase) by dissociating the complement fragment C2a. Alpha chain binds C4b. It interacts also with anticoagulant protein S and with serum amyloid P component.

[0228] SUBUNIT: Disulfide-linked complex of alpha and beta chains of 3 possible sorts: a 570 kDa complex of 7 alpha chains and 1 beta chain, a 530 kDa homoheptamer of alpha chains or a 500 kDa complex of 6 alpha chains and 1 beta chain. The central body of the alpha chain homopolymer supports tentacles, each with the binding site for C4b at the end.

[0229] SUBCELLULAR LOCATION: Secreted

[0230] TISSUE SPECIFICITY: Chylomicrons in the plasma.

[0231] It is uncertain whether Met-1 or Met-17 is the initiator

[0232] Additional information

[0233] CRP binds C4b binding proteins and regulations it inhibition of complement system (Regulation of Complement Activation by C-Reactive Protein: Targeting of the Inhibitory Activity of C4b-Binding Protein[1] AP Sjöberg et al., J. Immuno. 2006, 176: 7612-7620).

[0234] C4b-binding protein (C4BP), binds strongly to necrotic cells, irrespective of the cell type used or the method of induction. (C4b-binding protein binds to necrotic cells and

3. Alternative Names:

[0236] IC4b binding protein, C4b binding protein alpha chain, C4b receptor, C4bP, C4bPA, C4bPAL1, Complement component 4 binding protein, alpha like 1, PRP, Proline rich protein Complement component 4 binding protein, alpha. Q5VVQ8

Note on Sequence:

[0237] Most likely intact protein. Several patients had protein present in multiple fractions and although sequential appears to be due to PTM rather than bleed over between two fractions. E do not know what the PTM is at this time. This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

J. Carboxypeptidase N Catalytic Chain

[0238] Name: Carboxypeptidase N catalytic chain precursor

IPI ID: IPI00021439

[0239] UniProtKB/Swiss-Prot entry ID: P15169

Length: 458 AA [This is the length of the unprocessed precursor]

Molecular weight: 52286 Da [This is the MW of the unprocessed precursor]

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0240] FUNCTION: Protects the body from potent vasoactive and inflammatory peptides containing C-terminal Arg or Lys (such as kinins or anaphylatoxins) which are released into the circulation. Note cleaves bradykinin!

[0241] CATALYTIC ACTIVITY: Release of a C-terminal basic amino acid, preferentially lysine.

[0242] SUBUNIT: Tetramer of two catalytic chains and two glycosylated inactive chains.

[0243] SUBCELLULAR LOCATION: Secreted/extracellular space

[0244] SIMILARITY: Belongs to the peptidase M14 family

2. Sequence

[0245]

(SEQ ID NO: 10)

MSDLLSVFLH LLLLFKLVAP VTFRHHRYDD LVRTLYKVQN ECPGITRVYS IGRSVEGRHL

YVLEFSDHPG IHEPLEPEVK YVGNMHGNEA LGRELMLQLS EFLCEEFRNR NQRIVQLIQD

TRIHILPSMN PDGYEVAAAQ GPNKPGYLVG RNNANGVDLN RNFPDLNTYI YYNEKYGGPN

HHLPLPDNWK SQVEPETRAV IRWMHSFNFV LSANLHGGAV VANYPYDKSF EHRVRGVRRT

ASTPTPDDKL FQKLAKVYSY AHGWMFQGWN CGDYFPDGIT NGASWYSLSK GMQDFNYLHY

NCFEITLELS CDKFPPEEEL QREWLGNREA LIQFLEQVHQ GIKGMVLDEN YNNLANAVIS

VSGINHDVTS GDHGDYFRLL LPGIYTVSAT APGYDPETVT VTVGPAEPTL VNFHLKRSIP

QVSPVRRAPS RRHGVRAKVQ PQARKKEMEM RQLQRGPA

3. Alternative Names:

[0246] CPN, Carboxypeptidase N polypeptide 1, Carboxypeptidase N small subunit; Lysine carboxypeptidase, Arginine carboxypeptidase, Kininase-1, Serum carboxypeptidase NSCPN, Anaphylatoxin inactivator, Plasma carboxypeptidase B Q5T287

Note on Sequence: Signal Sequence 1-20

4. Summary

[0247] Interesting protein, which may alter bradykinin levels and creatine kinase levels. Involved in early inflammatory response. Has been shown to be elevated after AMI based on activity assays. Although it has been shown that there is a high degree of variability in carboxypeptidase N in healthy subjects and does not change with acute myocardial infarction patients but may reach maximum at 48 h after onset of chest pain. It has not been studied in the context of myocardial ischemia or events leading up to MI.

K. Profilaggrin/Filaggrin

Name: Profilaggrin (Filaggrin)

IPI ID: IPI00746718

[0248] UniProtKB/Swiss-Prot entry ID: P20930 (note only 70% homology)

Length: 4061AA

[0249] Molecular weight: 435170 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0250] FUNCTION: Aggregates keratin intermediate filaments and promotes disulfide-bond formation among the intermediate filaments during terminal differentiation of mammalian epidermis

[0251] PTM: Filaggrin is initially synthesized as a large, insoluble, highly phosphorylated precursor containing many tandem copies of 324 AA, which are not separated by "large linker". The precursor is deposited as keratohyalin granules. During terminal differentiation it is dephosphorylated and proteolytically cleaved.

[0252] PTM: Undergoes deimination of some arginine residues (citrullination).

[0253] DISEASE: Defects in FLG are the cause of ichthyosis vulgaris [MIM:146700]; also known as ichthyosis simplex. The phenotypic characteristics of ichthyosis vulgaris include palmar hyperlinearity, keratosis pilaris and a fine scale that is most prominent over the lower abdomen, arms, and legs. Ichthyosis vulgaris is characterized histologically by absent or reduced keratohyalin granules in the epidermis and mild hyperkeratosis. The disease can be associated with frequent asthma, eczema or hay fever. Inheritance is autosomal dominant.

2. Sequence (IPI Sequence)

[0254]

(SEQ ID NO: 11)

MSTLLENIFAIINLFKQYSKKDKNTDTLSKKELKELLEKEFRQILKNPDDPDMVDVFMDH

LDIDHNKKIDFTEFLLMVFKLAQAYYESTRKENLPISGHKHRKHSHHDKHEDNKQEENKE

-continued

NRKRPSSLERRNNRKGNKGRSKSPRETGGKRHESSSEKKERKGYSPTHREEEYGKNHHNS

SKKEKNKTENTRLGDNRKRLSERLEEKEDNEEGVYDYENTGRMTQKWIQSGHIATYYTIQ

DEAYDTTDSLLEENKIYERSRSSDGKSSSQVNRSRHENTSQVPLQESRTRKRRGSRVSQD

RDSEGHSEDSERHSGSASRNHHGSAWEQSRDGSRHPRSHDEDRASHGHSADSSRQSGTRH

AETSSRGQTASSHEQARSSPGERHGSGHQQSADSSRHSATGRGQASSAVSDRGHRGSSGS

QASDSEGHSENSDTQSVSGHGKAGLRQQSHQESTRGRSGERSGRSGSFIYQVSTHEQSES

AHGRTRTSTGRRQGSGGEQARDSSRHSASQEGQDTIRAHPGSRRGGRQGSHHEQSVDRSG

HSGSHHSHTTSQGRSDVSRGQSGSRSVSRQTRNEKQSGDGSRHSGSRHHEASSRADSSRH

SQVGQGQSSGPRTSRNQGSSVSQDSDSQGHSEDSERRSGSASRNHHGSAQEQSRDGSRHP

RSHHEDRAHGHGSAESSRQSGTHHAENSSGGQAASSHEQARSSAGERHGSHHQQSADSSR

HSGIGHGQASSAVRDSGHRGSSGSQASDSEGHSEDSDTQSVSAHGQAGPHQQSHQESTRG

RSAGRSGRSGSFLYQVSTHEQSESAHGRTRTSTGRRQGSHHEQARDSSRHSASQEGQDTI

RGHPGSSRRGRQGSHYEQSVDRSGHSGSGGSGTTSQGTSDASRGQSGSRSASRQTRNDEQ

SGDGSRHSWSHHHEASTQADSSRHSQSGQGQSAGPRTSRNQGSSVSQDSDSQGHSEDSER

WSGSASRNHRGSAQEQSRDGSRHPTSHHEDRAGHGHSAESSRQSGTHHAENSSGGQAASS

HEQARSSAGERHGSHHQQSADSSRHSGIGHGQASSAVRDSGHRGSSGSQASDSEGHSEDS

DTQSVSAHGQAGPHQQSHQESTRGRSAGRSGRSGSFLYQVSTHEQSESAHGRAGPSTGGR

QGSRHEQARDSSRHSASQEGQDTIRGHPGSRRGGRQGSYHEQSVDRSGNSGSHHSHTTSQ

GRSDASHGQSGS

3. Summary

[0255] Peptides observed are unique to Filaggrin (and not to Ifapsoriasin or Hornerin). This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

L. Proteoglycan-4

[0256] Name: Isoform A and D of Proteoglycan-4 (we cannot distinguish isoforms due to high degree of sequence homology)

IPI ID: IPI00024825 and IPI00655676

[0257] UniProtKB/Swiss-Prot entry ID: Q92954, Q6DNC4, Q6DNC5, Q6ZMZ5, Q9BX49

Length: 1404 aa, molecular weight: 151077 Da

1. Sequence

[0258]

(SEQ ID NO: 12)

*MAWKTLPTYLLLLLSVFVIQQVSS*QDLSSCAGRCGEGYSRDATCNCDYNCQHYMECCPDF

KRVCTAELSCKGRCFESFERGRECDCDAQCKKYDKCCPDYESFCAEVHNPTSPPSSKKAP

PPSGASQTIKSTTKRSPKPPNKKKTKKVIESEEITEEHSVSENQESSSSSSSSSSSTIR

KIKSSKNSAANRELQKKLKVKDNKKNRTKKKPTPKPPVVDEAGSGLDNGDFKVTTPDTST

TQHNKVSTSPKITTAKPINPRPSLPPNSDTSKETSLTVNKETTVETKETTTTNKQTSTDG

KEKTTSAKETQSIEKTSAKDLAPTSKVLAKPTPKAETTTKGPALTTPKEPTPTTPKEPAS

TTPKEPTPTTIKSAPTTPKEPAPTTTKSAPTTPKEPAPTTTKEPAPTTPKEPAPTTTKEP

APTTTKSAPTTPKEPAPTTPKKPAPTTPKEPAPTTPKEPTPTTPKEPAPTTKEPAPTTPK

EPAPTAPKKPAPTTPKEPAPTTPDEPAPTTTKEPSPTTPKEPAPTTTKSAPTTTKEPAPT

TTKSAPTTPKEPSPTTTKEPAPTTPKEPAPTTPKKPAPTTPKEPAPTTPKEPAPTTTKKP

-continued

APTTPKEPAPTTPKETAPTTPKKLTPTTPEKLAPTTPEKPAPTTPEELAPTTPEEPTPTT

PEEPAPTTPKAAAPNTPKEPAPTTPKEPAPTTPKEPAPTTPKETAPTTPKGTAPTTLKEP

APTTPKKPAPKELAPTTTKEPTSTTCDKPAPTTPKGTAPTTPKEPAPTTPKEPAPTTPKG

TAPTTLKEPAPTTPKKPAPKELAPTTTKGPTSTTSDKPAPTTPKETAPTTPKEPAPTTPK

KPAPTTPETPPPTTSEVSTPTTTKEPTTIHKSPDESTPELSAEPTKALENSPKEPGVPT

TKTPAATKPEMTTTAKDKTTERDLRTTPETTTAAPKMTKETATTTEKTTESKITATTTQV

TSTTTQDTTPFKITTLKTTTLAPKVTTTKKTITTTEIMNKPEETAKPKDRATNSKATTPK

PQKPTKAPKKPTSTKKPKTMPRVRKPKTTPTPRKMTSTMPELNPTSRIAEAMLQTTTRPN

QTPNSKLVEVNPKSEDAGGAEGETPHMLLRPHVFMPEVTPDMDYLPRVPNQGIIINPMLS

DETNICNGKPVDGLTTLRNGTLVAFRGHYFWMLSPFSPPSPARRITEVWGIPSPIDTVFT

RCNCEGKTFFFKDSQYWRFTNDIKDAGYPKPIFKGFGGLTGQIVAALSTAKYKNWPESVY

FFKRGGSIQQYIYKQEPVQKCPGRRPALNYPVYGETTQVRRRRFERAIGPSQTHTIRIQY

SPARLAYQDKGVLHNEVKVSILWRGLPNVVTSAISLPNIRKPDGYDYYAFSKDQYYNIDV

PSRTARAITTRSGQTLSKVWYNCP

1	24	24	Potential. signal
25	1404	1380	Proteoglycan-4.
1307	1404	98	Proteoglycan-4 C-terminal part.
26	66	41	Missing (in isoform B, isoform D and isoform E).
107	199	93	Missing (in isoform C and isoform D).
157	199	43	Missing (in isoform F).
412	841	430	Missing (in isoform E).

2. Alternative Names:

[0259] Proteoglycan-4 precursor (Lubricin) (Megakaryocyte-stimulating factor) (Superficial zone proteoglycan) [Contains: Proteoglycan-4 C-terminal part].

3. Summary

[0260] PRG4 (proteoglycan 4) is a megakaryocyte stimulating factor and articular superficial zone protein which is expressed in cartilage, liver, heart, lung, and bone. It is known to be involved in the lubrication of mammalian joints. This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

M. Alpha-2-HS-Glycoprotein

Name: Alpha-2-HS-glycoprotein

IPI ID: IPI00022431

[0261] UniProtKB/Swiss-Prot entry ID: P02765

Length: 367 aa, molecular weight: 39325 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0262] FUNCTION Promotes endocytosis, possesses opsonic properties and influences the mineral phase of bone. Shows affinity for calcium and barium ions.

[0263] SUBUNIT Alpha-2-HS glycoprotein derives from this precursor, when the connecting peptide is cleaved off. The two chains A and B are held together by a single disulfide bond.

[0264] SUBCELLULAR LOCATION Secreted.

[0265] TISSUE SPECIFICITY Synthesized in liver and selectively concentrated in bone matrix. Secreted in plasma. It is also found in dentin in much higher quantities than other plasma proteins.

2. Sequence

[0266]

(SEQ ID NO: 13)

*MKSLVLLLCLAQLWGC*HSAPHGPGLIYRQPNCDDPETEEAALVAIDYINQ

NLPWGYKHTLNQIDEVKVWPQQPSGELFEIEIDTLETTCHVLDPTPVARC

SVRQLKEHAVEGDCDFQLLKLDGKFSVVYAKCDSSPDSAEDVRKVCQDC

PLLAPLNDTRVVHAAKAALAAFNAQNNGSNFQLEEISRAQLVPLPPSTY

VEFTVSGTDCVAKEATEAAKCNLLAEKQYGFCKATLSEKLGGAEVAVTC

TVFQTQPVTSQPQPEGANEAVPTPVVDPDAPPSPPLGAPGLPPAGSPP

DSHVLLAAPPGHQLHRAHYDLRHTFMGVVSLGSPSGEVSHPRKTRTVVQ

PSVGAAAGPVVPPCPGRIRHFKV

1-18 Signal Sequence

3. Alternative Names:

[0267] Alpha-2-HS-glycoprotein precursor (Fetuin-A) (Alpha-2-Z-globulin) (Ba-alpha-2-glycoprotein) [Contains: Alpha-2-HS-glycoprotein chain A; Alpha-2-HS-glycoprotein chain B].

[0268] 4. Summary
Very high abundant protein and found to change in many diseases and acts as a calcification inhibitor. It inhibits inflammation. It is elevated late after acute myocardial infarction but did not correlate with peak cardiac troponin values. This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

N. Protease, Serine, 3 (Mesotrypsinogen) IPI00748381

[0269] Name: Protease, serine, 3

IPI ID: IPI00748381

[0270] UniProtKB/Swiss-Prot entry ID: Q5JT15
Length: 249AA [This is the length of the unprocessed precursor]
Molecular weight: 26914 Da [This is the MW of the unprocessed precursor
1. Basic Information from UniProtKB/Swiss-Prot Entry
[0271] FUNCTION (mesotrypsinogen data): Preferential cleavage: Arg-|-Xaa, Lys-|-Xaa. Cofactor Binds 1 calcium ion per subunit.
[0272] INTERACTIONS: This protein binds to Amyloid beta A4 (which we observe but do not see changed) and tissue factor pathway inhibitor (see HPRD)
[0273] SUBCELLULAR LOCATION: Secreted.
[0274] TISSUE SPECIFICITY: Pancreas and brain.
2. Sequence Information from 2DLC
Note: this protein was identified in different fractions for ischemia vs AMI. This suggests that this protein has undergone a PTM with AMI and thus is physically distinct from the form present during ischemia. We do not know what this PTM(s) is at this time.

Sequence

[0275]

(SEQ ID NO: 14)

MSPFLILAFVGAAGEVAVPFDDDD**KIVGGYTCEENSLPYQVSLNSGSHFCGGSLISEQWV**

VSAAHCYKTRIQVRLGEHNIKVLEGNEQFINAAKIIRHPKYNRDTLDNDIMLIKLSSPAV

INARVSTISLPTTPPAAGTECLISGWGNTLSFGADYPDELKCLDAPVLTQAECKASYPGK

ITNSMFCVGFLEGGKDSCQRDSGGPVVCNGQLQGVVSWGHGCAWKNRPGVYTKVYNYVDW

IKDTIAANS

bold amino acids are trypsin-like domain

3. Alternative Names:

[0276] Uncharacterized protein PRSS3 A6NN76, Mesotrypsin C Q6ISJ4, Mesotrypsinogen C P35030-3 (98% homologous and not in region of the observed peptides), Isoform C of P35030 P35030-3, Isoform B of P35030 P35030-2. Based on HPRD this is the same protein as trypsinogen IV (has same sequence), protease serine, 4, TRY3, TRY4, trypsin 3, trypsin 4 (Brain), trypsinogen III (pancreatic).

Note: In swiss prot, mesotrysinogen has three isoforms—two of which are longer proteins at the N-terminus. We can not distinguish between the three isoforms.

Note on Sequence:

[0277] We cannot distinguish between the three highly conserved isoforms of mesotrypsinogen based on MS data.

4. Summary

[0278] Mesotrypsin is an inhibitor-resistant protease and is secreted from pancreatic juice. Whether it is present in the heart is not known. This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

O. Alpha-2-Glycoprotein 1, zinc IPI00166729

Name: alpha-2-glycoprotein 1, zinc

IPI ID: IPI00166729

[0279] UniProtKB/Swiss-Prot entry ID: Q8N4N0 Q5XKQ4

Length: 298 AA [This is the length of the unprocessed precursor]

Molecular weight: 34259 Da [This is the MW of the unprocessed precursor

1. Basic Information from UniProtKB/Swiss-Prot Entry

[0280] FUNCTION: Stimulates lipid degradation in adipocytes and causes the extensive fat losses associated with some advanced cancers. May bind polyunsaturated fatty acids.

[0281] SUBCELLULAR LOCATION: Secreted.

[0282] TISSUE SPECIFICITY: Blood plasma, seminal plasma, urine, saliva, sweat, epithelial cells of various human glands, liver.

2. Sequence

[0283]

(SEQ ID NO: 15)

MVRMVPVLLSLLLLLGPAVPQENQDGRYSLTYIYTGLSKHVEDVPAFQALGSLNDLQFFR

YNSKDRKSQPMGLWRQVEGMEDWKQDSQLQKAREDIFMETLKDIVEYYNDSNGSHVLQGR

FGCEIENNRSSGAFWKYYYDGKDYIEFNKEIPAWVPFDPAAQITKQKWEAEPVYVQRAKA

YLEEECPATLRKYLKYSKNILDRQDPPSVVVTSHQAPGEKKKLKCLAYDFYPGKIDVHWT

RAGEVQEPELRGDVLHNGNGTYQSWVVVAVPPQDTAPYSCHVQHSSLAQPLVVPWEAS

Note on sequence: note initiating Met is cleaved. There maybe a PTM with ischemia as the peptides elute at different fractions at T-1 and T-2. We do not know what the PTM is.

3. Alternative Names:

[0284] Alpha-2-glycoprotein 1 Q5XKQ4, zinc binding; zinc-alpha-2-glycoprotein P25311 (295 AA and 33872 Da, over 95% homology)

4. Summary

[0285] Zinc-alpha2-glycoprotein (ZAG) is a a lipid mobilizing factor found in adipose tissue. It is increased in a number of cancers. Nothing is known about with respect to the heart and myocardial ischemia. It has not been studied in the context of myocardial ischemia or events leading up to MI.

P. Desmoglein-1

Name: Desmoglein-1

IPI ID: IPI00025753

UniProtKB/Swiss-Prot: Q02413

[0286] Length: 1049 AA [This is the length of the unprocessed precursor]

Molecular Weight: 113716 Da

[0287] 1. Basic Information from UniProtKB/Swiss-Prot Entry Q02413

[0288] FUNCTION: Component of intercellular desmosome junctions. Involved in the interaction of plaque proteins and intermediate filaments mediating cell-cell adhesion.

[0289] SUBCELLULAR LOCATION: Cell membrane; Single-pass type I membrane protein (By similarity).

[0290] SIMILARITY: Contains 4 cadherin domains

[0291] TISSUE SPECIFICITY: Epidermis, tongue, tonsil and esophagus.

[0292] DISEASE: Defects in DSG1 are the cause of keratosis palmoplantaris striata I (PPKS1) [MIM: 148700]; also known as striate palmoplantar keratoderma I (SPPK1). PPKS1 is an autosomal dominant disease characterized by thickening of the skin on the palms and soles, and longitudinal hyperkeratotic lesions on the palms, running the length of each finger.

Protein ID data

SEPARATION METHOD: 2DE

EXPECTED MOLECULAR WEIGHT/PI: 113716 Da/4.90

OBSERVED MOLECULAR WEIGHT/PI: 59 KD/5.8

[0293] NOTE: It could be processed the product.

2. Sequence

[0294]

(SEQ ID NO: 16)

MDWSFFRVVAVLFIFLVVVEVNSEFRIQVRDYNTKNGTIKWHSIRRQKREWIKFAAACRE

GEDNSKRNPIAKIHSDCAANQQVTYRISGVGIDQPPYGIFVINQKTGEINITSIVDREVT

PFFIIYCRALNSMGQDLERPLELRVRVLDINDNPPVFSMATFAGQIEENSNANTLVMILN

ATDADEPNNLNSKIAFKIIRQEPSDSPMFIINRNTGEIRTMNNFLDREQYGQYALAVRGS

DRDGGADGMSAECECNIKILDVNDNIPYMEQSSYTIEIQENTLNSNLLEIRVIDLDEEFS

ANWMAVIFFISGNEGNWFEIEMNERTNVGILKVVKPLDYEAMQSLQLSIGVRNKAEFHHS

IMSQYKLKASAISVTVLNVIEGPVFRPGSKTYVVTGNMGSNDKVGDFVATDLDTGRPSTT

-continued

VRYVMGNNPADLLAVDSRTGKLTLKNKVTKEQYNMLGGKYQGTILSIDDNLQRTCTGTIN

INIQSFGNDDRTNTEPNTKITTNTGRQESTSSTNYDTSTTSTDSSQVYSSEPGNGAKDLL

SDNVHFGPAGIGLLIMGFLVLGLVPFLMICCDCGGAPRSAAGFEPVPECSDGAIHSWAVE

GPQPEPRDITTVIPQIPPDNANIIECIDNSGVYTNEYGGREMQDLGGGERMTGFELTEGV

KTSGMPEICQEYSGTLRRNSMRECREGGLMNFMESYFCQKAYAYADEDEGRPSNDCLLI

YDIEGVGSPAGSVGCCSFIGEDLDDSFLDTLGPKFKKLADISLGKESYPDLDPSWPPQST

EPVCLPQETEPVVSGHPPISPHFGTTTVISESTYPSGPGVLHPKPILDPLGYGNVTVTES

YTTSDTLKPSVHVHDNRPASNVVVTERVVGPISGADLHGMLEMPDLRDGSNVIVTERVIA

PSSSLPTSLTIHHPRESSNVVVTERVIQPTSGMIGSLSMHPELANAHNVIVTERVVSGAG

VTGISGTTGISGGIGSSGLVGTSMGAGSGALSGAGISGGGIGLSSLGGTASIGHMRSSSD

HHFNQTIGSASPSTARSRITKYSTVQYSK

3. Summary

[0295] This protein is part of the desmosome cell junctions in many cell types including the heart. The protein is the antigen for Pemphigus foliaceus is an autoimmune skin disease. It binds to plakophilin 1, plakophilin 2, desmoplakin, desmoglein 1, desmoglein 4, plakoglobin and corneodesmosin, all of which maybe potential biomarkers in myocardial ischemia. It has not been studied in the context of myocardial ischemia or events leading up to MI.

Q. Caspase-14

Name: Caspase-14

IPI ID: IPI00013885

UniProtKB/Swiss-Prot: P31944

[0296] Length: 242 AA [this is the length of the unprocessed precursor]

[0297] propeptide=1-? AA

[0298] sub-unit 1=?-146 AA,

[0299] sub-unit 2=147-242 AA

Molecular Weight: 27680 Da [this is the MW of the unprocessed precursor]

1. Basic information from UniProtKB/Swiss-Prot Entry P31944

[0300] FUNCTION: May be involved in the death receptor and granzyme B apoptotic pathways. May function as a downstream signal transducer of cell death.

[0301] SUBUNIT: May dimerize with large prodomain caspases.

[0302] SUBCELLULAR LOCATION: Cytoplasm (By similarity).

Protein ID data

Separation method: 2DE

Expected molecular weight/pI: 27680 Da/5.44 (pro-caspase-14=242 AA)

Observed molecular weight/pI: 68000 Da/6.8,

Note: There is difference in observed and expected MW, multiple proteins complex?

2. Sequence

[0303]

(SEQ ID NO: 17)

MSNPRSLEEE KYDMSGARLA LILCVTKARE GSEEDLDALE HMFRQLRFES TMKRDPTAEQ

FQEELEKFQQ AIDSREDPVS CAFVVLMAHG REGFLKGEDG EMVKLENLFE ALNNKNCQAL

RAKPKVYIIQ ACRGEQRDPG ETVGGDEIVM VIKDSPQTIP TYTDALHVYS TVEGYIAYRH

DQKGSCFIQT LVDFTKRKG HILELLTEVT RRMAEAELVQ EGKARKTNPE IQSTLRKRLY

LQ

3. Summary

[0304] Casp14 may play a role in ontogenesis and skin physiology. CASP14 cDNA and determined that CASP14 contains 7 exons encoding a 242-amino acid protein, 2 CASP14 transcripts (CASP14a and CASP14b) differ in the C terminus while an alternative splice acceptor site within intron 5 results in a 74-nucleotide insertion in CASP14b. CASP14b lacks homology with the caspase consensus sequence. CASP14 has been found in epidermis, hair follicles, the sebaceous gland. NO treatment of neonatal mouse cardiomyocytes in culture causes increase in caspase 14. There is also increase in this protein in canine brain during cardiac arrest and resuscitation. This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

R. Hornerin

Name: HORNERIN

IPI ID: IPI00398625

UniProtKB/Swiss-Prot ID: Q86YZ3

[0305] Length: 2850 aa, molecular weight: 282390 Da
1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	May play a role in cornification.
SUBCELLULAR LOCATION	Cytoplasmic granule (By similarity). Note = Found in keratohyalin granules in the granular cells of the epidermis (By similarity).

2. Sequence:

[0306]

(SEQ ID NO: 18)

MPKLLQGVITVIDVFYQYATQHGEYDTLNKAELKELLENEFHQILKNPND

PDTVDIILQSLDRDHNKKVDFTEYLLMIFKLVQARNKIIGKDYCQVSGSK

LRDDTHQHQEEQEETEKEENKRQESSFSHSSWSAGENDSYSRNVRGSLKP

GTESISRRLSFQRDFSGQHNSYSGQSSSYGEQNSDSHQSSGRGQCGSGSG

QSPNYGQHGSGSGQSSSNDTHGSGSGQSSGFSQHKSSSGQSSGYSQHGSG

SGHSSGYGQHGSRSGQSSRGERHRSSSGSSSSYGQHGSGSRQSLGHGRQG

SGSRQSPSHVRHGSGSGHSSSHGQHGSGSSYSYSRGHYESGSGQTSGFGQ

HESGSGQSSGYSKHGSGSGHSSSQGQHGSTSGQASSSGQHGSSSRQSSSY

GQHESASRHSSGRGQHSSGSGQSPGHGQRGSGSGQSPSSGQHGTGFGRSS

SSGPYVSGSGYSSGFGHHESSSEHSSGYTQHGSGSGHSSGHGQHGSRSGQ

SSRGERQGSSAGSSSSYGQHGSGSRQSLGHSRHGSGSGQSPSPSRGRHES

GSRQSSSYGPHGYGSGRSSSRGPYESGSGHSSGLGHQESRSGQSSGYGQH

GSSSGHSSTHGQHGSTSGQSSSCGQHGATSGQSSSHGQHGSGSSQSSRYG

QQGSGSGQSPSRGRHGSDFGHSSSYGQHGSGSGWSSSNGPHGSVSGQSSG

FGHKSGSGQSSGYSQHGSGSSHSSGYRKHGSRSGQSSRSEQHGSSSGLSS

SYGQHGSGSHQSSGHGRQGSGSGHSPSRVRHGSSSGHSSSHGQHGSGTSC

-continued

SSSCGHYESGSGQASGFGQHESGSGQGYSQHGSASGHFSSQGRHGSTSGQ

SSSSGQHDSSSGQSSSYGQHESASHHASGRGRHGSGSGQSPGHGQRGSGS

GQSPSYGRHGSGSGRSSSSGRHGSGSGQSSGFGHKSSSGQSSGYTQHGSG

SGHSSSYEQHGSRSGQSSRSEQHGSSSGSSSSYGQHGSGSRQSLGHGQHG

SGSGQSPSPSRGRHGSGSGQSSSYGPYRSGSGWSSSRGPYESGSGHSSGL

GHRESRSGQSSGYGQHGSSSGHSSTHGQHGSTSGQSSSCGQHGASSGQSS

SHGQHGSGSSQSSGYGRQGSGSGQSPGHGQRGSGSRQSPSYGRHGSGSGR

SSSSGQHGSGLGESSGFGHHESSSGQSSSYSQHGSGSGHSSGYGQHGSRS

GQSSRGERHGSSSGSSSHYGQHGSGSRQSSGHGRQGSGSGHSPSRGRHGS

GLGHSSSHGQHGSGSGRSSSRGPYESRSGHSSVFGQHESGSGHSSAYSQH

GSGSGHFCSQGQHGSTSGQSSTFDQEGSSTGQSSSYGHRGSGSSQSSGYG

RHGAGSGQSPSRGRHGSGSGHSSSYGQHGSGSGWSSSSGRHGSGSGQSSG

FGHHESSSWQSSGCTQHGSGSGHSSSYEQHGSRSGQSSRGERHGSSSGSS

SSYGQHGSGSRQSLGHGQHGSGSGQSPSPSRGRHGSGSGQSSSYSPYGSG

SGWSSSRGPYESGSSHSSGLGHRESRSGQSSGYGQHGSSSGHSSTHGQHG

STSGQSSSCGQHGASSGQSSSHGQHGSGSSQSSGYGRQGSGSGQSPGHGQ

RGSGSRQSPSYGRHGSGSGRSSSSGQHGSGLGESSGFGHHESSSGQSSSY

SQHGSGSGHSSGYGQHGSRSGQSSRGERHGSSSRSSSRYGQHGSGSRQSS

GHGRQGSGSGQSPSRGRHGSGLGHSSSHGQHGSGSGRSSSRGPYESRSGH

SSVFGQHESGSGHSSAYSQHGSGSGHFCSQGQHGSTSGQSSTFDQEGSST

GQSSSHGQHGSGSSQSSSYGQQGSGSGQSPSRGRHGSGSGHSSSYGQHGS

GSGWSSSSGRHGSGSGQSSGFGHHESSSWQSSGYTQHGSGSGHSSSYEQH

GSRSGQSSRGEQHGSSSGSSSSYGQHGSGSRQSLGHGQHGSGSGQSPSPS

RGRHGSGSGQSSSYGPYGSGSGWSSSRGPYESGSGHSSGLGHRESRSGQS

SGYGQHGSSSGHSSTHGQHGSASGQSSSCGQHGASSGQSSSHGQHGSGSS

QSSGYGRQGSGSGQSPGHGQRGSGSRQSPSYGRHGSGSGRSSSSGQHGPG

LGESSGFGHHESSSGQSSSYSQHGSGSGHSSGYGQHGSRSGQSSRGERHG

SSSGSSSRYGQHGSGSRQSSGHGRQGSGSGHSPSRGRHGSGSGHSSSHGQ

HGSGSGRSSSRGPYESRSGHSSVFGQHESGSGHSSAYSQHGSGSGHFCSQ

GQHGSTSGQSSTFDQEGSSTGQSSSHGQHGSGSSQSSSYGQQGSGSGQSP

SRGRHGSGSGHSSSYGQHGSGSGWSSSSGRHGSGSGQSSGFGHHESSSWQ

SSGYTQHGSGSGHSSSYEQHGSRSGQSSRGERHGSSSGSSSSYGQHGSGS

RQSLGHGQHGSGSGQSPSPSRGRHGSGSGQSSSYSPYGSGSGWSSSRGPY

ESGSGHSSGLGHRESRSGQSSGYGQHGSSSGHSSTHGQHGSTSGQSSSCG

QHGASSGQSSSHGQHGSGSSQSSGYGRQGSGSGQSPGHGQRGSGSRQSPS

YGRHGSGSGRSSSSGQHGSGLGESSGFGHHESSSGQSSSYSQHGSGSGHS

SGYGQHGSRSGQSSRGERHGSSSGSSSHYGQHGSGSRQSSGHGRQGSGSG

QSPSRGRHGSGLGHSSSHGQHGSGSGRSSSRGPYESRLGHSSVFGQHESG

SGHSSAYSQHGSGSGHFCSQGQHGSTSGQSSTFDQEGSSTGQSSSYGHRG

-continued

SGSSQSSGYGRHGAGSGQSLSHGRHGSGSGQSSSYGQHGSGSGQSSGYSQ

HGSGSGQDGYSYCKGGSNHDGGSSGSYFLSFPSSTSPYEYVQEQRCYFYQ

Little is known about this protein. It has not been studied in the context of myocardial ischemia or events leading up to MI.

S. Kininogen

Name: ISOFORM LMW OF KININOGEN-1

IPI ID: IPI00215894

UniProtKB/Swiss-Prot ID: P01042

[0307] Length: 427 aa, molecular weight: 47883 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	(1) Kininogens are inhibitors of thiol proteases; (2) HMW-kininogen plays an important role in blood coagulation by helping to position optimally prekallikrein and factor XI next to factor XII; (3) HMW-kininogen inhibits the thrombin- and plasmin- induced aggregation of thrombocytes; (4) the active peptide bradykinin that is released from HMW-kininogen shows a variety of physiological effects: (4A) influence in smooth muscle contraction, (4B) induction of hypotension, (4C) natriuresis and diuresis, (4D) decrease in blood glucose level, (4E) it is a mediator of inflammation and causes (4E1) increase in vascular permeability, (4E2) stimulation of nociceptors (4E3) release of other mediators of inflammation (e.g. prostaglandins), (4F) it has a cardioprotective effect (directly via bradykinin action, indirectly via endothelium-derived relaxing factor action); (5) LMW-kininogen inhibits the aggregation of thrombocytes; (6) LMW-kininogen is in contrast to HMW-kininogen not involved in blood clotting.
SUBCELLULAR LOCATION	Secreted, extracellular space.

2. Sequence:

[0308]

(SEQ ID NO: 19)

MKLITILFLCSRLLLSLTQESQSEEIDCNDKDLFKAVDAALKKYNSQN

QSNNQFVLYRITEATKTVGSDTFYSFKYEIKEGDCPVQSGKTWQDCE

YKDAAKAATGECTATVGKRSSTKFSVATQTCQITPAEGPVVTAQYD

CLGCVHPISTQSPDLEPILRHGIQYFNNNTQHSSLFMLNEVKRAQRQ

VVAGLNFRITYSIVQTNCSKENFLFLTPDCKSLWNGDTGECTDNAYI

DIQLRIASFSQNCDIYPGKDFVQPPTKICVGCPRDIPTNSPELEETLTH

TITKLNAENNATFYFKIDNVKKARVQVVAGKKYFIDFVARETTCSKES

NEELTESCETKKLGQSLDCNAEVYVVPWEKKIYPTVNCQPLGMISL

MKRPPGFSPFRSSRIGEIKEETTSHLRSCEYKGRPPKAGAEPASER

EVS

3. Alternative Name(s):

[0309] High molecular weight kininogen, Short name=HMWK; Williams-Fitzgerald-Flaujeac factor; Fitzgerald factor; Alpha-2-thiol proteinase inhibitor

This protein has not been studied in the context of myocardial ischemia or events leading up to MI.

Example III

Further Studies to Identify Cardiac Biomarkers, Using as a Cohort of Patients, a Valve Replacement Cardioplegia Human Model (Cohort II)

A. Overview of the Studies

[0310] The 21 patients in this cohort all underwent aortic valve replacement surgery (See FIGS. **6** and **7**). Table 10 provides cohort information of this model.

TABLE 10

patient sampling
T1 pre-op sample (before incision).
T2 immediately before the heart gets stopped (prior to CPB).
T6 5 min after the heart went off CPB and was beating on its own again.
T7 30 min after bypass

TABLE 10-continued

patient sampling
T8 60 min after bypass
T9 120 min after bypass

There were 6 plasma samples taken. Note that only 19 (out of 21) patients have samples at T9. The sample were normalized to total protein concentration for both targeted and de novo discovery. In the targeted analysis, 15 biomarkers were determined for each sample, specifically, CRP, GM-CSF, IFNγ, IL10, IL12p70, IL1β, IL-2, IL-6, IL-8, NT proBNP, SAA, TNFα, cTnI, sICAM, sVCAM. All time points were analyzed. These analyses were done using the MESOSCALE multiplex assay in triplicate. FIG. **7** shows the box blot for cTnI measurement for all patients. For de novo discovery, only T2 and T6 were analyzed.

B. Methods

1. High Abundant Protein Depletion

[0311] IgY depletion of the top 12 abundant proteins of samples from each individual sample.

2. Intact Protein Separation by Hydrophobicity

[0312] 1DLC analysis was carried out for cohort II (20 patients with two time points). All 1DLC analyses were done in duplicate using the optimized gradient developed to elimi-

nate the interference of the unknown contaminates that eluted at the beginning and end of the run. Optimization was required as the contaminants were not MS compatible and co-eluted with proteins found to be interesting in cohort I. The duplicate run for each patient time point were collected into a single plate and stored at −80° C. until analyzed. A total of 80 @ 1DLC runs were carried out (20×2×2=80 (2 time points, 20 patients, in duplicate)). The fractions obtained for each 1DLC run were pooled into 16 fractions, neutralized and dried down, prior to resolublization in buffer compatible for tryptic digestion.

3. MS Analysis

[0313] MS analysis for each digested fraction was carried using the LTQ Orbitrap LC MSMS instrument. Each fraction was run in duplicate. A total 1216 MS runs were carried out (19×2×16×2=1216 (19 patients, 16 fractions per time point, two time points, in duplicate). For LC-MS/MS experiments on the LTQ-Orbitrap (ThermoFinnigan, San Jose, Calif.), peptides were dissolved in 6 μl resuspension buffer (4% acetonitrile in water with 0.1% formic acid). Samples (3 μl were loaded onto a 75 um×10 cm BioBasic C18 column (New Objective, Woburn, Mass.). Peptides were eluted into an LTQ-Orbitrap (ThermoFinnigan, San Jose, Calif.) using an Agilent 1200 nano-LC system (Agilent, Santa Clara, Calif.). The HPLC gradient was 5% to 60% B (90% acetonitrile/water in 0.1% Formic acid) over 30 or 60 min depended on sample complexity. The mass spectrometer was operated in data-dependent mode in which every FT-MS scan (survey 350-2000 Da) was followed by MS/MS scans of the 5 most abundant ions.

[0314] Mass spectrometry data were analyzed, and data reanalysis was carried out, as described in Example 1D2 above.

C. Results

1. Optimization of 1DLC

[0315] In order for cohort II to be analyzed, optimization of the 1DLC gradient was required to resolve a contaminating peak eluting early on the chromatogram. The contaminating peak overlaid a region in which we found several potential biomarkers and resulted in suppression of the peptides of interest.

2. Optimization and Testing of Reproducibility of MS Analysis

[0316] In table 11, the MS reproducibility of several fractions is shown.

TABLE 11

MS reproducibility cohort II sequential. MS run 1 vs. run 2
Same LC fraction, digested, split and MS analyzed

Method for cohort II Fraction 1 Protein name	run 1 # peptides Fraction 1	run 2 # peptides fraction 1	run 1 # total spectra Fraction 1	run 2 # total spectra Fraction 1
histidine-rich glycoprotein	14	13	35	32
factor H	12	11	27	24
Kininogen 1	10	11	15	18
complement component 4 binding protein	8	10	14	19
Lactoferrin	7	8	16	14
apolipoprotein H	5	4	12	13
Transferrin	5	5	20	18
alpha-1-acid glycoprotein 1	4	4	13	11
haptoglobin	3	4	6	7
fibrinogen, alpha p	3	3	5	5
plasminogen	3	3	6	6
Alpha-1B-glycoprotein	2	0	2	0
alpha2-HS glycoprotein	2	2	3	3
collagen 1 pro-alpha-2 chain	2	1	3	2
selenoprotein P	2	2	5	6
Extracellular matrix protein 1	2	2	3	4
Fraction 2 **Protein name**	**# peptides** **Fraction 2**	**# peptides** **Fraction 2**	**# total spectra** **Fraction 2**	**# total spectra** **Fraction 2**
complement component C4	27	26	49	47
Antithrombin	22	20	52	78
complement component 3	22	24	42	50
Fibronectin 1	21	24	38	55
Ceruloplasmin	19	21	49	52
Inter-alpha-trypsin inhibitor heavy chain H4	14	12	29	25
Inter-alpha-trypsin inhibitor heavy chain H2	13	15	29	30
Alpha-1B-glycoprotein	11	10	28	24
Alphal Antichymotrypsin	10	11	46	50
Complement factor B	9	11	23	28
gelsolin isoform b	9	9	19	16
leucine-rich alpha-2-glycoprotein 1	9	7	28	16
Inter-alpha-trypsin inhibitor heavy chain H1	9	8	28	37
Kininogen	8	10	18	20
histidine-rich glycoprotein	7	7	15	13
apolipoprotein A-IV	6	9	12	16
alpha2-HS glycoprotein	5	5	8	9

TABLE 11-continued

MS reproducibility cohort II sequential. MS run 1 vs. run 2
Same LC fraction, digested, split and MS analyzed

peroxiredoxin 2 isoform	5	4	10	19
Transthyretin	4	4	9	10
complement component C6	4	2	13	4
lumican	3	3	14	5
carboxypeptidase B2 isoform a preproprotein	3	2	5	6
apolipoprotein H precursor	2	4	6	21
Transferrin	2	2	3	3
amyloid P	2	0	2	0
alpha-l-microglobulin	2	2	4	4
Retinol binding protein 4	2	2	3	4
complement component 8, alpha	2	1	3	1
serine or cysteine proteinase inhibitor	2	2	2	2
complement component 4 binding protein	1	1	2	1
hemoglobin	1	0	3	0
C9 complement protein	1	0	2	0
alpha-l-acid glycoprotein 1	0	0	0	0
complement factor H-related 1	0	1	0	2
alpha-l-antichymotrypsin	0	2	0	8

3. Cohort II Analysis

[0317] 343 non-redundant proteins were compared. Table 12 shows those proteins which were most significantly increased in T6 compared to T0 for cohort II.

TABLE 12

Target proteins in cohort II

Top hits from cohort II clustered based on related protein family. Below listed the number of individuals the protein was elevated in T6 compared to T2 (increased due to induced ischemia). 20 individuals were analyzed.

1. PRDX2 Peroxiredoxin 2 - increased in 17 patients
2. S100A9 Protein S100-A9 - increased in 17 patients
   S100 A8 - increased in 11 patients
   S100 A7- increased in 4 patients
3. Lactotransferrin increased in 14 patients
4. CA1 Carbonic anhydrase 1 - increased in 17 patients
   CA2 Carbonic anhydrase 2 - increased in 3 patients
5. Conserved hypothetical protein - increased in 12 patients
6. NCOR2 CTG26 alternate open reading frame (Fragment) - increased in 11 patients
7. LOC729968 Conserved hypothetical protein - increased in 11 patients
8. Conserved hypothetical protein - increased in 9 patients
9. SORL1 Sortilin-related receptor - increased in 11 patients
10. COL1A1 Collagen alpha-1(I) chain precursor - increased in 11 patients
    COL1A2 130 kDa protein - increased in 10 patients
11. CPB2 Isoform 1 of Carboxypeptidase B2 precursor - increased in 10 patients
    Carboxypeptidase subunit 2 - increased in 8 patients
12. HBB Hemoglobin subunit beta - increased in 12 patients
    HBA Hemoglobin subunit alpha - increased in 4 patients
13. Lactotransferrin - increased in 12 patients
14. LRP1 Prolow-density lipoprotein receptor-related protein 1 precursor - increased in 9 patients
    LRP2 Low-density lipoprotein receptor-related protein 2 precursor - increased in 9 patients
    Together a total of 13 unique patients
15. CAT Catalase - increased in 11 patients
16. STX3 Isoform A of Syntaxin-3 - increased in 9 patients
17. ECM1 Extracellular matrix protein 1 - increased in 10 patients
18. SERPINA10 Protein Z-dependent protease inhibitor precursor - increased in 8 patients
19. PTPRK Isoform 1 of Receptor-type tyrosine-protein phosphatase kappa precursor increased in 8 patients
20. ATRN Isoform 2 of Attractin precursor - increased in 8 patients
21. PTPRK Protein tyrosine phosphatase, receptor type, K increased in 6 patients

Others of interest due to biology (there are low abundant proteins and may not be observed in higher number of patients due to detection issues)

22. MST1 Hepatocyte growth factor-like protein precursor - increased in 7 patients
    HGFAC Hepatocyte growth factor activator precursor - increased in 4 patients

TABLE 12-continued

Target proteins in cohort II
23. IGFBP6 Insulin-like growth factor-binding protein 6 precursor - increased in 5 patients IGFBP5 Insulin-like growth factor-binding protein 5 precursor - increased in 1 patients IGFBP2 Insulin-like growth factor-binding protein 2 precursor - increased in 7 patients (same ones as 7) IGFBP7 Insulin-like growth factor-binding protein 7 precursor - increased in 7 patients (same ones as 2) IGFALS Insulin-like growth factor-binding protein complex acid labile chain precursor - increased in 3 patients Total for group 8 patients
24. SERPINF1 Pigment epithelium-derived factor precursor - increased in 4 patients
25. GPX3 Glutathione peroxidase 3 precursor - increased in 4 patients
26. CD14 Monocyte differentiation antigen CD14 precursor - increased in 4 patients
27. Note there are interesting proteins seen in 2-3 patients which may still be important alternations which are not seen in more patients due to their low abundance. These should be discussed. A summary of some of the properties of these proteins is presented in Example IV.

4. Cohort II and I Comparison

[0318] Comparison of the top candidate proteins between cohort I and II are shown in Table 13.

TABLE 13

Protein	IPI number	Cohort I	Cohort II	FUNCTION	Is protein secreted?
Tier One					
Lumican	IPI00020986	Top	Found	May be involved in cell response to injury	Yes
Extracellular matrix protein	IPI00645849	Top	Found	Involved in extracellular matrix compostition	Yes
Carboxypeptidase N catalytic chain	IPI00010295	Mid	Found	Protease involved in regulation of vasoactive and inflammatory peptides	Yes
angiogenin	IPI00008554	Top	no	May be involved in angiogeneisis	Yes
semenogelin	IPI00414684	Top	no	Forms gel matrix around sperm, unknown role in other cells	Yes
Lung PLNECA-1	IPI00291410	Top	no	May play a role in innate immunity	Yes
Perioxiredoxin 2	IPI00027350	No	Elevated in 17, Top	Involved in redox regulation of the cell.	No
S100 A9	IPI00027462	No	Elevated in 17, Top	Expressed by macrophages in acutely inflamed tissues and in chronic inflammations.	No
S100 A8	IPI00007047	No	Elevated in 11, Top	Expressed by macrophages in chronic inflammations. Also expressed in epithelial cells constitutively or induced during dermatoses.	unknown
S100 A7	IPI00219806	No	Elevated in 4, Lower	unknown	Secreted
Sortilin-related receptor	IPI00022608	No	Elevated in 11, Mid	Likely to be a multifunctional endocytic receptor, which implicates it in the uptake of lipoproteins and of proteases.	No, is a plasma membrane protein
Catalase	IPI00465436	No	Elevated in 11, Mid	Serves to protect cells from the toxic effects of hydrogen peroxide.	No
Low density lipoprotein receptor related protein 1	IPI00020557	No	Elevated in 9, Mid	Endocytic receptor involved in endocytosis and in phagocytosis of apoptotic cells.	No
Low density lipoprotein receptor related protein 2	IPI00024292	No	Elevated in 9, Top	Acts together with cubilin to mediate HDL endocytosis (By similarity).	No
Syntaxin-3	IPI00395768	No	Evelated in 9, Mid	Potentially involved in docking of synaptic vesicles at presynaptic active zones.	No

TABLE 13-continued

Protein	IPI number	Cohort I	Cohort II	FUNCTION	Is protein secreted?
Tier two					
Hepatocyte growth factor like protein	IPI00292218		+	Unknown	Unknown
Hepatocyte growth factor activator	IPI00029193		+	Activates hepatocyte growth factor (HGF).	Secreted.
Insulin like growth factor protein 6	IPI00029235		+	GF-binding proteins prolong the half-life of the IGFs.	Secreted.
Pigment epithelium-derived factor	IPI00006114		+	Neurotrophic protein; induces extensive neuronal differentiation in retinoblastoma cells. Potent inhibitor of angiogenesis.	Secreted.
Glutathione peroxidase 3	IPI00026199		+	Protects cells and enzymes from oxidative damage.	Secreted.
Monocyte differentiation antigen CD14	IPI00029260		+	Involved in the innate immune response to bacterial lipopolysaccharide (LPS).	No
Lactotransferrin, cDNA FLJ58679, highly similar to Lactotransferrin	IPI00789477		+	unknown	unknown
Attractin	IPI00162735			Involved in the initial immune cell clustering during inflammatory response.	Secreted
Conserved hypothetical protein	IPI00883661		+	Unknown	Unknown
NCOR2 CTG26 alternate open reading frame	IPI00006659		+	unknown	unknown
LOC729968 Conserved hypothetical protein	IPI00884334		+	unknown	unknown
Protein Z-dependent protease inhibitor	IPI00007199		+	Inhibits factor Xa activity.	Secreted.
Conserved hypothetical protein	IPI00847894			unknown	unknown
Isoform 1 of Receptor-type tyrosine-protein phosphatase kappa	IPI00015756		+	Regulation of processes involving cell contact and adhesion such as growth control, tumor invasion, and metastasis.	No, but present on plasma membrane
Protein tyrosine phosphatase, receptor type, K	IPI00552690		+	Receptor	Unknown, but present on plasma membrane
Sodium channel subunit beta-4	IPI00217376		Elevated in 7 people	Part of sodium channel	No, but present on plasma membrane
Alpha2-HS-glycoprotein	IPI00022431	+	Elevated in 4 people	See previous write up for cohort I	See previous write up for cohort I
Galectin 7	IPI00219221	+	–	See previous write up for cohort I	See previous write up for cohort I
Hornerin	IPI00398625	+	Elevated and seen only in one person	See previous write up for cohort I	See previous write up for cohort I
Proteoglycan 4 (isoforms A and D)	IPI00655676	+	Elevated in 4 people	See previous write up for cohort I	See previous write up for cohort I
Proflaggrin (Filaggrin)	IPI00654788	+	–	See previous write up for cohort I	See previous write up for cohort 1
Vitamin D binding protein	IPI00555812	+	–	See previous write up for cohort I	See previous write up for cohort 1
C4b binding proteins	IPI00021727	+	–	See previous write up for cohort I	See previous write up for cohort 1

TABLE 13-continued

Protein	IPI number	Cohort I	Cohort II	FUNCTION	Is protein secreted?
Thyroxine binding globulin	IPI00292946	+	–	See previous write up for cohort I	See previous write up for cohort 1
Alpha 2 glycoprotein 1, zinc	IPI00166729	+	Elevated in 3 people	See previous write up for cohort I	See previous write up for cohort I
Caspase 14		+		See previous write up for cohort I	See previous write up for cohort 1
Desmogelin		+		See previous write up for cohort I	See previous write up for cohort 1
Kininogen -1	IPI00215894	+		See previous write up for cohort I	See previous write up for cohort I

[0319] Some additional proteins were found to be elevated in a subset of the patients in cohort II that exhibit ischemia. See Table 14 below for details.

TABLE 14

Protein name	Protein accession numbers	# individal with ischemic induced increase (max. 20)
PRDX2 Peroxiredoxin-2	IPI00027350	17
S100A9 Protein S100-A9	IPI00027462	17
LTF Similar to Lactotransferrin	IPI00789477	14
Conserved hypothetical protein	IPI00883661	12
HBB Hemoglobin subunit beta	IPI00654755	12
NCOR2 CTG26 alternate open reading frame	IPI00006659	11
S100A8 Protein S100-A8	IPI00007047	11
SORL1 Sortilin-related receptor	IPI00022608	11
CA1 Carbonic anhydrase 1	IPI00215983	11
COL1A1 Collagen alpha-1(I) chain	IPI00297646	11
CAT Catalase	IPI00465436	11
ALB Isoform 1 of Serum albumin	IPI00745872	11
LOC729968 Conserved hypothetical protein	IPI00884334	11
CFI Complement factor I	IPI00291867	10
CPB2 Isoform 1 of Carboxypeptidase B2	IPI00329775	10
Ig heavy chain V-II region OU	IPI00382534	10
Ig kappa chain V-I region Ka	IPI00387095	10
COL1A2 130 kDa protein	IPI00873137	10
ECM1 Extracellular matrix protein 1	IPI00645849	10
LRP1 Prolow-density lipoprotein receptor-related protein 1	IPI00020557	9
LRP2 Low-density lipoprotein receptor-related protein 2	IPI00024292	9
C7 Complement component C7	IPI00296608	9
STX3 Isoform A of Syntaxin-3	IPI00395768	9
SERPINA1 Isoform 1 of Alpha-1-antitrypsin	IPI00553177	9
LOC440786 Ig kappa chain V-II region TEW	IPI00736885	9
Conserved hypothetical protein	IPI00847894	9
SERPINA10 Protein Z-dependent protease inhibitor	IPI00007199	8
PTPRK Isoform 1 of Receptor-type tyrosine-protein phosphatase kappa	IPI00015756	8
AMBP AMBP protein	IPI00022426	8
TF Serotransferrin	IPI00022463	8
C5 Complement C5	IPI00032291	8
ATRN Isoform 2 of Attractin	IPI00162735	8
C1QB complement component 1, q subcomponent, B chain	IPI00477992	8
CPN2 Carboxypeptidase N subunit 2	IPI00479116	8
SERPINA5 Plasma serine protease inhibitor	IPI00007221	7
LUM Lumican	IPI00020986	7
APOB Apolipoprotein B-100	IPI00022229	7
C1QC Complement C1q subcomponent subunit C	IPI00022394	7
SHBG Isoform 1 of Sex hormone-binding globulin	IPI00023019	7
SCN4B Isoform 1 of Sodium channel subunit beta-4	IPI00217376	7
MST1 Hepatocyte growth factor-like protein	IPI00292218	7

TABLE 14-continued

Protein name	Protein accession numbers	# individual with ischemic induced increase (max. 20)
MDFI 19 kDa protein	IPI00385435	7
QSOX1 Isoform 2 of Sulfhydryl oxidase 1	IPI00465016	7
FETUB GUGU beta form	IPI00552199	7
SEPP1 selenoprotein P isoform 2	IPI00847381	7
HBA2; HBA1 Alpha 2 globin variant (Fragment)	IPI00853068	7
CPN1 Carboxypeptidase N catalytic chain	IPI00010295	6
AFM Afamin	IPI00019943	6
SOD1 Superoxide dismutase	IPI00218733	6
VTN Vitronectin	IPI00298971	6
SERPINA4 Kallistatin	IPI00328609	6
SERPINA4 Kallistatin	IPI00328609	6
PTPRK Protein tyrosine phosphatase, receptor type, K	IPI00552690	6
SERPINA3 Isoform 1 of Alpha-1-antichymotrypsin	IPI00847635	6
OU domain class 5 transcription factor 1 (Fragment)	IPI00868800	6
ORM1 orosomucoid 1	IPI00884926	6
F12 Coagulation factor XII	IPI00019581	5
APOA1 Apolipoprotein A-I	IPI00021841	5
IGFBP6 Insulin-like growth factor-binding protein 6	IPI00029235	5
FN1 Isoform 3 of Fibronectin	IPI00339223	5
g heavy chain V-III region CAM	IPI00382482	5
LOC388720 similar to ubiquitin and ribosomal protein S27a	IPI00397808	5
CLU clusterin isoform 1	IPI00400826	5
BTD Uncharacterized protein BTD (Fragment)	IPI00744685	5
PROS1 80 kDa protein	IPI00873445	5
SERPINF1 Pigment epithelium-derived factor	IPI00006114	4
C8G Complement component C8 gamma chain	IPI00011261	4
ORM1 Alpha-1-acid glycoprotein 1	IPI00022429	4
AHSG Alpha-2-HS-glycoprotein	IPI00022431	4
GGH Gamma-glutamyl hydrolase	IPI00023728	4
EFNB1 Ephrin-B1	IPI00024307	4
GPX3 Glutathione peroxidase 3	IPI00026199	4
HGFAC Hepatocyte growth factor activator	IPI00029193	4
CD14 Monocyte differentiation antigen CD14	IPI00029260	4
FGA Isoform 2 of Fibrinogen alpha chain	IPI00029717	4
LRP1B Similar to Candidate tumor suppressor protein	IPI00032063	4
S100A7 Protein S100-A7	IPI00219806	4
C8B Complement component C8 beta chain	IPI00294395	4
DMXL1 DmX-like protein 1	IPI00294728	4
ARSB Arylsulfatase B	IPI00306576	4
LRP8 Isoform 3 of Low-density lipoprotein receptor-related protein 8	IPI00384247	4
HBA2; HBA1 Hemoglobin subunit alpha	IPI00410714	4
ASPN ASPN protein	IPI00418431	4
A2M Alpha-2-macroglobulin	IPI00478003	4
CDH3 Isoform 2 of Cadherin-3	IPI00645614	4
KLKB1 Plasma kallikrein	IPI00654888	4
SERPINA1 Isoform 2 of Alpha-1-antitrypsin	IPI00790784	4
ICAM2 28 kDa protein	IPI00793958	4
C1RL cDNA FLJ14022 fis, clone HEMBA1003538, weakly similar to COMPLEMENT C1R COMPONENT	IPI00795055	4
B2M B2M protein	IPI00796379	4
APOA1 Apolipoprotein A1	IPI00853525	4
Transthyretin	IPI00855916	4
ITIH3 Uncharacterized protein ITIH3	IPI00873416	4
MB 16 kDa protein	IPI00878623	4
SERPINF2 Alpha-2-antiplasmin	IPI00879231	4
COL5A2 Collagen alpha-2(V) chain	IPI00844306	4
JUP Junction plakoglobin	IPI00554711	4
PRG4 Isoform D of Proteoglycan-4	IPI00655676	4
GPR37 Probable G-protein coupled receptor 37	IPI00006166	3
F13B Coagulation factor XIII B chain	IPI00007240	3
CLEC3B Tetranectin	IPI00009028	3
C6 Complement component 6	IPI00009920	3
C8A Complement component C8 alpha chain	IPI00011252	3
DSP Isoform DPI of Desmoplakin	IPI00013933	3
COPS2 Isoform 2 of COP9 signalosome complex subunit 2	IPI00018813	3
F2 Prothrombin (Fragment)	IPI00019568	3
IGFALS Insulin-like growth factor-binding protein complex acid labile chain	IPI00020996	3
ACTG1 Actin, cytoplasmic 2	IPI00021440	3
FGA Isoform 1 of Fibrinogen alpha chain	IPI00021885	3

TABLE 14-continued

Protein name	Protein accession numbers	# individual with ischemic induced increase (max. 20)
RBP4 Plasma retinol-binding protein	IPI00022420	3
RBP4 Retinol binding protein 4, plasma	IPI00022420	3
HPX Hemopexin	IPI00022488	3
NPR1 Atrial natriuretic peptide receptor A	IPI00027200	3
SEPP1 Selenoprotein P	IPI00029061	3
ZAK Isoform 2 of Mitogen-activated protein kinase kinase kinase MLT	IPI00029643	3
CST3 Cystatin-C	IPI00032293	3
AZGP1 alpha-2-glycoprotein 1, zinc	IPI00166729	3
CA2 Carbonic anhydrase 2	IPI00218414	3
SELL L-selectin	IPI00218795	3
FGG Isoform Gamma-A of Fibrinogen gamma chain	IPI00219713	3
IGSF5 Immunoglobulin superfamily member 5	IPI00245940	3
LYVE1 Lymphatic vessel endothelial hyaluronic acid receptor 1	IPI00290856	3
SERPING1 Plasma protease C1 inhibitor	IPI00291866	3
C17orf13; ACYP1; C1R Complement C1r subcomponent	IPI00296165	3
F9 Coagulation factor IX	IPI00296176	3
FGB Fibrinogen beta chain	IPI00298497	3
LILRB2 leukocyte immunoglobulin-like receptor, subfamily B, member 2 isoform 1	IPI00303952	3
IGHG1 Putative uncharacterized protein DKFZp686N02209	IPI00384938	3
cDNA FLJ43303 fis, clone NOVAR2000136, moderately similar to Calsequestrin, skeletal muscle isoform	IPI00445889	3
IGHM IGHM protein	IPI00472610	3
PTGDS Prostaglandin D2 synthase 21 kDa	IPI00513767	3
GC Vitamin D-binding protein	IPI00555812	3
HP Haptoglobin	IPI00641737	3
LCN2 Lipocalin 2, Neutrophil gelatinase-associated lipocalin	IPI00643623	3
ITIH2 Inter-alpha (Globulin) inhibitor H2	IPI00645038	3
FETUB GUGU beta form, Fetuin-B	IPI00743766	3
HABP2 Hyaluronan-binding protein 2	IPI00746623	3
C1S Uncharacterized protein C1S	IPI00749179	3
LRP1B Low-density lipoprotein receptor-related protein 1B	IPI00877809	3
SERPIND1 Heparin cofactor 2	IPI00879573	3
APOA4 Apolipoprotein A-IV	IPI00304273	3
CDH22 Cadherin-22	IPI00000436	2
TAF9 Transcription initiation factor TFIID subunit 9	IPI00002993	2
MBL2 Mannose-binding protein C	IPI00004373	2
CRISP3 cDNA FLJ75207	IPI00004798	2
EFNA4 Isoform 1 of Ephrin-A4	IPI00005125	2
COMT Isoform Membrane-bound of Catechol O-methyltransferase	IPI00011284	2
LRRC4C Netrin-G1 ligand	IPI00014223	2
IGFBP7 Insulin-like growth factor-binding protein 7	IPI00016915	2
C1S Complement C1s subcomponent	IPI00017696	2
GGT1 Isoform 1 of Gamma-glutamyltranspeptidase 1	IPI00018901	2
PLG Plasminogen	IPI00019580	2
ORM2 Alpha-1-acid glycoprotein 2	IPI00020091	2
PLXNA3 Plexin-A3	IPI00020884	2
C4BPA C4b-binding protein alpha chain	IPI00021727	2
SERPINB3 Serpin B3	IPI00022204	2
BAI1 Brain-specific angiogenesis inhibitor 1	IPI00022333	2
HRG Histidine-rich glycoprotein	IPI00022371	2
APCS Serum amyloid P-component	IPI00022391	2
C1QA Complement C1q subcomponent subunit A	IPI00022392	2
C9 Complement component C9	IPI00022395	2
NRGN Neurogranin	IPI00022640	2
CDH1 Epithelial cadherin	IPI00025861	2
SOD3 Extracellular superoxide dismutase [Cu—Zn]	IPI00027827	2
KNG1 Isoform HMW of Kininogen-1	IPI00032328	2
PTH2 Tuberoinfundibular peptide of 39 residues	IPI00059307	2
PTPRU protein tyrosine phosphatase, receptor type, U isoform 3	IPI00107472	2
PTPRF Receptor-type tyrosine-protein phosphatase F	IPI00107831	2
UBA52 ubiquitin and ribosomal protein L40 , UBB; RPS27A; UBC ubiquitin and ribosomal protein S27a	IPI00179330	2
UBB; RPS27A; UBC ubiquitin and ribosomal protein S27a	IPI00179330	2
TTN Isoform 7 of Titin	IPI00179357	2
CLCN6 Isoform A of Chloride channel protein 6	IPI00180121	2
HIST1H1C Histone H1.2	IPI00217465	2
MB Myoglobin	IPI00217493	2

TABLE 14-continued

Protein name	Protein accession numbers	# individal with ischemic induced increase (max. 20)
HRC Sarcoplasmic reticulum histidine-rich calcium-binding protein	IPI00219226	2
SP140 Isoform LYSp100-A of Nuclear body protein SP140	IPI00219535	2
PTPRO Receptor-type tyrosine-protein phosphatase O	IPI00241041	2
CLU Clusterin	IPI00291262	2
SLC44A2 Isoform 2 of Choline transporter-like protein 2	IPI00293074	2
ITIH4 Isoform 1 of Inter-alpha-trypsin inhibitor heavy chain H4	IPI00294193	2
IGFBP2 Insulin-like growth factor-binding protein 2	IPI00297284	2
LTF Growth-inhibiting protein 12	IPI00298860	2
LCN2 Neutrophil gelatinase-associated lipocalin	IPI00299547	2
THBS4 Thrombospondin-4	IPI00328550	2
Ig heavy chain V-III region TEI	IPI00382494	2
VASN Vasorin	IPI00395488	2
FLG2 Ifapsoriasin	IPI00397801	2
SEMG1 Isoform 2 of Semenogelin-1	IPI00414684	2
IGHG1 Putative uncharacterized protein DKFZp686N02209	IPI00423466	2
HUWE1 Isoform 2 of E3 ubiquitin-protein ligase HUWE1	IPI00445401	2
PTPRK Protein tyrosine phosphatase, receptor type, K	IPI00470937	2
HP HP protein	IPI00478493	2
FCGR3A Fc fragment of IgG, low affinity IIIa, receptor for	IPI00640044	2
C2 Complement component 2	IPI00643506	2
CPN2 similar to Carboxypeptidase N subunit 2	IPI00738433	2
A1BG alpha 1 B-glycoprotein	IPI00745089	2
LOC732428 Uncharacterized protein ENSP00000375150	IPI00787862	2
SOD1 Uncharacterized protein SOD1	IPI00789078	2
CLEC3B Putative uncharacterized protein DKFZp686H17246	IPI00792115	2
8 kDa protein	IPI00792845	2
FCGR3B Protein	IPI00795501	2
C5 Complement component 5 variant (Fragment)	IPI00816741	2
PRAP1 Isoform 4 of Proline-rich acidic protein 1	IPI00855875	2
SH3BGRL 13 kDa protein	IPI00872670	2

Example IV

Summary of Some of the Properties of Proteins Discussed with Regard to Cohort II

A. Pigment Epithelium-Derived Factor

Name: PIGMENT EPITHELIUM-DERIVED FACTOR

IPI ID: IPI00006114

UniProtKB/Swiss-Prot ID: P36955

[0320] Length: 418 aa, molecular weight: 46342 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Neurotrophic protein; induces extensive neuronal differentiation in retinoblastoma cells. Potent inhibitor of angiogenesis. As it does not undergo the S (stressed) to R (relaxed) conformational transition characteristic of active serpins, it exhibits no serine protease inhibitory activity.
SUBCELLULAR LOCATION	Secreted. Melanosome. Note = Enriched in stage I melanosomes.
PTM	The N-terminus is blocked. Extracellular phosphorylation enhances antiangiogenic activity.

2. Sequence:

[0321]

(SEQ ID NO: 20)

MQALVLLLCIGALLGHSSCQNPASPPEEGSPDPDSTGALVEEEDPFFKV

PVNKLAAAVSNFGYDLYRVRSSMSPTTNVLLSPLSVATALSALSLGAEQR

TESIIHRALYYDLISSPDIHGTYKELLDTVTAPQKNLKSASRIVFEKKL

RIKSSFVAPLEKSYGTRPRVLTGNPRLDLQEINNWVQAQMKGKLARSTKE

IPDEISILLLGVAHFKGQWVTKFDSRKTSLEDFYLDEERTVRVPMMSDP

KAVLRYGLDSDLSCKIAQLPLTGSMSIIFFLPLKVTQNLTLIEESLTSE

FIHDIDRELKTVQAVLTVPKLKLSYEGEVTKSLQEMKLQSLFDSPDFS

KITGKPIKLTQVEHRAGFEWNEDGAGTTPSPGLQPAHLTFPLDYHLNQ

PFIFVLRDTDTGALLFIGKILDPRGP

3. Alternative Name(s):

Serpin-F1, EPC-1

[0322] Has been used in treatment of retinal ischemic injury. As well, increased levels are observed with retinal

diseases and diabetes but none have been related to heart disease including myocardial ischemia.

B. Protein S100-A7

Name: Protein S100-A7

IPI ID: IPI00219806

UniProtKB/Swiss-Prot ID: P31151

[0323] Length: 101 aa, molecular weight: 11471 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry:

Subcellular location	Cytoplasm. Secreted.
Subunit structure	Interacts with RANBP9.

2. Sequence:

[0324]

(SEQ ID NO: 21)

MSNTQAERSIIGMIDMFHKYTRRDDKIEKPSLLTMMKENFPNFLSACDK

KGTNYLADVFEKKDKNEDKKIDFSEFLSLLGDIATDYHKQSHGAAPCS

GGSQ

3. Alternative Name(s):

[0325] S100 calcium-binding protein A7; Psoriasin

This protein has not been linked to myocardial ischemia or events leading up to MI.

C. Protein S100-A8

Name: Protein S100 A8

IPI ID: IPI00007047

UniProtKB/Swiss-Prot ID: P05109

[0326] Length: 93 aa, molecular weight: 10835 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry:

[0327] Function: Expressed by macrophages in chronic inflammations. Also expressed in epithelial cells constitutively or induced during dermatoses. May interact with components of the intermediate filaments in monocytes and epithelial cells.

2. Sequence:

[0328]

(SEQ ID NO: 22)

MLTELEKALNSIIDVYHKYSLIKGNFHAVYRDDLKKLLETECPQYIRKK

GADVWFKELDINTDGAVNFQEFLILVIKMGVAAHKKSHEESHKE

3. Alternative Name(s):

[0329] S100 calcium-binding protein A8

[0330] Calgranulin-A

[0331] Migration inhibitory factor-related protein 8

[0332] Short name=MRP-8

[0333] Short name=P8

[0334] Cystic fibrosis antigen

[0335] Short name=CFAG

[0336] Leukocyte L1 complex light chain

[0337] Calprotectin L1L subunit

[0338] Urinary stone protein band A

This protein has not been linked to myocardial ischemia or events leading up to MI.

D. Protein S100-A9

Name: PROTEIN S100-A9

IPI ID: IPI00027462

UniProtKB/Swiss-Prot ID: P06702

[0339] Length: 114 aa, molecular weight: 13242 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry:

[0340] Function: Expressed by macrophages in acutely inflammated tissues and in chronic inflammations. Seem to be an inhibitor of protein kinases. Also expressed in epithelial cells constitutively or induced during dermatoses. May interact with components of the intermediate filaments in monocytes and epithelial cells.

[0341] Subcellular location: cytoplasm and nucleus.

2. Sequence:

[0342]

(SEQ ID NO: 23)

MTCKMSQLERNIETIINTFHQYSVKLGHPDTLNQGEFKELVRKDLQNFL

KKENKNEKVIEHIMEDLDTNADKQLSFEEFIMLMARLTWASHEKMHE

GDEGPGHHHKPGLGEGTP

3. Alternative Name(s):

[0343] Full=S 100 calcium-binding protein A9;

[0344] Full=Calgranulin-B;

[0345] Full=Migration inhibitory factor-related protein 14;

[0346] Short=MRP-14;

[0347] Short=P14;

[0348] Full=Leukocyte L1 complex heavy chain;

[0349] Full=Calprotectin L1H subunit;

The mRNA levels of 5100 A9 have been shown to increase after ischemic brain injury and after stroke. The protein level was not determined. This protein has not been linked to myocardial ischemia or events leading up to MI.

E. Protein Tyrosine Phosphatase, Receptor Type, K

Name: PROTEIN TYROSINE PHOSPHATASE, RECEPTOR TYPE, K

IPI ID: IPI00552690

UniProtKB/TrEMBL ID: Q5JY45

[0350] Length: 202 aa, molecular weight: 22792 Da

Sequence:

[0351]

(SEQ ID NO: 24)

MSSVEKETKTQCVRIATKAAATEEPEVIPDPAKQTDRVVKIAGISAGI

LVFILLLLVVILIVKKRRSYYSYSYYLKLAKKRKDAMGNTRQEMTHMVN

AMDRSYADQSTLHAEDPLSITFMDQHNFSPRLPNDPLVPTAVLDEN

HSATAESSRLLDVPRYLCEGTESPYQTGQLHPAIRVADLLQHINLMK

TSDSYGFKEEYE

This protein has not been linked to myocardial ischemia or events leading up to MI.

F. Protein Z-Dependent Protease Inhibitor

[0352] Name: Protein Z-dependent protease inhibitor

IPI ID: IPI00007199

UniProtKB/Swiss-Prot ID: Q9UK55

[0353] Length: 484 aa, molecular weight: 55114 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Inhibits factor Xa activity in the presence of protein Z, calcium and phospholipid.
SUBCELLULAR LOCATION	Secreted.

2. Sequence:

[0354]

(SEQ ID NO: 25)

MSRSTQELLGYHCRLQDKLQEQEGSLAAEGRHSLASAADHMKVVPSLLL

SVLLAQVWLVPGLAPSPQSPETPAPQNQTSRVVQAPKEEEEDEQEASEE

KASEEEKAWLMASRQQLAKETSNFGFSLLRKISMRHDGNMVFSPFGMSL

AMTGLMLGATGPTETQIKRGLHLQALKPTKPGLLPSLFKGLRETLSRNLE

LGLTQGSFAFIHKDFDVKETFFNLSKRYFDTECVPMNFRNASQAKRLMN

HYINKETRGKIPKLFDEINPETKLILVDYILFKGKWLTPFDPVFTEVDTF

HLDKYKTIKVPMMYGAGKFASTFDKNFRCHVLKLPYQGNATMLVVLMEK

MGDHLALEDYLTTDLVETWLRNMKTRNMEVFFPKFKLDQKYEMHELL

RQMGIRRIFSPFADLSELSATGRNLQVSRVLQRTVIEVDERGTEAVAGIL

SEITAYSMPPVIKVDRPFHFMIYEETSGMLLFLGRVVNPTLL

3. Alternative Name(s):

Serpin A10

[0355] Protein Z was recently shown to act as an essential cofactor for protein Z-dependent protease inhibitor, a potent downregulator of coagulation Factor Xa. Low levels of protein Z have been correlated with increased risk of stroke. However, protein Z dependent protease inhibitor was not studied. This protein has not been linked to myocardial ischemia or events leading up to MI.

G. Sodium Channel Subunit Beta-4

Name: ISOFORM 10F SODIUM CHANNEL SUBUNIT BETA-4

IPI ID: IPI00217376

UniProtKB/Swiss-Prot ID: Q81WT1-1

[0356] Length: 228 aa, molecular weight: 24969 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTON	Modulates channel gating kinetics. Causes negative shifts in the voltage dependence of activation of certain alpha sodium channels, but does not affect the voltage dependence of inactivation (By similarity).
SUBCELLULAR LOCATION	Membrane; Single-pass type I membrane protein (Probable).

2. Sequence:

[0357]

(SEQ ID NO: 26)

MPGAGDGGKAPARWLGTGLLGLFLLPVTLSLEVSVGKATDIYAVNGT

EILLPCTFSSCFGFEDLHFRWTYNSSDAFKILIEGTVKNEKSDPKVTLK

DDDRITLVGSTKEKMNNISIVLRDLEFSDTGKYTCHVKNPKENNLQHH

ATIFLQVVDRLEEVDNTVTLIILAVVGGVIGLLILILLIKKLIIFILKKT

REKKKECLVSSSGNDNTENGLPGSKAEEKPPSKV

[0358] This protein has not been linked to myocardial ischemia or events leading up to MI.

H. Sortilin-Related Receptor

Name: SORTILIN-RELATED RECEPTOR

IPI ID: IPI00022608

UniProtKB/Swiss-Prot ID: Q92673

[0359] Length: 2214 aa, molecular weight: 248441 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNTION	Likely to be a multifunctional endocytic receptor, that may be implicated in the uptake of lipoproteins and of proteases. Binds LDL, the major cholesterol-carrying lipoprotein of plasma, and transports it into cells by endocytosis. Binds the receptor-associated protein (RAP). Could play a role in cell-cell interaction.
SUBCELLULAR LOCATION	Membrane; Single-pass type I membrane protein (Potential).

2. Sequence:

[0360]

(SEQ ID NO: 27)

MATRSSRRESRLPFLFTLVALLPPGALCEVWTQRLHGGSAPLPQDRGFLV

VQGDPRELRLWARGDARGASRADEKPLRRKRSAALQPEPIKVYGQVSLND

SHNQMVVHWAGEKSNVIVALARDSLALARPKSSDVYVSYDYGKSFKKISD

KLNFGLGNRSEAVIAQFYHSPADNKRYIFADAYAQYLWITFDFCNTLQGF

SIPFRAADLLLLHSKASNLLLGFDRSHPNKQLWKSDDFGQTWIMIQEHVKS

FSWGIDPYDKPNTIYIERHEPSGYSTVFRSTDFFQSRENQEVILEEVRDF

QLRDKYMFATKVVHLLGSEQQSSVQLWVSFGRKPMRAAQFVTRHPINEYY

IADASEDQVFVCVSHSNNRTNLYISEAEGLKFSLSLENVLYYSPGGAGSD

TLVRYFANEPFADFHRVEGLQGVYIATLINGSMNEENMRSVITFDKGGTW

EFLQAPAFTGYGEKINCELSQGCSLHLAQRLSQLLNLQLRRMPILSKESA

PGLIIATGSVGKNLASKTNVYISSSAGARWREALPGPHYYTWGDHGGIIT

AIAQGMETNELKYSTNEGETWKTFIFSEKPVFVYGLLTEPGEKSTVFTIF

GSNKENVHSWLILQVNATDALGVPCTENDYKLWSPSDERGNECLLGHKTV

FKRRTPHATCFNGEDFDRPVVVSNCSCTREDYECDFGFKMSEDLSLEVCV

PDPEFSGKSYSPPVPCPVGSTYRRTRGYRKISGDTCSGGDVEARLEGELV

PCPLAEENEFILYAVRKSIYRYDLASGATEQLPLTGLRAAVALDFDYEHN

CLYWSDLALDVIQRLCLNGSTGQEVIINSGLETVEALAFEPLSQLLYWVD

AGFKKIEVANPDGDFRLTIVNSSVLDRPRALVLVPQEGVMFWTDWGDLKP

GIYRSNMDGSAAYHLVSEDVKWPNGISVDDQWIYWTDAYLECIERITFSG

QQRSVILDNLPHPYAIAVFKNEIYWDDWSQLSIFRASKYSGSQMEILANQ

LTGLMDMKIFYKGKNTGSNACVPRPCSLLCLPKANNSRSCRCPEDVSSSV

LPSGDLMCDCPQGYQLKNNTCVKEENTCLRNQYRCSNGNCINSIWWCDFD

NDCGDMSDERNCPTTICDLDTQFRCQESGTCIPLSYKCDLEDDCGDNSDE

SHCEMHQCRSDEYNCSSGMCIRSSWVCDGDNDCRDWSDEANCTAIYHTCE

ASNFQCRNGHCIPQRWACDGDTDCQDGSDEDPVNCEKKCNGFRCPNGTCI

PSSKHCDGLRDCSDGSDEQHCEPLCTHFMDFVCKNRQQCLFHSMVCDGII

QCRDGSDEDAAFAGCSQDPEFHKVCDEFGFQCQNGVCISLIWKCDGMDDC

GDYSDEANCENPTEAPNCSRYFQFRCENGHCIPNRWKCDRENDCGDWSDE

KDCGDSHILPFSTPGPSTCLPNYYRCSSGTCVMDTWVCDGYRDCADGSDE

EACPLLANVTAASTPTQLGRCDRFEFECHQPKTCIPNWKRCDGHQDCQDG

RDEANCPTHSTLTCMSREFQCEDGEACIVLSERCDGFLDCSDESDEKACS

DELTVYKVQNLQWTADFSGDVTLTWMRPKKMPSASCVYNVYYRVVGESIW

KTLETHSNKTNTVLKVLKPDTTYQVKVQVQCLSKAHNTNDFVTLRTPEGL

PDAPRNLQLSLPREAEGVIVGHWAPPIHTHGLIREYIVEYSRSGSKMWAS

QRAASNFTEIKNLLVNTLYTVRVAAVTSRGIGNWSDSKSITTIKGKVIPP

PDIHIDSYGENYLSFTLTMESDIKVNGYVVNLFWAFDTHKQERRTLNFRG

-continued

SILSHKVGNLTAHTSYEISAWAKTDLGDSPLAFEHVMTRGVRPPAPSLKA

KAINQTAVECTWTGPRNVVYGIFYATSFLDLYRNPKSLTTSLHNKTVIVS

KDEQYLFLVRVVVPYQGPSSDYVVVKMIPDSRLPPRHLHVVHTGKTSVVI

KWESPYDSPDQDLLYAIAVKDLIRKTDRSYKVKSRNSTVEYTLNKLEPGG

KYHIIVQLGNMSKDSSIKITTVSLSAPDALKIITENDHVLLFWKSLALKE

KHFNESRGYEIHMFDSAMNITAYLGNTTDNFFKISNLKMGHNYTFTVQAR

CLFGNQICGEPAILLYDELGSGADASATQAARSTDVAAVVVPILFLILLS

LGVGFAILYTKHRRLQSSFTAFANSHYSSRLGSAIFSSGDDLGEDDEDAP

MITGFSDDVPMVIA

3. Alternative Name(s):

[0361] Sorting protein-related receptor containing LDLR class A repeats

[0362] Short name=SorLA

[0363] SorLA-1

[0364] Low-density lipoprotein receptor relative with 11 ligand-binding repeats

[0365] Short name=LDLR relative with 11 ligand-binding repeats

[0366] Short name=LR11

This protein has not been linked to myocardial ischemia or events leading up to MI.

I. Conserved Hypothetical Protein

[0367] Name Conserved hypothetical protein

IPI ID: IPI00884334

[0368] Length: 168 aa, molecular weight: 18798 Da

Sequence:

[0369]

(SEQ ID NO: 28)

MRSFLLVWKLFRRKDMKHQRKTATEFKTTEEGETRQDGKDGSLTYRADT

CSPCPEAGGPPSSSIASGSSISVGNSPSHSHSHTSRRCGGSSRSRECCS

SLHSSRGSRGSSWSSSPPGSTCRWCSCHSHHHSHHRSHHRSHHCSHH

HSHHHSGHHSHHNFHNHSNPWCQ

This protein has not been linked to myocardial ischemia or events leading up to MI.

J. Catalase

Name: Catalase

IPI ID: IPI00465436

UniProtKB/Swiss-Prot ID: P04040

[0370] Length: 527 aa, molecular weight: 59756 Da

1. Basic Information from UniProtKB/Swiss-Prot Entry:

Function	Occurs in almost all aerobically respiring organisms and serves to protect cells from the toxic effects of hydrogen

-continued

	peroxide. Promotes growth of cells including T-cells, B-cells, myeloid leukemia cells, melanoma cells, mastocytoma cells and normal and transformed fibroblast cells.
Subcellular location	Peroxisome.

2. Sequence:

[0371]

(SEQ ID NO: 29)
MADSRDPASDQMQHWKEQRAAQKADVLTTGAGNPVGDKLNVITVGPRG

PLLVQDVVFTDEMAHFDRERIPERVVHAKGAGAFGYFEVTHDITKYSKAK

VFEHIGKKTPIAVRFSTVAGESGSADTVRDPRGFAVKFYTEDGNWDLVGN

NTPIFFIRDPILFPSFIHSQKRNPQTHLKDPDMVWDFWSLRPESLHQVSF

LFSDRGIPDGHRHMNGYGSHTFKLVNANGEAVYCKFHYKTDQGIKNLSVE

DAARLSQEDPDYGIRDLFNAIATGKYPSWTFYIQVMTFNQAETFPFNPFD

LTKVWPHKDYPLIPVGKLVLNRNPVNYFAEVEQIAFDPSNMPPGIEASPD

KMLQGRLFAYPDTHRHRLGPNYLHIPVNCPYRARVANYQRDGPMCMQDN

QGGAPNYYPNSFGAPEQQPSALEHSIQYSGEVRRFNTANDDNVTQVRAF

YVNVLNEEQRKRLCENIAGHLKDAQIFIQKKAVKNFTEVHPDYGSHIQA

LLDKYNAEKPKNAIHTFVQSGSHLAAREKANL

Catalase is an important enzyme in the heart's regulation of oxidative stress. It has been linked to preconditioning in the heart tissue. As a serum marker, it has not been linked to myocardial ischemia or events leading up to MI.

K. Conserved Hypothetical Protein

[0372] Name: Conserved hypothetical protein

IPI ID: IPI00883661

UniProt/TrEMBL ID: A6NFT5

[0373] Length: 175 aa, molecular weight: 20933 Da

2. Sequence:

[0374]

(SEQ ID NO: 30)
MNIHIHTCMHIYTHAHTHAHIHTCIHTHTHMHTHTLTYTHIHMHTHTQTH

IYTQAHIHSCTQINIYTYAYTLTCTQTHTHICTHAHTLTYTHIHTCTYKR

TYIQGHIHTHMHTYTCTCTHTHKHIHAHIHIHTHTHIYTHTDAYTHMDTY

THTYPHTHICIHSHTHAHTYTHIRT

This protein has not been linked to myocardial ischemia or events leading up to MI.

L. Glutathione peroxidase 3
Name: Glutathione peroxidase 3

IPI ID: IPI00026199

UniProtKB/Swiss-Prot ID: P22352

[0375] Length: 226 aa, molecular weight: 25505 Da
1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Protects cells and enzymes from oxidative damage, by catalyzing the reduction of hydrogen peroxide, lipid peroxides and organic hydroperoxide, by glutathione.
SUBCELLULAR LOCATION	Secreted.
TISSUE SPECIFICITY	Secreted in plasma.

2. Sequence:

[0376]

(SEQ ID NO: 31)
MARLLQASCLLSLLLAGFVSQSRGQEKSKMDCHGGISGTIYEYGALTIDG

EEYIPFKQYAGKYVLFVNVASYCGLTGQYIELNALQEELAPFGLVILGFP

CNQFGKQEPGENSEILPTLKYVRPGGGFVPNFQLFEKGDVNGEKEQKFYT

FLKNSCPPTSELLGTSDRLFWEPMKVHDIRWNFEKFLVGPDGIPIMRWHH

RTTVSNVKMDILSYMRRQAALGVKRK

3. Alternative Name(s):

[0377] GSHPx-3
[0378] Short name=GPx-3
[0379] Extracellular glutathione peroxidase
[0380] Plasma glutathione peroxidase
[0381] GSHPx-P
[0382] Short name=GPx-P

GPx 3 is an important enzyme involved in many cells regulation of oxidative stress. As a serum marker it has not been linked to myocardial ischemia or events leading up to MI.

M. Hepatocyte Growth Factor Activator

Name: HEPATOCYTE GROWTH FACTOR ACTIVATOR

IPI ID: IPI00029193

UniProtKB/Swiss-Prot ID: Q04756

[0383] Length: 655 aa, molecular weight: 70682 Da (of Precursor)
1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Activates hepatocyte growth factor (HGF) by converting it from a single chain to a heterodimeric form.
SUBCELLULAR LOCATION	Secreted. Note = Secreted as an inactive single-chain precursor and is then activated to a heterodimeric form.

2. Sequence:

[0384]

(SEQ ID NO: 32)
MGRWAWVPSPWPPPGLGPFLLLLLLLLLLPRGFQPQPGGNRTESPEPNAT

ATPAIPTILVTSVTSETPATSAPEAEGPQSGGLPPPPRAVPSSSSPQAQA

LTEDGRPCRFPPFRYGGRMLHACTSEGSAHRKWCATTHNYDRDRAWGYCVE

ATPPPGGPAALDPCASGPCLNGGSCSNTQDPQSYHCSCPRAFTGKDCGTE

KCFDETRYEYLEGGDRWARVRQGHVEQCECFGGRTWCEGTRHTACLSSPC

LNGGTCHLIVATGTTVCACPPGFAGRLCNIEPDERCFLGNGTGYRGVAST

SASGLSCLAWNSDLLYQELHVDSVGAAALLGLGPHAYCRNPDNDERPWCY

VVKDSALSWEYCRLEACESLTRVQLSPDLLATLPEPASPGRQACGRRHKK

RTFLRPRIIGGSSSLPGSHPWLAAIYIGDSFCAGSLVHTCWVVSAAHCFS

HSPPRDSVSVVLGQHFFNRTTDVTQTFGIEKYIPYTLYSVFNPSDHDLVL

IRLKKKGDRCATRSQFVQPICLPEPGSTFPAGHKCQIAGWGHLDENVSGY

SSSLREALVPLVADHKCSSPEVYGADISPNMLCAGYFDCKSDACQGDSGG

PLACEKNGVAYLYGIISWGDGCGRLHKPGVYTRVANYVDWINDRIRPPRR

LVAPS

This protein has not been linked to myocardial ischemia or events leading up to MI.

N. Hepatocyte Growth Factor-Like Protein Homolog

Name: HEPATOCYTE GROWTH FACTOR-LIKE PROTEIN HOMOLOG

IPI ID: IPI00292218

UniProtKB/TrEMBL ID: B7Z557

[0385] Length: 697 aa, molecular weight: 78787 Da

Sequence:

[0386]

(SEQ ID NO: 33)
MLRGPCSPLNDFQVLRGTELQHLLHAVVPGPWQEDVADAEECAGRCGPLM

DCRAFHYNVSSHGCQLLPWTQHSPHTRLRRSGRCDLFQKKDYVRTCIMNN

GVGYRGTMATTVGGLPCQAWSHKFPNDHKYTPTLRNGLEENFCRNPDGDP

GGPWCYTTDPAVRFQSCGIKSCREAACVWCNGEEYRGAVDRTESGRECQR

WDLQHPHQHPFEPGKFLDQGLDDNYCRNPDGSERPWCYTTDPQIEREFCD

LPRCGSEAQPRQEATTVSCFRGKGEGYRGTANTTTAGVPCQRWDAQIPHQ

HRFTPEKYACKDLRENFCRNPDGSEAPWCFTLRPGMRAAFCYQIRRCTDD

VRPQDCYHGAGEQYRGTVSKTRKGVQCQRWSAETPHKPQFTFTSEPHAQL

EENFCRNPDGDSHGPWCYTMDPRTPFDYCALRRCADDQPPSILDPPDQVQ

FEKCGKRVDRLDQRRSKLRVVGGHPGNSPWTVSLRNRQGQHFCGGSLVKE

QWILTARQCFSSCHMPLTGYEVWLGTLFQNPQHGEPSLQRVPVAKMVCGP

-continued
SGSQLVLLKLERSVTLNQRVALICLPPEWYVVPPGTKCEIAGWGETKGTG

NDTVLNVALLNVISNQECNIKHRGRVRESEMCTEGLLAPVGACEGDYGGP

LACFTHNCWVLEGIIIPNRVCARSRWPAVFTRVSVFVDWIHKVMRLG

This protein has not been linked to myocardial ischemia or events leading up to MI

O. Insulin-Like Growth Factor-Binding Protein 6

Name: INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 6

IPI ID: IPI00029235

UniProtKB/Swiss-Prot ID: P24592

[0387] Length: 240 aa, molecular weight: 25322 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	IGF-binding proteins prolong the half-life of the IGFs and have been shown to either inhibit or stimulate the growth promoting effects of the IGFs on cell culture. They alter the interaction of IGFs with their cell surface receptors.
SUBCELLULAR LOCATION	Secreted.

2. Sequence:

[0388]

(SEQ ID NO: 34)
MTPHRLLPPLLLLLALLLAASPGGALARCPGCGQGVQAGCPGGCVEEEDG

GSPAEGCAEAEGCLRREGQECGVYTPNCAPGLQCHPPKDDEAPLRALLLG

RGRCLPARAPAVAEENPKESKPQAGTARPQDVNRRDQQRNPGTSTTPSQP

NSAGVQDTEMGPCRRHLDSVLQQLQTEVYRGAQTLYVPNCDHRGFYRKRQ

CRSSQGQRRGPCWCVDRMGKSLPGSPDGNGSSSCPTGSSG

3. Synonym:

IBP-6

[0389] In a swine model of myocardial injury, studied at 3-24, 72, or 168 hrs, it was shown that there was an increased level of mRNA of IGFBP-6 at all time points. In situ hybridisation identified myocytes as the main producers of IGFBP-6 mRNA. However, the protein itself was not investigated. As well, this protein was found to be elevated in a young multiple myeloma patient with high-output cardiac failure. To date, there has been no study indicating the association of this protein with myocardial ischemia or events leading up to MI.

P. Conserved Hypothetical Protein

[0390] Name: Conserved hypothetical protein

IPI ID: IPI00847894

[0391] Length: 88 aa, molecular weight: 9931 Da

Sequence:

[0392]

(SEQ ID NO: 35)

MFTLRLFAGKACWPVLYTMLKEVTCDVCVCVRARACTCMCMCVCECMDVC

VRLYTMLKEVTCDMCVCARTCVHVCVSAWMCVCTCTQC

This protein has not been linked to myocardial ischemia or events leading up to MI.

Q. Isoform 1 of Receptor-Type Tyrosine-Protein Phosphatase Kappa

Name: ISOFORM 10F RECEPTOR-TYPE TYROSINE-PROTEIN PHOSPHATASE KAPPA

IPI ID: IPI00015756

UniProtKB/Swiss-Prot ID: Q15262-1

[0393] Length: 1439 aa, molecular weight: 162102 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Regulation of processes involving cell contact and adhesion such as growth control, tumor invasion, and metastasis. Forms complexes with beta-catenin and gamma-catenin/plakoglobin. Beta-catenin may be a substrate for the catalytic activity of PTP-kappa.
SUBCELLULAR LOCATION	Cell junction, adherens junction. Cell membrane; Single-pass type I membrane protein.

2. Sequence:

[0394]

(SEQ ID NO: 36)

MDTTAAAALPAFVALLLLSPWPLLGSAQGQFSAGGCTFDDGPGACDYHQD

LYDDFEWVHVSAQEPHYLPPEMPQGSYMIVDSSDHDPGEKARLQLPTMKE

NDTHCIDFSYLLYSQKGLNPGTLNILVRVNKGPLANPIWNVTGFTGRDWL

RAELAVSTFWPNEYQVIFEAEVSGGRSGYIAIDDIQVLSYPCDKSPHFLR

LGDVEVNAGQNATFQCIATGRDAVHNKLWLQRRNGEDIPVAQTKNINHRR

FAASFRLQEVTKTDQDLYRCVTQSERGSGVSNFAQLIVREPPRPIAPPQL

LGVGPTYLLIQLNANSIIGDGPIILKEVEYRMTSGSWTETHAVNAPTYKL

WHLDPDTEYEIRVLLTRPGEGGTGLPGPPLITRTKCAEPMRTPKTLKIAE

IQARRIAVDWESLGYNITRCHTFNVTICYHYFRGHNESKADCLDMDPKAP

QHVVNHLPPYTNVSLKMILTNPEGRKESEETIIQTDEDVPGPVPVKSLQG

TSFENKIFLNWKEPLDPNGIITQYEISYSSIRSFDPAVPVAGPPQTVSNL

WNSTHHVFMHLHPGTTYQFFIRASTVKGFGPATAINVTTNISAPTLPDYE

GVDASLNETATTITVLLRPAQAKGAPISAYQIVVEELHPHRTKREAGAME

CYQVPVTYQNAMSGGAPYYFAAELPPGNLPEPAPFTVGDNRTYQGFWNPP

LAPRKGYNIYFQAMSSVEKETKTQCVRIATKAATEEPEVIPDPAKQTDRV

-continued

VKIAGISAGILVFILLLLVVILIVKKSKLAKKRKDAMGNTRQEMTHMVNA

MDRSYADQSTLHAEDPLSITFMDQHNFSPRYENHSATAESSRLLDVPRYL

CEGTESPYQTGQLHPAIRVADLLQHINLMKTSDSYGFKEEYESFFEGQSA

SWDVAKKDQNRAKNRYGNIIAYDHSRVILQPVEDDPSSDYINANYIDGYQ

RPSHYIATQGPVHETVYDFWRMIWQEQSACIVMVTNLVEVGRVKCYKYWP

DDTEVYGDFKVTCVEMEPLAEYVVRTFTLERRGYNEIREVKQFHFTGWPD

HGVPYHATGLLSFIRRVKLSNPPSAGPIVVHCSAGAGRTGCYIVIDIMLD

MAEREGVVDIYNCVKALRSRRINMVQTEEQYIFIHDAILEACLCGETAIP

VCEFKAAYFDMIRIDSQTNSSHLKDEFQTLNSVTPRLQAEDCSIACLPRN

HDKNRFMDMLPPDRCLPFLITIDGESSNYINAALMDSYRQPAAFIVTQYP

LPNTVKDFWRLVYDYGCTSIVMLNEVDLSQGCPQYWPEEGMLRYGPIQVE

CMSCSMDCDVINRIFRICNLTRPQEGYLMVQQFQYLGWASHREVPGSKRS

FLKLILQVEKWQEECEEGEGRTIIHCLNGGGRSGMFCAIGIVVEMVKRQN

VVDVFHAVKTLRNSKPNMVEAPEQYRFCYDVALEYLESS

This protein has not been linked to myocardial ischemia or events leading up to MI.

R. Isoform 2 of Attractin

Name: ISOFORM 20F ATTRACTIN

IPI ID: IPI00162735

UniProtKB/Swiss-Prot ID: O75882-2

[0395] Length: 1272 aa, molecular weight: 141429 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Involved in the initial immune cell clustering during inflammatory response and may regulate chemotactic activity of chemokines. May play a role in melanocortin signaling pathways that regulate energy homeostasis and hair color. Low-affinity receptor for agouti (By similarity). Has a critical role in normal myelination in the central nervous system (By similarity).
SUBCELLULAR LOCATION	Secreted.

2. Sequence:

[0396]

(SEQ ID NO: 37)

MVAAAAATEARLRRRTAATAALAGRSGGPHWDWDVTRAGRPGLGAGLRLP

RLLSPPLRPRLLLLLLLLSPPLLLLLLPCEAEAAAAAAAVSGSAAAEAKE

CDRPCVNGGRCNPGTGQCVCPAGWVGEQCQHCGGRFRLTGSSGFVTDGPG

NYKYKTKCTWLIEGQPNRIMRLRFNHFATECSWDHLYVYDGDSIYAPLVA

AFSGLIVPERDGNETVPEVVATSGYALLHFFSDAAYNLTGFNITYSFDMC

PNNCSGRGECKISNSSDTVECECSENWKGEACDIPHCTDNCGFPHRGICN

-continued

SSDVRGCSCFSDWQGPGCSVPVPANQSFWTREEYSNLKLPRASHKAVVNG

NIMWVVGGYMFNHSDYNMVLAYDLASREWLPLNRSVNNVVVRYGHSLALY

KDKIYMYGGKIDSTGNVTNELRVFHIHNESWVLLTPKAKEQYAVVGHSAH

IVTLKNGRVVMLVIFGHCPLYGYISNVQEYDLDKNTWSILHTQGALVQGG

YGHSSVYDHRTRALYVHGGYKAFSANKYRLADDLYRYDVDTQMWTILKDS

RFFRYLHTAVIVSGTMLVFGGNTHNDTSMSHGAKCFSSDFMAYDIACDRW

SVLPRPDLHHDVNRFGHSAVLHNSTMYVFGGFNSLLLSDILVFTSEQCDA

HRSEAACLAAGPGIRCVWNTGSSQCISWALATDEQEEKLKSECFSKRTLD

HDRCDQHTDCYSCTANTNDCHWCNDHCVPRNHSCSEGQISIFRYENCPKD

NPMYYCNKKTSCRSCALDQNCQWEPRNQECIALPENICGIGWHLVGNSCL

KITTAKENYDNAKLFCRNHNALLASLTTQKKVEFVLKQLRIMQSSQSMSK

LTLTPWVGLRKINVSYWCWEDMSPFTNSLLQWMPSEPSDAGFCGILSEPS

TRGLKAATCINPLNGSVCERPANHSAKQCRTPCALRTACGDCTSGSSECM

WCSNMKQCVDSNAYVASFPPFGQCMEWYTMSTCPPENCSGYCTCSHCLEQP

GCGWCTDPSNTGKGKCIEGSYKGPVKMPSQAPTGNFYPQPLLNSSMCLED

SRYNWSFIHCPACQCNGHSKCINQSICEKCENLTTGKHCETCISGFYGDP

TNGGKCQPCKCNGHASLCNTNTGKCFCTTKGVKGDECQLCEVENRYQGNP

LRGTCYYTLLIDYQFTFSLSQEDDRYYTAINFVATPDEQNRDLDMFINAS

KNFNLNITWAASFSAGTQAGEEMPVVSKTNIKEYKDSFSNEKFDFRNHPN

ITFFVYVSNFTWPIKIQVQTEQ

3. Alternative Name(s):

[0397] Mahogany homolog; DPPT-L

This protein has not been linked to myocardial ischemia and events leading up to MI.

S. Isoform a of Syntaxin-3

Name: Syntaxin-3 (STX3A)

IPI ID: IPI00395768

UniProtKB/Swiss-Prot ID: Q13277-1 and Q13277-2

[0398] Length: 289 aa, molecular weight: 33155 Da--------Q13277-1

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Potentially involved in docking of synaptic vesicles at presynaptic active zones.
SUBCELLULAR LOCATION	Membrane; Single-pass type IV membrane protein (Potential).

2. Sequence:

[0399]

(SEQ ID NO: 38)

MKDRLEQLKAKQLTQDDDTDAVEIAIDNTAFMDEFFSEIEETRLNIDKIS

EHVEEAKKLYSIILSAPIPEPKTKDDLEQLTTEIKKRANNVRNKLKSMEK

-continued

HIEEDEVRSSADLRIRKSQHSVLSRKFVEVMTKYNEAQVDFRERSKGRIQ

RQLEITGKKTTDEELEEMLESGNPAIFTSGIIDSQISKQALSEIEGRHKD

IVRLESSIKELHDMFMDIAMLVENQGEMLDNIELNVMHTVDHVEKARDET

KKAVKYQSQARKKLIIIIVLVVVLLGILALIIGLSVGLN

This protein has not been linked to myocardial ischemia and events leading up to MI.

T. Lactotransferrin

Name: Lactotransferrin

IPI ID: IPI00789477

UniProtKB/TrEMBL ID: B2MV14, B7Z4X2

[0400] Length: 666 aa, molecular weight: 73161 Da

Sequence:

[0401]

(SEQ ID NO: 39)

MRKVRGPPVSCIKRDSPIQCIQAIAENRADAVTLDGGFIYEAGLAPYKLR

PVAAEVYGTERQPRTHYYAVAVVKKGGSFQLNELQGLKSCHTGLRRTAGW

NVPIGTLRPFLNWTGPPEPIEAAVARFFSASCVPGADKGQFPNLCRLCAG

TGENKCAFSSQEPYFSYSGAFKCLRDGAGDVAFIRESTVFEDLSDEAERD

EYELLCPDNTRKPVDKFKDCHLARVPSHAVVARSVNGKEDAIWNLLRQAQ

EKFGKDKSPKFQLFGSPSGQKDLLFKDSAIGFSRVPPRIDSGLYLGSGYF

TAIQNLRKSEEEVAARRARVVWCAVGEQELRKCNQWSGLSEGSVTCSSAS

TTEDCIALVLKGEADAMSLDGGYVYTAGKCGLVPVLAENYKSQQSSDPDP

NCVDRPVEGYLAVAVVRRSDTSLTWNSVKGKKSCHTAVDRTAGWNIPMGL

LFNQTGSCKFDEYFSQSCAPGSDPRSNLCALCIGDEQGENKCVPNSNERY

YGYTGAFRCLAENAGDVAFVKDVTVLQNTDGNNNEAWAKDLKLADFALLC

LDGKRKPVTEARSCHLAMAPNHAVVSRMDKVERLKQVLLHQQAKFGRNGS

DCPDKFCLFQSETKNLLFNDNTECLARLHGKTTYEKYLGPQYVAGITNLK

KCSTSPLLEACEFLRK

Levels have been shown to increase with leukocyte activation. Therefore, there are increases found during ischemic stroke, following by-pass surgery and after direct stenting in patients with angina. However, no studies that have linked this protein to myocardial ischemia or events leading up to MI.

U. Low-Density Lipoprotein Receptor-Related Protein 2

Name: LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 2

IPI ID: IPI00024292

UniProtKB/Swiss-Prot ID: P98164

[0402] Length: 4655 aa, molecular weight: 521958 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Acts together with cubilin to mediate HDL endocytosis (By similarity). May participate in regulation of parathyroid-hormone and para-thyroid-hormone-related protein release.
SUBCELLULAR LOCATION	Membrane; Single-pass type I membrane protein. Membrane, coated pit.

2. Sequence:

[0403]

(SEQ ID NO: 40)

MDRGPAAVACTLLLALVACLAPASGQECDSAHFRCGSGHCIPADWRCDGT

KDCSDDADEIGCAVVTCQQGYFKCQSEGQCIPNSWVCDQDQDCDDGSDER

QDCSQSTCSSHQITCSNGQCIPSEYRCDHVRDCPDGADENDCQYPTCEQL

TCDNGACYNTSQKCDWKVDCRDSSDEINCTEICLHNEFSCGNGECIPRAY

VCDHDNDCQDGSDEHACNYPTCGGYQFTCPSGRCIYQNWVCDGEDDCKDN

GDEDGCESGPHDVHKCSPREWSCPESGRCISIYKVCDGILDCPGREDENN

TSTGKYCSMTLCSALNCQYQCHETPYGGACFCPPGYIINHNDSRTCVEFD

DCQIWGICDQKCESRPGRHLCHCEEGYILERGQYCKANDSFGEASIIFSN

GRDLLIGDIHGRSFRILVESQNRGVAVGVAFHYHLQRVFWTDTVQNKVFS

VDINGLNIQEVLNVSVETPENLAVDWVNNKIYLVETKVNRIDMVNLDGSY

RVTLITENLGHPRGIAVDPTVGYLFFSDWESLSGEPKLERAFMDGSNRKD

LVKTKLGWPAGVTLDMISKRVYWVDSRFDYIETVTYDGIQRKTVVHGGSL

IPHPFGVSLFEGQVFFTDWTKMAVLKANKFTETNPQVYYQASLRPYGVTV

YHSLRQPYATNPCKDNNGGCEQVCVLSHRTDNDGLGFRCKCTFGFQLDTD

ERHCIAVQNFLIFSSQVAIRGIPFTLSTQEDVMVPVSGNPSFFVGIDFDA

QDSTIFFSDMSKHMIFKQKIDGTGREILAANRVENVESLAFDWISKNLYW

TDSHYKSISVMRLADKTRRTVVQYLNNPRSVVVHPFAGYLFFTDWFRPAK

IMRAWSDGSHLLPVINTTLGWPNGLAIDWAASRLYWVDAYFDKIEHSTFD

GLDRRRLGHIEQMTHPFGLAIFGEHLFFTDWRLGAIIRVRKADGGEMTVI

RSGIAYILHLKSYDVNIQTGSNACNQPTHPNGDCSHFCFPVPNFQRVCGC

PYGMRLASNHLTCEGDPTNEPPTEQCGLFSFPCKNGRCVPNYYLCDGVDD

CHDNSDEQLCGTLNNTCSSSAFTCGHGECIPAHWRCDKRNDCVDGSDEHN

CPTHAPASCLDTQYTCDNHQCISKNWVCDTDNDCGDGSDEKNCNSTETCQ

PSQFNCPNHRCIDLSFVCDGDKDCVDGSDEVGCVLNCTASQFKCASGDKC

IGVTNRCDGVFDCSDNSDEAGCPTRPPGMCHSDEFQCQEDGICIPNFWEC

DGHPDCLYGSDEHNACVPKTCPSSYFHCDNGNCIHRAWLCDRDNDCGDMS

DEKDCPTQPFRCPSWQWQCLGHNICVNLSVVCDGIFDCPNGTDESPLCNG

NSCSDFNGGCTHECVQEPFGAKCLCPLGFLLANDSKTCEDIDECDILGSC

SQHCYNMRGSFRCSCDTGYMLESDGRTCKVTASESLLLLVASQNKIIADS

VTSQVHNIYSLVENGSYIVAVDFDSISGRIFWSDATQGKTWSAFQNGTDR

-continued

RVVFDSSIILTETIAIDWVGRNLYWTDYALETIEVSKIDGSHRTVLISKN

LTNPRGLALDPRMNEHLLFWSDWGHHPRIERASMDGSMRTVIVQDKIFWP

CGLTIDYPNRLLYFMDSYLDYMDFCDYNGHHRRQVIASDLIIRHPYALTL

FEDSVYWTDRATRRVMRANKWHGGNQSVVMYNIQWPLGIVAVHPSKQPNS

VNPCAPSRCSHLCLLSSQGPHFYSCVCPSGWSLSPDLLNCLRDDQPFLIT

VRQHIIFGISLNPEVKSNDAMVPIAGIQNGLDVEFDDAEQYIYWVENPGE

IHRVKTDGTNRTVFASISMVGPSMNLALDWISRNLYSTNPRTQSIEVLTL

HGDIRYRKTLIANDGTALGVGFPIGITVDPARGKLYWSDQGTDSGVPAKI

ASANMDGTSVKTLFTGNLEHLECVTLDIEEQKLYWAVTGRGVIERGNVDG

TDRMILVHQLSHPWGIAVHDSFLYYTDEQYEVIERVDKATGANKIVLRDN

VPNLRGLQVYHRRNAAESSNGCSNNMNACQQICLPVPGGLFSCACATGFK

LNPDNRSCSPYNSFIVVSMLSAIRGFSLELSDHSETMVPVAGQGRNALHV

DVDVSSGFIYWCDFSSSVASDNAIRRIKPDGSSLMNIVTHGIGENGVRGI

AVDWVAGNLYFTNAFVSETLIEVLRINTTYRRVLLKVTVDMPRHIVVDPK

NRYLFWADYGQRPKIERSFLDCTNRTVLVSEGIVTPRGLAVDRSDGYVYW

VDDSLDIIARIRINGENSEVIRYGSRYPTPYGITVFENSIIWVDRNLKKI

FQASKEPENTEPPTVIRDNINWLRDVTIFDKQVQPRSPAEVNNNPCLENN

GGCSHLCFALPGLHTPKCDCAFGTLQSDGKNCAISTENFLIFALSNSLRS

LHLDPENHSPPFQTINVERTVMSLDYDSVSDRIYFTQNLASGVGQISYAT

LSSGIHTPTVIASGIGTADGIAFDWITRRIYYSDYLNQMINSMAEDGSNR

TVIARVPKPRAIVLDPCQGYLYWADWDTHAKIERATLGGNFRVPIVNSSL

VMPSGLTLDYEEDLLYWVDASLQRIERSTLTGVDREVIVNAAVHAFGLTL

YGQYIYWTDLYTQRIYRANKYDGSGQIAMTTNLLSQPRGINTVVKNQKQQ

TCNNPCEQFNGGCSHICAPGPNGAECQCPHEGNWYLANNRKHCIVDNGER

CGASSFCSNGRCISEEWKCDNDNDCGDGSDEMESVCALHTCSPTAFTCAN

GRCVQYSYRCDYYNDCGDGSDEAGCLFRDCNATTEFMCNNRRCIPREFIC

NGVDNCHDNNTSDEKNCPDRTCQSGYTKCHNSNICIPRVYLCDGDNDCGD

NSDENPTYCTTHTCSSSEFQCASGRCIPQHWYCDQETDCFDASDEPASCG

HSERTCLADEFKCDGGRCIPSEWICDGDNDCGDMSDEDKRHQCQNQNCSD

SEFLCVNDRPPDRRCIPQSWVCDGDVDCTDGYDENQNCTRRTCSENEFTC

GYGLCIPKIFRCDRHNDCGDYSDERGCLYQTCQQNQFTCQNGRCISKTFV

CDEDNDCGDGSDELMHLCHTPEPTCPPHEFKCDNGRCIEMMKLCNHLDDC

LDNSDEKGCGINECHDPSISGCDHNCTDTLTSFYCSCRPGYKLMSDKRTC

VDIDECTEMPFVCSQKCENVIGSYICKCAPGYLREPDGKTCRQNSNIEPY

LIFSNRYYLRNLTIDGYFYSLILEGLDNVVALDFDRVEKRLYWIDTQRQV

IERMFLNKTNKETIINHRLPAAESLAVDWVSRKLYWLDARLDGLFVSDLN

GGHRRMLAQHCVDANNTFCFDNPRGLALHPQYGYLYWADWGHRAYIGRVG

MDGTNKSVIISTKLEWPNGITIDYTNDLLYWADAHLGYIEYSDLEGHHRH

TVYDGALPHPFAITIFEDTIYWTDWNTRTVEKGNKYDGSNRQTLVNTTHR

-continued

PFDIHVYHPYRQPIVSNPCGTNNGGCSHLCLIKPGGKGFTCECPDDFRTL

QLSGSTYCMPMCSSTQFLCANNEKCIPIWWKCDGQKDCSDGSDELALCPQ

RFCRLGQFQCSDGNCTSPQTLCNAHQNCPDGSDEDRLLCENHHCDSNEWQ

CANKRCIPESWQCDTFNDCEDNSDEDSSHCASRTCRPGQFRCANGRCIPQ

AWKCDVDNDCGDHSDEPIEECMSSAHLCDNFTEFSCKTNYRCIPKWAVCN

GVDDCRDNSDEQGCEERTCHPVGDFRCKNHHCIPLRWQCDGQNDCGDNSD

EENCAPRECTESEFRCVNQQCIPSRWICDHYNDCGDNSDERDCEMRTCHP

EYFQCTSGHCVHSELKCDGSADCLDASDEADCPTRFPDGAYCQATMFECK

NHVCIPPYWKCDGDDDCGDGSDEELHLCLDVPCNSPNRFRCDNNRCIYSH

EVCNGVDDCGDGTDETEEHCRKPTPKPCTEYEYKCGNGHCIPHDNVCDDA

DDCGDWSDELGCNKGKERTCAENICEQNCTQLNEGGFICSCTAGFETNVF

DRTSCLDINECEQFGTCPQHCRNTKGSYECVCADGFTSMSDRPGKRCAAE

GSSPLLLLPDNVRIRKYNLSSERFSEYLQDEEYIQAVDYDWDPKDIGLSV

VYYTVRGEGSRFGAIKRAYIPNFESGRNNLVQEVDLKLKYVMQPDGIAVD

WVGRHIYWSDVKNKRIEVAKLDGRYRKWLISTDLDQPAAIAVNPKLGLMF

WTDWGKEPKIESAWMNGEDRNILVFEDLGWPTGLSIDYLNNDRIYWSDFK

EDVIETIKYDGTDRRVIAKEAMNPYSLDIFEDQLYWISKEKGEVWKQNKF

GQGKKEKTLVVNPWLTQVRIFHQLRYNKSVPNLCKQICSHLCLLRPGGYS

CACPQGSSFIEGSTTECDAAIELPINLPPPCRCMHGGNCYFDETDLPKCK

CPSGYTGKYCEMAFSKGISPGTTAVAVLLTILLIVVIGALAIAGFFHYRR

TGSLLPALPKLPSLSSLVKPSENGNGVTFRSGADLNMDIGVSGFGPETAI

DRSMAMSEDFVMEMGKQPIIFENPMYSARDSAVKVVQPIQVTVSENVDNK

NYGSPINPSEIVPETNPTSPAADGTQVTKWNLFKRKSKQTTNFENPIYAQ

MENEQKESVAATPPPSPSLPAKPKPPSRRDPTPTYSATEDTFKDTANLVK
EDSEV

3. Alternative Name(s):

[0404] Megalin; Glycoprotein 330; Short name=gp330
This protein has not been directly linked to myocardial ischemia or events leading up to MI.

V. Prolow Density Lipoprotein Receptor Related Protein 1

[0405] Name: Prolow density lipoprotein receptor related protein 1

IPI ID: IPI00020557

UniProtKB/Swiss-Prot ID: Q07954

[0406] Length: 4544 aa, molecular weight: 504575 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

[0407] Function: Endocytic receptor involved in endocytosis and in phagocytosis of apoptotic cells. Required for early embryonic development. Involved in cellular lipid homeostasis. Involved in the plasma clearance of chylomicron remnants and activated LRPAP1 (alpha 2-macroglobulin), as well as the local metabolism of complexes between plasminogen activators and their endogenous inhibitors. May modulate cellular events, such as APP metabolism, kinase-dependent intracellular signaling, neuronal calcium signaling as well as neurotransmission.

[0408] Subcellular location: Low-density lipoprotein receptor-related protein 1 85 kDa subunit: Cell membrane; Single-pass type I membrane protein. Membrane>coated pit. Low-density lipoprotein receptor-related protein 1 515 kDa subunit: Cell membrane; Peripheral membrane protein; Extracellular side. Membrane>coated pit. Low-density lipoprotein receptor-related protein 1 intracellular domain: Cytoplasm. Nucleus. Note=

[0409] After cleavage, the intracellular domain (LRPICD) is detected both in the cytoplasm and in the nucleus.

2. Sequence:

[0410]

(SEQ ID NO: 41)

MLTPPLLLLLPLLSALVAAAIDAPKTCSPKQFACRDQITCISKGWRCDGE

RDCPDGSDEAPEICPQSKAQRCQPNEHNCLGTELCVPMSRLCNGVQDCMD

GSDEGPHCRELQGNCSRLGCQHHCVPTLDGPTCYCNSSFQLQADGKTCKD

FDECSVYGTCSQLCTNTDGSFICGCVEGYLLQPDNRSCKAKNEPVDRPPV

LLIANSQNILATYLSGAQVSTITPTSTRQTTAMDFSYANETVCWVHVGDS

AAQTQLKCARMPGLKGFVDEHTINISLSLHHVEQMAIDWLTGNFYFVDDI

DDRIFVCNRNGDTCVTLLDLELYNPKGIALDPAMGKVFFTDYGQIPKVER

CDMDGQNRTKLVDSKIVFPHGITLDLVSRLVYWADAYLDYIEVVDYEGKG

RQTIIQGILIEHLYGLTVFENYLYATNSDNANAQQKTSVIRVNRFNSTEY

QVVTRVDKGGALHIYHQRRQPRVRSHACENDQYGKPGGCSDICLLANSHK

ARTCRCRSGFSLGSDGKSCKKPEHELFLVYGKGRPGIIRGMDMGAKVPDE

HMIPIENLMNPRALDFHAETGFIYFADTTSYLIGRQKIDGTERETILKDG

IHNVEGVAVDWMGDNLYWTDDGPKKTISVARLEKAAQTRKTLIEGKMTHP

RAIVVDPLNGWMYWTDWEEDPKDSRRGRLERAWMDGSHRDIFVTSKTVLW

PNGLSLDIPAGRLYWVDAFYDRIETILLNGTDRKIVYEGPELNHAFGLCH

HGNYLFWTEYRSGSVYRLERGVGGAPPTVTLLRSERPPIFEIRMYDAQQQ

QVGTNKCRVNNGGCSSLCLATPGSRQCACAEDQVLDADGVTCLANPSYVP

PPQCQPGEFACANSRCIQERWKCDGDNDCLDNSDEAPALCHQHTCPSDRF

KCENNRCIPNRWLCDGDNDCGNSEDESNATCSARTCPPNQFSCASGRCIP

ISWTCDLDDDCGDRSDESASCAYPTCFPLTQFTCNNGRCININWRCDNDN

DCGDNSDEAGCSHSCSSTQFKCNSGRCIPEHWTCDGDNDCGDYSDETHAN

CTNQATRPPGGCHTDEFQCRLDGLCIPLRWRCDGDTDCMDSSDEKSCEGV

THVCDPSVKFGCKDSARCISKAWVCDGDNDCEDNSDEENCESLACRPPSH

PCANNTSVCLPPDKLCDGNDDCGDGSDEGELCDQCSLNNGGCSHNCSVAP

GEGIVCSCPLGMELGPDNHTCQIQSYCAKHLKCSQKCDQNKFSVKCSCYE

GWVLEPDGESCRSLDPFKPFIIFSNRHEIRRIDLHKGDYSVLVPGLRNTI

-continued

ALDFHLSQSALYWTDVVEDKIYRGKLLDNGALTSFEVVIQYGLATPEGLA
VDWIAGNIYWVESNLDQIEVAKLDGTLRTTLLAGDIEHPRAIALDPRDGI
LFWTDWDASLPRIEAASMSGAGRRTVHRETGSGGWPNGLTVDYLEKRILW
IDARSDAIYSARYDGSGHMEVLRGHEFLSHPFAVTLYGGEVYWTDWRTNT
LAKANKWTGHNVTVVQRTNTQPFDLQVYHPSRQPMAPNPCEANGGQGPCS
HLCLINYNRTVSCACPHLMKLHKDNTTCYEFKKFLLYARQMEIRGVDLDA
PYYNYIISFTVPDIDNVTVLDYDAREQRVYWSDVRTQAIKRAFINGTGVE
TVVSADLPNAHGLAVDWVSRNLFWTSYDTNKKQINVARLDGSFKNAVVQG
LEQPHGLVVHPLRGKLYWTDGDNISMANMDGSNRTLLFSGQKGPVGLAID
FPESKLYWISSGNHTINRCNLDGSGLEVIDAMRSQLGKATALAIMGDKLW
WADQVSEKMGTCSKADGSGSVVLRNSTTLVMHMKVYDESIQLDHKGTNPC
SVNNGDCSQLCLPTSETTRSCMCTAGYSLRSGQQACEGVGSFLLYSVHEG
IRGIPLDPNDKSDALVPVSGTSLAVGIDFHAENDTIYWVDMGLSTISRAK
RDQTWREDVVTNGIGRVEGIAVDWIAGNIYWTDQGFDVIEVARLNGSFRY
VVISQGLDKPRAITVHPEKGYLFWTEWGQYPRIERSRLDGTERVVLVNVS
ISWPNGISVDYQDGKLYWCDARTDKIERIDLETGENREVVLSSNNMDMFS
VSVFEDFIYWSDRTHANGSIKRGSKDNATDSVPLRTGIGVQLKDIKVFNR
DRQKGTNVCAVANGGCQQLCLYRGRGQRACACAHGMLAEDGASCREYAGY
LLYSERTILKSIHLSDERNLNAPVQPFEDPEHMKNVIALAFDYRAGTSPG
TPNRIFFSDIHFGNIQQINDDGSRRITIVENVGSVEGLAYHRGWDTLYWT
SYTTSTITRHTVDQTRPGAFERETVITMSGDDHPRAFVLDECQNLMFWTN
WNEQHPSIMRAALSGANVLTLIEKDIRTPNGLAIDHRAEKLYFSDATLDK
IERCEYDGSHRYVILKSEPVHPFGLAVYGEHIFWTDWVRRAVQRANKHVG
SNMKLLRVDIPQQPMGIIAVANDTNSCELSPCRINNGGCQDLCLLTHQGH
VNCSCRGGRILQDDLTCRAVNSSCRAQDEFECANGECINFSLTCDGVPHC
KDKSDEKPSYCNSRRCKKTFRQCSNGRCVSNMLWCNGADDCGDGSDEIPC
NKTACGVGEFRCRDGTCIGNSSRCNQFVDCEDASDEMNCSATDCSSYFRL
GVKGVLFQPCERTSLCYAPSWVCDGANDCGDYSDERDCPGVKRPRCPLNY
FACPSGRCIPMSWTCDKEDDCEHGEDETHCNKFCSEAQFECQNHRCISKQ
WLCDGSDDCGDGSDEAAHCEGKTCGPSSFSCPGTHVCVPERWLCDGDKDC
ADGADESIAAGCLYNSTCDDREFMCQNRQCIPKHFVCDHDRDCADGSDES
PECEYPTCGPSEFRCANGRCLSSRQWECDGENDCHDQSDEAPKNPHCTSP
EHKCNASSQFLCSSGRCVAEALLCNGQDDCGDSSDERGCHINECLSRKLS
GCSQDCEDLKIGFKCRCRPGFRLKDDGRTCADVDECSTTFPCSQRCINTH
GSYKCLCVEGYAPRGGDPHSCKAVTDEEPFLIFANRYYLRKLNLDGSNYT
LLKQGLNNAVALDFDYREQMIYWTDVTTQGSMIRRMHLNGSNVQVLHRTG
KLSNPDGLAVDWVGGNLYWCDGRDTIEVSKLNGAYRTVLVSSGLREPRAL
VVDVQNGYLYWTDWGDHSLIGRIGMDGSSRSVIVDTKITWPNGLTLDYVT
ERIYWADAREDYIEFASLDGSNRHVVLSQDIPHIFALTLFEDYVYWTDWE

-continued

TKSINRAHKTTGTNKTLLISTLHRPMDLHVFHALRQPDVPNHPCKVNNGG
CSNLCLLSPGGGHKCACPTNFYLGSDGRTCVSNCTASQFVCKNDKCIPFW
WKCDTEDDCGDHSDEPPDCPEFKCRPGQFQCSTGICTNPAFICDGDNDCQ
DNSDEANCDIHVCLPSQFKCTNTNRCIPGIFRCNGQDNCGDGEDERDCPE
VTCAPNQFQCSITKRCIPRVWVCDRDNDCVDGSDEPANCTQMTCGVDEFR
CKDSGRCIPARWKCDGEDDCGDGSDEPKEECDERTCEPYQFRCKNNRCVP
GRWQCDYDNDCGDNSDEESCTPRPCSESEFSCANGRCIAGRWKCDGDHDC
ADGSDEKDCTPRCDMDQFQCKSGHCIPLRWRCDADADCMDGSDEEACGTG
VRTCPLDEFQCNNTLCKPLAWKCDGEDDCGDNSDENPEECARFVCPPNRP
FRCKNDRVCLWIGRQCDGTDNCGDGTDEEDCEPPTAHTTHCKDKKEFLCR
NQRCLSSSLRCNMFDDCGDGSDEEDCSIDPKLTSCATNASICGDEARCVR
TEKAAYCACRSGFHTVPGQPGCQDINECLRFGTCSQLCNNTKGGHLCSCA
RRNFMKTHNTCKAEGSEYQVLYIADDNEIRSLFPGHPHSAYEQAFQGDES
VIDAMDVHVKAGRVYWTNWHTGTISYRSLPPAAPPTTSNRHRRQIDRGVT
RHLNISGLKMPGIAIDWVAGNVYWTDSGRDVIEVAQMKGENRKTLISGMI
DEPHAIVVDPLRGTMYWSDWGNHPKIETAAMDGTLRETLVQDNIQWPTGL
AVDYHNERLYWADAKLSVIGSIRLNGTDPIVAADSKRGLSHPFSIDVFED
YIYGVTYINNRVFKIHKFGHSPLVNLTGGLSHASDVVLYHQHKQPEVTNP
CDRKKCEWLCLLSPSGPVCTCPNGKRLDNGTCVPVPSPTPPPDAPRPGTC
NLQCFNGGSCFLNARRQPKCRCQPRYTGDKCELDQCWEHCRNGGTCAASP
SGMPTCRCPTGFTGPKCTQQVCAGYCANNSTCTVNQGNQPQCRCLPGFLG
DRCQYRQCSGYCENFGTCQMAADGSRQCRCTAYFEGSRCEVNKCSRCLEG
ACVVNKQSGDVTCNCTDGRVAPSCLTCVGHCSNGGSCTMNSKMMPECQCP
PHMTGPRCEEHVFSQQQPGHIASILIPLLLLLLLVLVAGVVFWYKRRVQG
AKGFQHQRMTNGAMNVEIGNPTYKMYEGGEPDDVGGLLDADFALDPDKPT
NFTNPVYATLYMGGHGSRHSLASTDEKRELLGRGPEDEIGDPLA

3. Alternative Name(s):

[0411] Alpha-2-macroglobulin receptor
[0412] Short name=A2MR
[0413] Apolipoprotein E receptor
[0414] Short name=APOER
[0415] CD_antigen=CD91

This protien has not been directly linked to myocardial ischemia or events leading up to MI.

W. Monocyte Differentiation Antigen CD14

Name: MONOCYTE DIFFERENTIATION ANTIGEN CD14

IPI ID: IPI00029260

UniProtKB/Swiss-Prot ID: P08571

[0416] Length: 375 aa, molecular weight: 40076 Da (of Precursor)

1. Basic Information from UniProtKB/Swiss-Prot Entry:

FUNCTION	Cooperates with MD-2 and TLR4 to mediate the innate immune response to bacterial lipopolysaccharide (LPS). Acts via MyD88, TIRAP and TRAF6, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response. Up-regulates cell surface molecules, including adhesion molecules.
SUBCELLULAR LOCATION	Cell membrane; Lipid-anchor, GPI-anchor.

2. Sequence:

[0417]

(SEQ ID NO: 42)

MERASCLLLLLLPLVHVSATTPEPCELDDEDFRCVCNFSEPQPDWSEAFQ

CVSAVEVEIHAGGLNLEPFLKRVDADADPRQYADTVKALRVRRLTVGAAQ

VPAQLLVGALRVLAYSRLKELTLEDLKITGTMPPLPLEATGLALSSLRLR

NVSWATGRSWLAELQQWLKPGLKVLSIAQAHSPAFSCEQVRAFPALTSLD

LSDNPGLGERGLMAALCPHKFPAIQNLALRNTGMETPTGVCAALAAAGVQ

PHSLDLSHNSLRATVNPSAPRCMWSSALNSLNLSFAGLEQVPKGLPAKLR

VLDLSCNRLNRAPQPDELPEVDNLTLDGNPFLVPGTALPHEGSMNSGVVP

ACARSTLSVGVSGTLVLLQGARGFA

3. Alternative Name(s):

[0418] Myeloid cell-specific leucine-rich glycoprotein; CD_antigen=CD14 Monocytes and T-cells play an important role in the development of atherosclerotic coronary artery disease. C14 is located on the monocytes and, therefore, changes to this protein can and have been linked to alterations to monocytes (including with coronary artery disease). However, this protein has not been measured in serum in context to myocardial ischemia or events leading up to a MI.

X. Peroxiredoxin-2

Name: Peroxiredoxin-2

IPI ID: IPI00027350

UniProtKB/Swiss-Prot ID: P32119; PRDX2_HUMAN; M.

[0419] Length: 198 aa, molecular weight: 21892 Da, CRC64 checksum: 1AC781D908B32B46

1. Basic Information from UniProtKB/Swiss-Prot Entry:

Function	Involved in redox regulation of the cell. Reduces peroxides with reducing equivalents provided through the thioredoxin system. It is not able to receive electrons from glutaredoxin. May play an important role in eliminating peroxides generated during metabolism. Might participate in the signaling cascades of growth factors and tumor necrosis factor-alpha by regulating the intracellular concentrations of H_2O_2.

-continued

Catalytic activity	2 R'—SH + ROOH = R'—S—S—R' + H_2O + ROH.
Subunit structure	Homodimer; disulfide-linked, upon oxidation. May be found as a toroid-shaped decamer composed of 5 dimers, depending on pH and calcium concentration. Interacts with TIPIN.
Subcellular location	Cytoplasm.
Miscellaneous	The active site is the redox-active Cys-51 oxidized to Cys-SOH. Cys-SOH rapidly reacts with Cys-172-SH of the other subunit to form an intermolecular disulfide with a concomitant homodimer formation. The enzyme may be subsequently regenerated by reduction of the disulfide by thioredoxin. Inactivated upon oxidative stress by overoxidation of Cys-51 to Cys-SO_2H and Cys-SO_3H. Cys-SO_2H is retroreduced to Cys-SOH after removal of H_2O_2, while Cys-SO_3H may be irreversibly oxidized.
Sequence similarities	Belongs to the ahpC/TSA family. Contains 1 thioredoxin domain.

2. Sequence:

[0420]

(SEQ ID NO: 43)

MASGNARIGKPAPDFKATAVVDGAFKEVKLSDYKGKYVVLFFYPLDFTFV

CPTEIIAFSNRAEDFRKLGCEVLGVSVDSQFTHLAWINTPRKEGGLGPLN

IPLLADVTRRLSEDYGVLKTDEGIAYRGLFIIDGKGVLRQITVNDLPVGR

SVDEALRLVQAFQYTDEHGEVCPAGWKPGSDTIKPNVDDSKEYFSKHN

3. Alternative Name(s):

[0421] Thioredoxin peroxidase 1

[0422] Thioredoxin-dependent peroxide reductase 1

[0423] Thiol-specific antioxidant protein

[0424] Short name=TSA

[0425] PRP

[0426] Natural killer cell-enhancing factor B

[0427] Short name=NKEF-B

This protein has been found to increase in the serum of a number diseases but none are cardiac related. This protein, to date, has not been shown to be increased in myocardial ischemia or events leading to MI.

Y. NCOR2 CTG26 Alternate Open Reading Frame

[0428] Name: CTG26 alternate open reading frame (Fragment)

IPI ID: IPI00006659.3

[0429] Basic information: Fragment

[0430] 1. Sequence:

(SEQ ID NO: 44)

SFSSMEASSALCWGVMASSLLASLAIERVMRPLRLPWLLAVLRPLEATAS

FSSLSSPEVSSVFSLRRSSLSFSTSGFSSSFSASFSFSFSSFSSWLLRGM

GCCCCCCCCCCCCCCCWLLPRRR

This protein has not be linked to myocardial ischemia or events leading up to MI.

Example V

Validation Studies

[0431] Antibodies to two or more epitopes on each protein will be generated and used to develop a sandwich ELISA assay (as single or multiplex) that is specific and sensitive for the analyte. The analyte will either be peptide, protein fragment or protein and will be used to generate standard curve. Analysis will be carried out using conventional ELISA or on a Luminex or Mesoscale platform. Assays will be carried out at least in duplicate. For MRM assays, peptides (generated most likely by trypsin, chymotrypsin or Lys C) that are unique to the protein of interest and showing high MS signal response (prototypic peptides) which will help maximize the sensitivity of the assay. 2. Selection of predominant peptide fragments specific (MS/MS) for the parent peptide (useful MRM transition). 3. For each peptide-fragment pair, optimization of specific MS parameters (e.g. the collision energy) to maximize the signal response/sensitivity. 4. Validation of the MRM assay to confirm peptide identity, e.g. by acquiring a full MS2 spectrum of the peptide in the triple quadrupole MS instrument used for MRM. 5. Extraction of the final "coordinates" of the MRM assay, including the selected peptide and peptide fragments, the corresponding mass-to-charge ratios, the fragment intensity ratios, the associated collision energy, and the chromatographic elution time to be optionally used in time-constrained MRM analyses. We will add isotopically labeled internal peptide standards (with known concentrations determined by amino acid analysis) to facilitate absolute quantitation of selected peptides. Assays will be performed on a triple quadropole mass spectrometer at least in duplicate.

[0432] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make changes and modifications of the invention to adapt it to various usage and conditions and to utilize the present invention to its fullest extent. The preceding preferred specific embodiments are to be construed as merely illustrative, and not limiting of the scope of the invention in any way whatsoever. The entire disclosure of all applications, patents, and publications (including provisional patent application 61/128,688, filed May 23, 2008) cited above and in the figures are hereby incorporated in their entirety by reference.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 44

<210> SEQ ID NO 1
<211> LENGTH: 474
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

```
Met Lys Arg Val Leu Val Leu Leu Leu Ala Val Ala Phe Gly His Ala
1               5                   10                  15

Leu Glu Arg Gly Arg Asp Tyr Glu Lys Asn Lys Val Cys Lys Glu Phe
            20                  25                  30

Ser His Leu Gly Lys Glu Asp Phe Thr Ser Leu Ser Leu Val Leu Tyr
        35                  40                  45

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

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

Pro Asp Cys Tyr Asp Thr Arg Thr Ser Ala Leu Ser Ala Lys Ser Cys
                85                  90                  95

Glu Ser Asn Ser Pro Phe Pro Val His Pro Gly Thr Ala Glu Cys Cys
            100                 105                 110

Thr Lys Glu Gly Leu Glu Arg Lys Leu Cys Met Ala Ala Leu Lys His
        115                 120                 125

Gln Pro Gln Glu Phe Pro Thr Tyr Val Glu Pro Thr Asn Asp Glu Ile
    130                 135                 140

Cys Glu Ala Phe Arg Lys Asp Pro Lys Glu Tyr Ala Asn Gln Phe Met
145                 150                 155                 160

Trp Glu Tyr Ser Thr Asn Tyr Gly Gln Ala Pro Leu Ser Leu Leu Val
                165                 170                 175

Ser Tyr Thr Lys Ser Tyr Leu Ser Met Val Gly Ser Cys Cys Thr Ser
            180                 185                 190

Ala Ser Pro Thr Val Cys Phe Leu Lys Glu Arg Leu Gln Leu Lys His
```

-continued

```
        195                 200                 205

Leu Ser Leu Leu Thr Thr Leu Ser Asn Arg Val Cys Ser Gln Tyr Ala
    210                 215                 220

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

Gln Lys Val Pro Thr Ala Asp Leu Glu Asp Val Leu Pro Leu Ala Glu
                245                 250                 255

Asp Ile Thr Asn Ile Leu Ser Lys Cys Cys Glu Ser Ala Ser Glu Asp
            260                 265                 270

Cys Met Ala Lys Glu Leu Pro Glu His Thr Val Lys Leu Cys Asp Asn
        275                 280                 285

Leu Ser Thr Lys Asn Ser Lys Phe Glu Asp Cys Cys Gln Glu Lys Thr
    290                 295                 300

Ala Met Asp Val Phe Val Cys Thr Tyr Phe Met Pro Ala Ala Gln Leu
305                 310                 315                 320

Pro Glu Leu Pro Asp Val Glu Leu Pro Thr Asn Lys Asp Val Cys Asp
                325                 330                 335

Pro Gly Asn Thr Lys Val Met Asp Lys Tyr Thr Phe Glu Leu Ser Arg
            340                 345                 350

Arg Thr His Leu Pro Glu Val Phe Leu Ser Lys Val Leu Glu Pro Thr
        355                 360                 365

Leu Lys Ser Leu Gly Glu Cys Cys Asp Val Glu Asp Ser Thr Thr Cys
    370                 375                 380

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

Asp Lys Gly Gln Glu Leu Cys Ala Asp Tyr Ser Glu Asn Thr Phe Thr
                405                 410                 415

Glu Tyr Lys Lys Lys Leu Ala Glu Arg Leu Lys Ala Lys Leu Pro Asp
            420                 425                 430

Ala Thr Pro Lys Glu Leu Ala Lys Leu Val Asn Lys Arg Ser Asp Phe
        435                 440                 445

Ala Ser Asn Cys Cys Ser Ile Asn Ser Pro Pro Leu Tyr Cys Asp Ser
    450                 455                 460

Glu Ile Asp Ala Glu Leu Lys Asn Ile Leu
465                 470


<210> SEQ ID NO 2
<211> LENGTH: 415
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Met Ser Pro Phe Leu Tyr Leu Val Leu Leu Val Leu Gly Leu His Ala
1               5                   10                  15

Thr Ile His Cys Ala Ser Pro Glu Gly Lys Val Thr Ala Cys His Ser
            20                  25                  30

Ser Gln Pro Asn Ala Thr Leu Tyr Lys Met Ser Ser Ile Asn Ala Asp
        35                  40                  45

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

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

Ser Phe Gly Ala Cys Cys Ser Thr Gln Thr Glu Ile Val Glu Thr Leu
```

-continued

```
                85                  90                  95

Gly Phe Asn Leu Thr Asp Thr Pro Met Val Glu Ile Gln His Gly Phe
            100                 105                 110

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

Gln Ile Gly Asn Ala Leu Phe Ile Gly Lys His Leu Lys Pro Leu Ala
    130                 135                 140

Lys Phe Leu Asn Asp Val Lys Thr Leu Tyr Glu Thr Glu Val Phe Ser
145                 150                 155                 160

Thr Asp Phe Ser Asn Ile Ser Ala Ala Lys Gln Glu Ile Asn Ser His
                165                 170                 175

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

Lys Pro Asn Thr Ile Met Val Leu Val Asn Tyr Ile His Phe Lys Ala
        195                 200                 205

Gln Trp Ala Asn Pro Phe Asp Pro Ser Lys Thr Glu Asp Ser Ser Ser
    210                 215                 220

Phe Leu Ile Asp Lys Thr Thr Thr Val Gln Val Pro Met Met His Gln
225                 230                 235                 240

Met Glu Gln Tyr Tyr His Leu Val Asp Met Glu Leu Asn Cys Thr Val
                245                 250                 255

Leu Gln Met Asp Tyr Ser Lys Asn Ala Leu Ala Leu Phe Val Leu Pro
            260                 265                 270

Lys Glu Gly Gln Met Glu Ser Val Glu Ala Ala Met Ser Ser Lys Thr
        275                 280                 285

Leu Lys Lys Trp Asn Arg Leu Leu Gln Lys Gly Trp Val Asp Leu Phe
    290                 295                 300

Val Pro Lys Phe Ser Ile Ser Ala Thr Tyr Asp Leu Gly Ala Thr Leu
305                 310                 315                 320

Leu Lys Met Gly Ile Gln His Ala Tyr Ser Glu Asn Ala Asp Phe Ser
                325                 330                 335

Gly Leu Thr Glu Asp Asn Gly Leu Lys Leu Ser Asn Ala Ala His Lys
            340                 345                 350

Ala Val Leu His Ile Gly Glu Lys Gly Thr Glu Ala Ala Ala Val Pro
        355                 360                 365

Glu Val Glu Leu Ser Asp Gln Pro Glu Asn Thr Phe Leu His Pro Ile
    370                 375                 380

Ile Gln Ile Asp Arg Ser Phe Met Leu Leu Ile Leu Glu Arg Ser Thr
385                 390                 395                 400

Arg Ser Ile Leu Phe Leu Gly Lys Val Val Asn Pro Thr Glu Ala
                405                 410                 415


<210> SEQ ID NO 3
<211> LENGTH: 338
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr
1               5                   10                  15

Ser Gly Gln Tyr Tyr Asp Tyr Asp Phe Pro Leu Ser Ile Tyr Gly Gln
            20                  25                  30

Ser Ser Pro Asn Cys Ala Pro Glu Cys Asn Cys Pro Glu Ser Tyr Pro
```

-continued

```
        35                  40                  45

Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val
    50                  55                  60

Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
65                  70                  75                  80

Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
                85                  90                  95

Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
            100                 105                 110

Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
        115                 120                 125

Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
    130                 135                 140

Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn
145                 150                 155                 160

Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
                165                 170                 175

Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
            180                 185                 190

Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
        195                 200                 205

Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
    210                 215                 220

Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
225                 230                 235                 240

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

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

Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys
        275                 280                 285

Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser
    290                 295                 300

Lys Ile Lys His Leu Arg Leu Asp Gly Asn Arg Ile Ser Glu Thr Ser
305                 310                 315                 320

Leu Pro Pro Asp Met Tyr Glu Cys Leu Arg Val Ala Asn Glu Val Thr
                325                 330                 335

Leu Asn


<210> SEQ ID NO 4
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Ser Asn Val Pro His Lys Ser Ser Leu Pro Glu Gly Ile Arg Pro
1               5                   10                  15

Gly Thr Val Leu Arg Ile Arg Gly Leu Val Pro Pro Asn Ala Ser Arg
            20                  25                  30

Phe His Val Asn Leu Leu Cys Gly Glu Glu Gln Gly Ser Asp Ala Ala
        35                  40                  45

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

-continued

```
Lys Glu Gln Gly Ser Trp Gly Arg Glu Glu Arg Gly Pro Gly Val Pro
65                  70                  75                  80

Phe Gln Arg Gly Gln Pro Phe Glu Val Leu Ile Ile Ala Ser Asp Asp
                85                  90                  95

Gly Phe Lys Ala Val Val Gly Asp Ala Gln Tyr His His Phe Arg His
            100                 105                 110

Arg Leu Pro Leu Ala Arg Val Arg Leu Val Glu Val Gly Gly Asp Val
        115                 120                 125

Gln Leu Asp Ser Val Arg Ile Phe
    130                 135


<210> SEQ ID NO 5
<211> LENGTH: 567
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Met Gly Thr Thr Ala Arg Ala Ala Leu Val Leu Thr Tyr Leu Ala Val
1               5                   10                  15

Ala Ser Ala Ala Ser Glu Gly Gly Phe Thr Ala Thr Gly Gln Arg Gln
            20                  25                  30

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

Pro Pro Leu Ser Arg Ser Leu Pro Met Asp His Pro Asp Ser Ser Gln
    50                  55                  60

His Gly Pro Pro Phe Glu Gly Gln Ser Gly Lys Glu Gly Arg Gly Pro
65                  70                  75                  80

Arg Pro His Ser Gln Pro Trp Leu Gly Glu Arg Val Gly Cys Ser His
                85                  90                  95

Ile Pro Pro Ser Ile Val Gln Pro Pro Pro Ser Gln Glu Ala Thr Pro
            100                 105                 110

Leu Gln Gln Glu Lys Leu Leu Pro Ala Gln Leu Pro Ala Glu Lys Glu
        115                 120                 125

Val Gly Pro Pro Leu Pro Gln Glu Ala Val Pro Leu Gln Lys Glu Leu
    130                 135                 140

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

Phe Gly Asp Gln Ser His Pro Glu Pro Glu Ser Trp Asn Ala Ala Gln
                165                 170                 175

His Cys Gln Gln Asp Arg Ser Gln Gly Gly Trp Gly His Arg Leu Asp
            180                 185                 190

Gly Phe Pro Pro Gly Arg Pro Ser Pro Asp Asn Leu Asn Gln Ile Cys
        195                 200                 205

Leu Pro Asn Arg Gln His Val Val Tyr Gly Pro Trp Asn Leu Pro Gln
    210                 215                 220

Ser Ser Tyr Ser His Leu Thr Arg Gln Gly Glu Thr Leu Asn Phe Leu
225                 230                 235                 240

Glu Ile Gly Tyr Ser Arg Cys Cys His Cys Arg Ser His Thr Asn Arg
                245                 250                 255

Leu Glu Cys Ala Lys Leu Val Trp Glu Glu Ala Met Ser Arg Phe Cys
            260                 265                 270

Glu Ala Glu Phe Ser Val Lys Thr Arg Pro His Trp Cys Cys Thr Arg
        275                 280                 285
```

-continued

```
Gln Gly Glu Ala Arg Phe Ser Cys Phe Gln Glu Glu Ala Pro Gln Pro
    290                 295                 300

His Tyr Gln Leu Arg Ala Cys Pro Ser His Gln Pro Asp Ile Ser Ser
305                 310                 315                 320

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

Lys Asn Ile Cys His Leu Arg Arg Phe Arg Ser Val Pro Arg Asn Leu
            340                 345                 350

Pro Ala Thr Asp Pro Leu Gln Arg Glu Leu Leu Ala Leu Ile Gln Leu
        355                 360                 365

Glu Arg Glu Phe Gln Arg Cys Cys Arg Gln Gly Asn Asn His Thr Cys
    370                 375                 380

Thr Trp Lys Ala Trp Glu Asp Thr Leu Asp Lys Tyr Cys Asp Arg Glu
385                 390                 395                 400

Tyr Ala Val Lys Thr His His His Leu Cys Cys Arg His Pro Pro Ser
                405                 410                 415

Pro Thr Arg Asp Glu Cys Phe Ala Arg Arg Ala Pro Tyr Pro Asn Tyr
            420                 425                 430

Asp Arg Asp Ile Leu Thr Ile Asp Ile Gly Arg Val Thr Pro Asn Leu
        435                 440                 445

Met Gly His Leu Cys Gly Asn Gln Arg Val Leu Thr Lys His Lys His
    450                 455                 460

Ile Pro Gly Leu Ile His Asn Met Thr Ala Arg Cys Cys Asp Leu Pro
465                 470                 475                 480

Phe Pro Glu Gln Ala Cys Cys Ala Glu Glu Glu Lys Leu Thr Phe Ile
                485                 490                 495

Asn Asp Leu Cys Gly Pro Arg Arg Asn Ile Trp Arg Asp Pro Ala Leu
            500                 505                 510

Cys Cys Tyr Leu Ser Pro Gly Asp Glu Gln Val Asn Cys Phe Asn Ile
        515                 520                 525

Asn Tyr Leu Arg Asn Val Ala Leu Val Ser Gly Asp Thr Glu Asn Ala
    530                 535                 540

Lys Gly Gln Gly Glu Gln Gly Ser Thr Gly Gly Thr Asn Ile Ser Ser
545                 550                 555                 560

Thr Ser Glu Pro Lys Glu Glu
                565


<210> SEQ ID NO 6
<211> LENGTH: 402
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Lys Pro Asn Ile Ile Phe Val Leu Ser Leu Leu Leu Ile Leu Glu
1               5                   10                  15

Lys Gln Ala Ala Val Met Gly Gln Lys Gly Gly Ser Lys Gly Arg Leu
            20                  25                  30

Pro Ser Glu Phe Ser Gln Phe Pro His Gly Gln Lys Gly Gln His Tyr
        35                  40                  45

Ser Gly Gln Lys Gly Lys Gln Gln Thr Glu Ser Lys Gly Ser Phe Ser
    50                  55                  60

Ile Gln Tyr Thr Tyr His Val Asp Ala Asn Asp His Asp Gln Ser Arg
65                  70                  75                  80
```

-continued

```
Lys Ser Gln Gln Tyr Asp Leu Asn Ala Leu His Lys Thr Thr Lys Ser
                85                  90                  95

Gln Arg His Leu Gly Gly Ser Gln Gln Leu Leu His Asn Lys Gln Glu
            100                 105                 110

Gly Arg Asp His Asp Lys Ser Lys Gly His Phe His Arg Val Val Ile
        115                 120                 125

His His Lys Gly Gly Lys Ala His Arg Gly Thr Gln Asn Pro Ser Gln
    130                 135                 140

Asp Gln Gly Asn Ser Pro Ser Gly Lys Gly Ile Ser Ser Gln Tyr Ser
145                 150                 155                 160

Asn Thr Glu Glu Arg Leu Trp Val His Gly Leu Ser Lys Glu Gln Thr
                165                 170                 175

Ser Val Ser Gly Ala Gln Lys Gly Arg Lys Gln Gly Gly Ser Gln Ser
            180                 185                 190

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

Glu Thr Lys Asn Ser His Gln Asn Lys Gly His Tyr Gln Asn Val Val
    210                 215                 220

Glu Val Arg Glu Glu His Ser Ser Lys Val Gln Thr Ser Leu Cys Pro
225                 230                 235                 240

Ala His Gln Asp Lys Leu Gln His Gly Ser Lys Asp Ile Phe Ser Thr
                245                 250                 255

Gln Asp Glu Leu Leu Val Tyr Asn Lys Asn Gln His Gln Thr Lys Asn
            260                 265                 270

Leu Asn Gln Asp Gln Gln His Gly Arg Lys Ala Asn Lys Ile Ser Tyr
        275                 280                 285

Gln Ser Ser Ser Thr Glu Glu Arg Arg Leu His Tyr Gly Glu Asn Gly
    290                 295                 300

Val Gln Lys Asp Val Ser Gln Arg Ser Ile Tyr Ser Gln Thr Glu Lys
305                 310                 315                 320

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

Pro Trp His Gly Glu Asn Ala Lys Gly Glu Ser Gly Gln Ser Thr Asn
            340                 345                 350

Arg Glu Gln Asp Leu Leu Ser His Glu Gln Lys Gly Arg His Gln His
        355                 360                 365

Gly Ser His Gly Gly Leu Asp Ile Val Ile Ile Glu Gln Glu Asp Asp
    370                 375                 380

Ser Asp Arg His Leu Ala Gln His Leu Asn Asn Asp Arg Asn Pro Leu
385                 390                 395                 400

Phe Thr


<210> SEQ ID NO 7
<211> LENGTH: 484
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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

Thr Leu Ile Gln Ala Thr Leu Ser Pro Thr Ala Val Leu Ile Leu Gly
            20                  25                  30
```

-continued

```
Pro Lys Val Ile Lys Glu Lys Leu Thr Gln Glu Leu Lys Asp His Asn
        35                  40                  45

Ala Thr Ser Ile Leu Gln Gln Leu Pro Leu Leu Ser Ala Met Arg Glu
    50                  55                  60

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

Leu Lys His Ile Ile Trp Leu Lys Val Ile Thr Ala Asn Ile Leu Gln
                85                  90                  95

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

Pro Leu Asp Met Val Ala Gly Phe Asn Thr Pro Leu Val Lys Thr Ile
        115                 120                 125

Val Glu Phe His Met Thr Thr Glu Ala Gln Ala Thr Ile Arg Met Asp
    130                 135                 140

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

Ser His Gly Ser Leu Arg Ile Gln Leu Leu His Lys Leu Ser Phe Leu
                165                 170                 175

Val Asn Ala Leu Ala Lys Gln Val Met Asn Leu Leu Val Pro Ser Leu
            180                 185                 190

Pro Asn Leu Val Lys Asn Gln Leu Cys Pro Val Ile Glu Ala Ser Phe
        195                 200                 205

Asn Gly Met Tyr Ala Asp Leu Leu Gln Leu Val Lys Val Pro Ile Ser
    210                 215                 220

Leu Ser Ile Asp Arg Leu Glu Phe Asp Leu Leu Tyr Pro Ala Ile Lys
225                 230                 235                 240

Gly Asp Thr Ile Gln Leu Tyr Leu Gly Ala Lys Leu Leu Asp Ser Gln
                245                 250                 255

Gly Lys Val Thr Lys Trp Phe Asn Asn Ser Ala Ala Ser Leu Thr Met
            260                 265                 270

Pro Thr Leu Asp Asn Ile Pro Phe Ser Leu Ile Val Ser Gln Asp Val
        275                 280                 285

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

Leu Leu Asp Ser Val Leu Pro Glu Ser Ala His Arg Leu Lys Ser Ser
305                 310                 315                 320

Ile Gly Leu Ile Asn Glu Lys Ala Ala Asp Lys Leu Gly Ser Thr Gln
                325                 330                 335

Ile Val Lys Ile Leu Thr Gln Asp Thr Pro Glu Phe Phe Ile Asp Gln
            340                 345                 350

Gly His Ala Lys Val Ala Gln Leu Ile Val Leu Glu Val Phe Pro Ser
        355                 360                 365

Ser Glu Ala Leu Arg Pro Leu Phe Thr Leu Gly Ile Glu Ala Ser Ser
    370                 375                 380

Glu Ala Gln Phe Tyr Thr Lys Gly Asp Gln Leu Ile Leu Asn Leu Asn
385                 390                 395                 400

Asn Ile Ser Ser Asp Arg Ile Gln Leu Met Asn Ser Gly Ile Gly Trp
                405                 410                 415

Phe Gln Pro Asp Val Leu Lys Asn Ile Ile Thr Glu Ile Ile His Ser
            420                 425                 430

Ile Leu Leu Pro Asn Gln Asn Gly Lys Leu Arg Ser Gly Val Pro Val
        435                 440                 445
```

-continued

```
Ser Leu Val Lys Ala Leu Gly Phe Glu Ala Ala Glu Ser Ser Leu Thr
    450                 455                 460

Lys Asp Ala Leu Val Leu Thr Pro Ala Ser Leu Trp Lys Pro Ser Ser
465                 470                 475                 480

Pro Val Ser Gln


<210> SEQ ID NO 8
<211> LENGTH: 147
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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

Gly Leu Thr Pro Pro Thr Leu Ala Gln Asp Asn Ser Arg Tyr Thr His
            20                  25                  30

Phe Leu Thr Gln His Tyr Asp Ala Lys Pro Gln Gly Arg Asp Asp Arg
        35                  40                  45

Tyr Cys Glu Ser Ile Met Arg Arg Arg Gly Leu Thr Ser Pro Cys Lys
    50                  55                  60

Asp Ile Asn Thr Phe Ile His Gly Asn Lys Arg Ser Ile Lys Ala Ile
65                  70                  75                  80

Cys Glu Asn Lys Asn Gly Asn Pro His Arg Glu Asn Leu Arg Ile Ser
                85                  90                  95

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

Trp Pro Pro Cys Gln Tyr Arg Ala Thr Ala Gly Phe Arg Asn Val Val
        115                 120                 125

Val Ala Cys Glu Asn Gly Leu Pro Val His Leu Asp Gln Ser Ile Phe
    130                 135                 140

Arg Arg Pro
145


<210> SEQ ID NO 9
<211> LENGTH: 597
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met His Pro Pro Lys Thr Pro Ser Gly Ala Leu His Arg Lys Arg Lys
1               5                   10                  15

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

Leu Phe Gln Met Thr Leu Ile Ala Ala Leu Leu Pro Ala Val Leu Gly
        35                  40                  45

Asn Cys Gly Pro Pro Pro Thr Leu Ser Phe Ala Ala Pro Met Asp Ile
    50                  55                  60

Thr Leu Thr Glu Thr Arg Phe Lys Thr Gly Thr Thr Leu Lys Tyr Thr
65                  70                  75                  80

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

Asn Ser Asp Gly Glu Trp Val Tyr Asn Thr Phe Cys Ile Tyr Lys Arg
            100                 105                 110

Cys Arg His Pro Gly Glu Leu Arg Asn Gly Gln Val Glu Ile Lys Thr
```

-continued

```
        115                 120                 125

Asp Leu Ser Phe Gly Ser Gln Ile Glu Phe Ser Cys Ser Glu Gly Phe
    130                 135                 140

Phe Leu Ile Gly Ser Thr Thr Ser Arg Cys Glu Val Gln Asp Arg Gly
145                 150                 155                 160

Val Gly Trp Ser His Pro Leu Pro Gln Cys Glu Ile Val Lys Cys Lys
                165                 170                 175

Pro Pro Pro Asp Ile Arg Asn Gly Arg His Ser Gly Glu Glu Asn Phe
            180                 185                 190

Tyr Ala Tyr Gly Phe Ser Val Thr Tyr Ser Cys Asp Pro Arg Phe Ser
        195                 200                 205

Leu Leu Gly His Ala Ser Ile Ser Cys Thr Val Glu Asn Glu Thr Ile
    210                 215                 220

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

Lys Pro Asp Val Ser His Gly Glu Met Val Ser Gly Phe Gly Pro Ile
                245                 250                 255

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

Leu Arg Gly Ser Ser Val Ile His Cys Asp Ala Asp Ser Lys Trp Asn
        275                 280                 285

Pro Ser Pro Pro Ala Cys Glu Pro Asn Ser Cys Ile Asn Leu Pro Asp
    290                 295                 300

Ile Pro His Ala Ser Trp Glu Thr Tyr Pro Arg Pro Thr Lys Glu Asp
305                 310                 315                 320

Val Tyr Val Val Gly Thr Val Leu Arg Tyr Arg Cys His Pro Gly Tyr
                325                 330                 335

Lys Pro Thr Thr Asp Glu Pro Thr Thr Val Ile Cys Gln Lys Asn Leu
            340                 345                 350

Arg Trp Thr Pro Tyr Gln Gly Cys Glu Ala Leu Cys Cys Pro Glu Pro
        355                 360                 365

Lys Leu Asn Asn Gly Glu Ile Thr Gln His Arg Lys Ser Arg Pro Ala
    370                 375                 380

Asn His Cys Val Tyr Phe Tyr Gly Asp Glu Ile Ser Phe Ser Cys His
385                 390                 395                 400

Glu Thr Ser Arg Phe Ser Ala Ile Cys Gln Gly Asp Gly Thr Trp Ser
                405                 410                 415

Pro Arg Thr Pro Ser Cys Gly Asp Ile Cys Asn Phe Pro Pro Lys Ile
            420                 425                 430

Ala His Gly His Tyr Lys Gln Ser Ser Ser Tyr Ser Phe Phe Lys Glu
        435                 440                 445

Glu Ile Ile Tyr Glu Cys Asp Lys Gly Tyr Ile Leu Val Gly Gln Ala
    450                 455                 460

Lys Leu Ser Cys Ser Tyr Ser His Trp Ser Ala Pro Ala Pro Gln Cys
465                 470                 475                 480

Lys Ala Leu Cys Arg Lys Pro Glu Leu Val Asn Gly Arg Leu Ser Val
                485                 490                 495

Asp Lys Asp Gln Tyr Val Glu Pro Glu Asn Val Thr Ile Gln Cys Asp
            500                 505                 510

Ser Gly Tyr Gly Val Val Gly Pro Gln Ser Ile Thr Cys Ser Gly Asn
        515                 520                 525
```

-continued

```
Arg Thr Trp Tyr Pro Glu Val Pro Lys Cys Glu Trp Glu Thr Pro Glu
    530                 535                 540

Gly Cys Glu Gln Val Leu Thr Gly Lys Arg Leu Met Gln Cys Leu Pro
545                 550                 555                 560

Asn Pro Glu Asp Val Lys Met Ala Leu Glu Val Tyr Lys Leu Ser Leu
                565                 570                 575

Glu Ile Glu Gln Leu Glu Leu Gln Arg Asp Ser Ala Arg Gln Ser Thr
            580                 585                 590

Leu Asp Lys Glu Leu
        595


<210> SEQ ID NO 10
<211> LENGTH: 458
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Ser Asp Leu Leu Ser Val Phe Leu His Leu Leu Leu Leu Phe Lys
1               5                   10                  15

Leu Val Ala Pro Val Thr Phe Arg His His Arg Tyr Asp Asp Leu Val
            20                  25                  30

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

Tyr Ser Ile Gly Arg Ser Val Glu Gly Arg His Leu Tyr Val Leu Glu
    50                  55                  60

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

Tyr Val Gly Asn Met His Gly Asn Glu Ala Leu Gly Arg Glu Leu Met
                85                  90                  95

Leu Gln Leu Ser Glu Phe Leu Cys Glu Glu Phe Arg Asn Arg Asn Gln
            100                 105                 110

Arg Ile Val Gln Leu Ile Gln Asp Thr Arg Ile His Ile Leu Pro Ser
        115                 120                 125

Met Asn Pro Asp Gly Tyr Glu Val Ala Ala Ala Gln Gly Pro Asn Lys
    130                 135                 140

Pro Gly Tyr Leu Val Gly Arg Asn Asn Ala Asn Gly Val Asp Leu Asn
145                 150                 155                 160

Arg Asn Phe Pro Asp Leu Asn Thr Tyr Ile Tyr Tyr Asn Glu Lys Tyr
                165                 170                 175

Gly Gly Pro Asn His His Leu Pro Leu Pro Asp Asn Trp Lys Ser Gln
            180                 185                 190

Val Glu Pro Glu Thr Arg Ala Val Ile Arg Trp Met His Ser Phe Asn
        195                 200                 205

Phe Val Leu Ser Ala Asn Leu His Gly Gly Ala Val Val Ala Asn Tyr
    210                 215                 220

Pro Tyr Asp Lys Ser Phe Glu His Arg Val Arg Gly Val Arg Arg Thr
225                 230                 235                 240

Ala Ser Thr Pro Thr Pro Asp Asp Lys Leu Phe Gln Lys Leu Ala Lys
                245                 250                 255

Val Tyr Ser Tyr Ala His Gly Trp Met Phe Gln Gly Trp Asn Cys Gly
            260                 265                 270

Asp Tyr Phe Pro Asp Gly Ile Thr Asn Gly Ala Ser Trp Tyr Ser Leu
        275                 280                 285
```

-continued

```
Ser Lys Gly Met Gln Asp Phe Asn Tyr Leu His Thr Asn Cys Phe Glu
    290                 295                 300

Ile Thr Leu Glu Leu Ser Cys Asp Lys Phe Pro Pro Glu Glu Glu Leu
305                 310                 315                 320

Gln Arg Glu Trp Leu Gly Asn Arg Glu Ala Leu Ile Gln Phe Leu Glu
                325                 330                 335

Gln Val His Gln Gly Ile Lys Gly Met Val Leu Asp Glu Asn Tyr Asn
            340                 345                 350

Asn Leu Ala Asn Ala Val Ile Ser Val Ser Gly Ile Asn His Asp Val
        355                 360                 365

Thr Ser Gly Asp His Gly Asp Tyr Phe Arg Leu Leu Leu Pro Gly Ile
    370                 375                 380

Tyr Thr Val Ser Ala Thr Ala Pro Gly Tyr Asp Pro Glu Thr Val Thr
385                 390                 395                 400

Val Thr Val Gly Pro Ala Glu Pro Thr Leu Val Asn Phe His Leu Lys
                405                 410                 415

Arg Ser Ile Pro Gln Val Ser Pro Val Arg Arg Ala Pro Ser Arg Arg
            420                 425                 430

His Gly Val Arg Ala Lys Val Gln Pro Gln Ala Arg Lys Lys Glu Met
        435                 440                 445

Glu Met Arg Gln Leu Gln Arg Gly Pro Ala
    450                 455


<210> SEQ ID NO 11
<211> LENGTH: 1212
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Met Ser Thr Leu Leu Glu Asn Ile Phe Ala Ile Ile Asn Leu Phe Lys
1               5                   10                  15

Gln Tyr Ser Lys Lys Asp Lys Asn Thr Asp Thr Leu Ser Lys Lys Glu
            20                  25                  30

Leu Lys Glu Leu Leu Glu Lys Glu Phe Arg Gln Ile Leu Lys Asn Pro
        35                  40                  45

Asp Asp Pro Asp Met Val Asp Val Phe Met Asp His Leu Asp Ile Asp
    50                  55                  60

His Asn Lys Lys Ile Asp Phe Thr Glu Phe Leu Leu Met Val Phe Lys
65                  70                  75                  80

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

Ser Gly His Lys His Arg Lys His Ser His His Asp Lys His Glu Asp
            100                 105                 110

Asn Lys Gln Glu Glu Asn Lys Glu Asn Arg Lys Arg Pro Ser Ser Leu
        115                 120                 125

Glu Arg Arg Asn Asn Arg Lys Gly Asn Lys Gly Arg Ser Lys Ser Pro
    130                 135                 140

Arg Glu Thr Gly Gly Lys Arg His Glu Ser Ser Ser Glu Lys Lys Glu
145                 150                 155                 160

Arg Lys Gly Tyr Ser Pro Thr His Arg Glu Glu Glu Tyr Gly Lys Asn
                165                 170                 175

His His Asn Ser Ser Lys Lys Glu Lys Asn Lys Thr Glu Asn Thr Arg
            180                 185                 190
```

-continued

```
Leu Gly Asp Asn Arg Lys Arg Leu Ser Glu Arg Leu Glu Glu Lys Glu
        195                 200                 205

Asp Asn Glu Glu Gly Val Tyr Asp Tyr Glu Asn Thr Gly Arg Met Thr
    210                 215                 220

Gln Lys Trp Ile Gln Ser Gly His Ile Ala Thr Tyr Tyr Thr Ile Gln
225                 230                 235                 240

Asp Glu Ala Tyr Asp Thr Thr Asp Ser Leu Leu Glu Glu Asn Lys Ile
                245                 250                 255

Tyr Glu Arg Ser Arg Ser Ser Asp Gly Lys Ser Ser Ser Gln Val Asn
            260                 265                 270

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

Thr Arg Lys Arg Arg Gly Ser Arg Val Ser Gln Asp Arg Asp Ser Glu
    290                 295                 300

Gly His Ser Glu Asp Ser Glu Arg His Ser Gly Ser Ala Ser Arg Asn
305                 310                 315                 320

His His Gly Ser Ala Trp Glu Gln Ser Arg Asp Gly Ser Arg His Pro
                325                 330                 335

Arg Ser His Asp Glu Asp Arg Ala Ser His Gly His Ser Ala Asp Ser
            340                 345                 350

Ser Arg Gln Ser Gly Thr Arg His Ala Glu Thr Ser Ser Arg Gly Gln
        355                 360                 365

Thr Ala Ser Ser His Glu Gln Ala Arg Ser Ser Pro Gly Glu Arg His
    370                 375                 380

Gly Ser Gly His Gln Gln Ser Ala Asp Ser Ser Arg His Ser Ala Thr
385                 390                 395                 400

Gly Arg Gly Gln Ala Ser Ser Ala Val Ser Asp Arg Gly His Arg Gly
                405                 410                 415

Ser Ser Gly Ser Gln Ala Ser Asp Ser Glu Gly His Ser Glu Asn Ser
            420                 425                 430

Asp Thr Gln Ser Val Ser Gly His Gly Lys Ala Gly Leu Arg Gln Gln
        435                 440                 445

Ser His Gln Glu Ser Thr Arg Gly Arg Ser Gly Glu Arg Ser Gly Arg
    450                 455                 460

Ser Gly Ser Phe Ile Tyr Gln Val Ser Thr His Glu Gln Ser Glu Ser
465                 470                 475                 480

Ala His Gly Arg Thr Arg Thr Ser Thr Gly Arg Arg Gln Gly Ser His
                485                 490                 495

His Glu Gln Ala Arg Asp Ser Ser Arg His Ser Ala Ser Gln Glu Gly
            500                 505                 510

Gln Asp Thr Ile Arg Ala His Pro Gly Ser Arg Arg Gly Gly Arg Gln
        515                 520                 525

Gly Ser His His Glu Gln Ser Val Asp Arg Ser Gly His Ser Gly Ser
    530                 535                 540

His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Val Ser Arg Gly
545                 550                 555                 560

Gln Ser Gly Ser Arg Ser Val Ser Arg Gln Thr Arg Asn Glu Lys Gln
                565                 570                 575

Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg His His Glu Ala Ser
            580                 585                 590

Ser Arg Ala Asp Ser Ser Arg His Ser Gln Val Gly Gln Gly Gln Ser
        595                 600                 605
```

-continued

```
Ser Gly Pro Arg Thr Ser Arg Asn Gln Gly Ser Ser Val Ser Gln Asp
    610                 615                 620

Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Arg Ser Gly Ser
625                 630                 635                 640

Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Ser Arg Asp Gly
                645                 650                 655

Ser Arg His Pro Arg Ser His His Glu Asp Arg Ala Gly His Gly His
            660                 665                 670

Ser Ala Glu Ser Ser Arg Gln Ser Gly Thr His His Ala Glu Asn Ser
        675                 680                 685

Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Ala
    690                 695                 700

Gly Glu Arg His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser Arg
705                 710                 715                 720

His Ser Gly Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp Ser
                725                 730                 735

Gly His Arg Gly Ser Ser Gly Ser Gln Ala Ser Asp Ser Glu Gly His
            740                 745                 750

Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala Gly
        755                 760                 765

Pro His Gln Gln Ser His Gln Glu Ser Thr Arg Gly Arg Ser Ala Gly
    770                 775                 780

Arg Ser Gly Arg Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu
785                 790                 795                 800

Gln Ser Glu Ser Ala His Gly Arg Thr Arg Thr Ser Thr Gly Arg Arg
                805                 810                 815

Gln Gly Ser His His Glu Gln Ala Arg Asp Ser Ser Arg His Ser Ala
            820                 825                 830

Ser Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg
        835                 840                 845

Arg Gly Arg Gln Gly Ser His Tyr Glu Gln Ser Val Asp Arg Ser Gly
    850                 855                 860

His Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp
865                 870                 875                 880

Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Gln Thr Arg
                885                 890                 895

Asn Asp Glu Gln Ser Gly Asp Gly Ser Arg His Ser Trp Ser His His
            900                 905                 910

His Glu Ala Ser Thr Gln Ala Asp Ser Ser Arg His Ser Gln Ser Gly
        915                 920                 925

Gln Gly Gln Ser Ala Gly Pro Arg Thr Ser Arg Asn Gln Gly Ser Ser
    930                 935                 940

Val Ser Gln Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg
945                 950                 955                 960

Trp Ser Gly Ser Ala Ser Arg Asn His Arg Gly Ser Ala Gln Glu Gln
                965                 970                 975

Ser Arg Asp Gly Ser Arg His Pro Thr Ser His His Glu Asp Arg Ala
            980                 985                 990

Gly His Gly His Ser Ala Glu Ser  Ser Arg Gln Ser Gly  Thr His His
        995                 1000                1005

Ala Glu  Asn Ser Ser Gly Gly  Gln Ala Ala Ser Ser  His Glu Gln
```

-continued

```
    1010                1015                1020

Ala Arg  Ser Ser Ala Gly Glu  Arg His Gly Ser His  His Gln Gln
    1025                1030                1035

Ser Ala  Asp Ser Ser Arg His  Ser Gly Ile Gly His  Gly Gln Ala
    1040                1045                1050

Ser Ser  Ala Val Arg Asp Ser  Gly His Arg Gly Ser  Ser Gly Ser
    1055                1060                1065

Gln Ala  Ser Asp Ser Glu Gly  His Ser Glu Asp Ser  Asp Thr Gln
    1070                1075                1080

Ser Val  Ser Ala His Gly Gln  Ala Gly Pro His Gln  Gln Ser His
    1085                1090                1095

Gln Glu  Ser Thr Arg Gly Arg  Ser Ala Gly Arg Ser  Gly Arg Ser
    1100                1105                1110

Gly Ser  Phe Leu Tyr Gln Val  Ser Thr His Glu Gln  Ser Glu Ser
    1115                1120                1125

Ala His  Gly Arg Ala Gly Pro  Ser Thr Gly Gly Arg  Gln Gly Ser
    1130                1135                1140

Arg His  Glu Gln Ala Arg Asp  Ser Ser Arg His Ser  Ala Ser Gln
    1145                1150                1155

Glu Gly  Gln Asp Thr Ile Arg  Gly His Pro Gly Ser  Arg Arg Gly
    1160                1165                1170

Gly Arg  Gln Gly Ser Tyr His  Glu Gln Ser Val Asp  Arg Ser Gly
    1175                1180                1185

His Ser  Gly Ser His His Ser  His Thr Thr Ser Gln  Gly Arg Ser
    1190                1195                1200

Asp Ala  Ser His Gly Gln Ser  Gly Ser
    1205                1210


<210> SEQ ID NO 12
<211> LENGTH: 1404
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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

Phe Val Ile Gln Gln Val Ser Ser Gln Asp Leu Ser Ser Cys Ala Gly
            20                  25                  30

Arg Cys Gly Glu Gly Tyr Ser Arg Asp Ala Thr Cys Asn Cys Asp Tyr
        35                  40                  45

Asn Cys Gln His Tyr Met Glu Cys Cys Pro Asp Phe Lys Arg Val Cys
    50                  55                  60

Thr Ala Glu Leu Ser Cys Lys Gly Arg Cys Phe Glu Ser Phe Glu Arg
65                  70                  75                  80

Gly Arg Glu Cys Asp Cys Asp Ala Gln Cys Lys Lys Tyr Asp Lys Cys
                85                  90                  95

Cys Pro Asp Tyr Glu Ser Phe Cys Ala Glu Val His Asn Pro Thr Ser
            100                 105                 110

Pro Pro Ser Ser Lys Lys Ala Pro Pro Pro Ser Gly Ala Ser Gln Thr
        115                 120                 125

Ile Lys Ser Thr Thr Lys Arg Ser Pro Lys Pro Pro Asn Lys Lys Lys
    130                 135                 140

Thr Lys Lys Val Ile Glu Ser Glu Glu Ile Thr Glu Glu His Ser Val
```

-continued

```
145                 150                 155                 160

Ser Glu Asn Gln Glu Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser Ser
                165                 170                 175

Ser Thr Ile Arg Lys Ile Lys Ser Ser Lys Asn Ser Ala Ala Asn Arg
            180                 185                 190

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

Lys Lys Lys Pro Thr Pro Lys Pro Pro Val Val Asp Glu Ala Gly Ser
    210                 215                 220

Gly Leu Asp Asn Gly Asp Phe Lys Val Thr Thr Pro Asp Thr Ser Thr
225                 230                 235                 240

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

Pro Ile Asn Pro Arg Pro Ser Leu Pro Pro Asn Ser Asp Thr Ser Lys
            260                 265                 270

Glu Thr Ser Leu Thr Val Asn Lys Glu Thr Thr Val Glu Thr Lys Glu
        275                 280                 285

Thr Thr Thr Thr Asn Lys Gln Thr Ser Thr Asp Gly Lys Glu Lys Thr
    290                 295                 300

Thr Ser Ala Lys Glu Thr Gln Ser Ile Glu Lys Thr Ser Ala Lys Asp
305                 310                 315                 320

Leu Ala Pro Thr Ser Lys Val Leu Ala Lys Pro Thr Pro Lys Ala Glu
                325                 330                 335

Thr Thr Thr Lys Gly Pro Ala Leu Thr Thr Pro Lys Glu Pro Thr Pro
            340                 345                 350

Thr Thr Pro Lys Glu Pro Ala Ser Thr Thr Pro Lys Glu Pro Thr Pro
        355                 360                 365

Thr Thr Ile Lys Ser Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr
    370                 375                 380

Thr Thr Lys Ser Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr
385                 390                 395                 400

Thr Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr
                405                 410                 415

Thr Lys Glu Pro Ala Pro Thr Thr Thr Lys Ser Ala Pro Thr Thr Pro
            420                 425                 430

Lys Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Thr Thr Pro
        435                 440                 445

Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro Thr Pro Thr Thr Pro
    450                 455                 460

Lys Glu Pro Ala Pro Thr Thr Lys Glu Pro Ala Pro Thr Thr Pro Lys
465                 470                 475                 480

Glu Pro Ala Pro Thr Ala Pro Lys Lys Pro Ala Pro Thr Thr Pro Lys
                485                 490                 495

Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Thr Lys
            500                 505                 510

Glu Pro Ser Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Thr Lys
        515                 520                 525

Ser Ala Pro Thr Thr Thr Lys Glu Pro Ala Pro Thr Thr Thr Lys Ser
    530                 535                 540

Ala Pro Thr Thr Pro Lys Glu Pro Ser Pro Thr Thr Thr Lys Glu Pro
545                 550                 555                 560
```

-continued

```
Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro
               565                 570                 575

Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro
            580                 585                 590

Ala Pro Thr Thr Thr Lys Lys Pro Ala Pro Thr Thr Pro Lys Glu Pro
        595                 600                 605

Ala Pro Thr Thr Pro Lys Glu Thr Ala Pro Thr Thr Pro Lys Lys Leu
    610                 615                 620

Thr Pro Thr Thr Pro Glu Lys Leu Ala Pro Thr Thr Pro Glu Lys Pro
625                 630                 635                 640

Ala Pro Thr Thr Pro Glu Glu Leu Ala Pro Thr Thr Pro Glu Glu Pro
               645                 650                 655

Thr Pro Thr Thr Pro Glu Glu Pro Ala Pro Thr Thr Pro Lys Ala Ala
            660                 665                 670

Ala Pro Asn Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Pro
        675                 680                 685

Ala Pro Thr Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Glu Thr
    690                 695                 700

Ala Pro Thr Thr Pro Lys Gly Thr Ala Pro Thr Thr Leu Lys Glu Pro
705                 710                 715                 720

Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Lys Glu Leu Ala Pro Thr
               725                 730                 735

Thr Thr Lys Glu Pro Thr Ser Thr Thr Cys Asp Lys Pro Ala Pro Thr
            740                 745                 750

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

Thr Pro Lys Glu Pro Ala Pro Thr Thr Pro Lys Gly Thr Ala Pro Thr
    770                 775                 780

Thr Leu Lys Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Lys
785                 790                 795                 800

Glu Leu Ala Pro Thr Thr Thr Lys Gly Pro Thr Ser Thr Thr Ser Asp
               805                 810                 815

Lys Pro Ala Pro Thr Thr Pro Lys Glu Thr Ala Pro Thr Thr Pro Lys
            820                 825                 830

Glu Pro Ala Pro Thr Thr Pro Lys Lys Pro Ala Pro Thr Thr Pro Glu
        835                 840                 845

Thr Pro Pro Pro Thr Thr Ser Glu Val Ser Thr Pro Thr Thr Thr Lys
    850                 855                 860

Glu Pro Thr Thr Ile His Lys Ser Pro Asp Glu Ser Thr Pro Glu Leu
865                 870                 875                 880

Ser Ala Glu Pro Thr Pro Lys Ala Leu Glu Asn Ser Pro Lys Glu Pro
               885                 890                 895

Gly Val Pro Thr Thr Lys Thr Pro Ala Ala Thr Lys Pro Glu Met Thr
            900                 905                 910

Thr Thr Ala Lys Asp Lys Thr Thr Glu Arg Asp Leu Arg Thr Thr Pro
        915                 920                 925

Glu Thr Thr Thr Ala Ala Pro Lys Met Thr Lys Glu Thr Ala Thr Thr
    930                 935                 940

Thr Glu Lys Thr Thr Glu Ser Lys Ile Thr Ala Thr Thr Thr Gln Val
945                 950                 955                 960

Thr Ser Thr Thr Thr Gln Asp Thr Thr Pro Phe Lys Ile Thr Thr Leu
               965                 970                 975
```

-continued

```
Lys Thr Thr Thr Leu Ala Pro Lys Val Thr Thr Thr Lys Lys Thr Ile
           980                 985                 990

Thr Thr Thr Glu Ile Met Asn Lys  Pro Glu Glu Thr Ala  Lys Pro Lys
        995                1000                1005

Asp Arg  Ala Thr Asn Ser Lys  Ala Thr Thr Pro Lys  Pro Gln Lys
    1010                1015                1020

Pro Thr  Lys Ala Pro Lys Lys  Pro Thr Ser Thr Lys  Lys Pro Lys
    1025                1030                1035

Thr Met  Pro Arg Val Arg Lys  Pro Lys Thr Thr Pro  Thr Pro Arg
    1040                1045                1050

Lys Met  Thr Ser Thr Met Pro  Glu Leu Asn Pro Thr  Ser Arg Ile
    1055                1060                1065

Ala Glu  Ala Met Leu Gln Thr  Thr Thr Arg Pro Asn  Gln Thr Pro
    1070                1075                1080

Asn Ser  Lys Leu Val Glu Val  Asn Pro Lys Ser Glu  Asp Ala Gly
    1085                1090                1095

Gly Ala  Glu Gly Glu Thr Pro  His Met Leu Leu Arg  Pro His Val
    1100                1105                1110

Phe Met  Pro Glu Val Thr Pro  Asp Met Asp Tyr Leu  Pro Arg Val
    1115                1120                1125

Pro Asn  Gln Gly Ile Ile Ile  Asn Pro Met Leu Ser  Asp Glu Thr
    1130                1135                1140

Asn Ile  Cys Asn Gly Lys Pro  Val Asp Gly Leu Thr  Thr Leu Arg
    1145                1150                1155

Asn Gly  Thr Leu Val Ala Phe  Arg Gly His Tyr Phe  Trp Met Leu
    1160                1165                1170

Ser Pro  Phe Ser Pro Pro Ser  Pro Ala Arg Arg Ile  Thr Glu Val
    1175                1180                1185

Trp Gly  Ile Pro Ser Pro Ile  Asp Thr Val Phe Thr  Arg Cys Asn
    1190                1195                1200

Cys Glu  Gly Lys Thr Phe Phe  Phe Lys Asp Ser Gln  Tyr Trp Arg
    1205                1210                1215

Phe Thr  Asn Asp Ile Lys Asp  Ala Gly Tyr Pro Lys  Pro Ile Phe
    1220                1225                1230

Lys Gly  Phe Gly Gly Leu Thr  Gly Gln Ile Val Ala  Ala Leu Ser
    1235                1240                1245

Thr Ala  Lys Tyr Lys Asn Trp  Pro Glu Ser Val Tyr  Phe Phe Lys
    1250                1255                1260

Arg Gly  Gly Ser Ile Gln Gln  Tyr Ile Tyr Lys Gln  Glu Pro Val
    1265                1270                1275

Gln Lys  Cys Pro Gly Arg Arg  Pro Ala Leu Asn Tyr  Pro Val Tyr
    1280                1285                1290

Gly Glu  Thr Thr Gln Val Arg  Arg Arg Arg Phe Glu  Arg Ala Ile
    1295                1300                1305

Gly Pro  Ser Gln Thr His Thr  Ile Arg Ile Gln Tyr  Ser Pro Ala
    1310                1315                1320

Arg Leu  Ala Tyr Gln Asp Lys  Gly Val Leu His Asn  Glu Val Lys
    1325                1330                1335

Val Ser  Ile Leu Trp Arg Gly  Leu Pro Asn Val Val  Thr Ser Ala
    1340                1345                1350

Ile Ser  Leu Pro Asn Ile Arg  Lys Pro Asp Gly Tyr  Asp Tyr Tyr
```

-continued

```
    1355                1360                1365

Ala Phe  Ser Lys Asp Gln Tyr  Tyr Asn Ile Asp Val  Pro Ser Arg
    1370                1375                1380

Thr Ala  Arg Ala Ile Thr Thr  Arg Ser Gly Gln Thr  Leu Ser Lys
    1385                1390                1395

Val Trp  Tyr Asn Cys Pro
    1400


<210> SEQ ID NO 13
<211> LENGTH: 367
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

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

His Ser Ala Pro His Gly Pro Gly Leu Ile Tyr Arg Gln Pro Asn Cys
            20                  25                  30

Asp Asp Pro Glu Thr Glu Glu Ala Ala Leu Val Ala Ile Asp Tyr Ile
        35                  40                  45

Asn Gln Asn Leu Pro Trp Gly Tyr Lys His Thr Leu Asn Gln Ile Asp
    50                  55                  60

Glu Val Lys Val Trp Pro Gln Gln Pro Ser Gly Glu Leu Phe Glu Ile
65                  70                  75                  80

Glu Ile Asp Thr Leu Glu Thr Thr Cys His Val Leu Asp Pro Thr Pro
                85                  90                  95

Val Ala Arg Cys Ser Val Arg Gln Leu Lys Glu His Ala Val Glu Gly
            100                 105                 110

Asp Cys Asp Phe Gln Leu Leu Lys Leu Asp Gly Lys Phe Ser Val Val
        115                 120                 125

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

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

Val His Ala Ala Lys Ala Ala Leu Ala Ala Phe Asn Ala Gln Asn Asn
                165                 170                 175

Gly Ser Asn Phe Gln Leu Glu Glu Ile Ser Arg Ala Gln Leu Val Pro
            180                 185                 190

Leu Pro Pro Ser Thr Tyr Val Glu Phe Thr Val Ser Gly Thr Asp Cys
        195                 200                 205

Val Ala Lys Glu Ala Thr Glu Ala Ala Lys Cys Asn Leu Leu Ala Glu
    210                 215                 220

Lys Gln Tyr Gly Phe Cys Lys Ala Thr Leu Ser Glu Lys Leu Gly Gly
225                 230                 235                 240

Ala Glu Val Ala Val Thr Cys Thr Val Phe Gln Thr Gln Pro Val Thr
                245                 250                 255

Ser Gln Pro Gln Pro Glu Gly Ala Asn Glu Ala Val Pro Thr Pro Val
            260                 265                 270

Val Asp Pro Asp Ala Pro Pro Ser Pro Pro Leu Gly Ala Pro Gly Leu
        275                 280                 285

Pro Pro Ala Gly Ser Pro Pro Asp Ser His Val Leu Leu Ala Ala Pro
    290                 295                 300

Pro Gly His Gln Leu His Arg Ala His Tyr Asp Leu Arg His Thr Phe
```

-continued

```
305                 310                 315                 320

Met Gly Val Val Ser Leu Gly Ser Pro Ser Gly Glu Val Ser His Pro
                325                 330                 335

Arg Lys Thr Arg Thr Val Val Gln Pro Ser Val Gly Ala Ala Ala Gly
            340                 345                 350

Pro Val Val Pro Pro Cys Pro Gly Arg Ile Arg His Phe Lys Val
        355                 360                 365


<210> SEQ ID NO 14
<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Met Asn Pro Phe Leu Ile Leu Ala Phe Val Gly Ala Ala Gly Glu Val
1               5                   10                  15

Ala Val Pro Phe Asp Asp Asp Asp Lys Ile Val Gly Gly Tyr Thr Cys
            20                  25                  30

Glu Glu Asn Ser Leu Pro Tyr Gln Val Ser Leu Asn Ser Gly Ser His
        35                  40                  45

Phe Cys Gly Gly Ser Leu Ile Ser Glu Gln Trp Val Val Ser Ala Ala
    50                  55                  60

His Cys Tyr Lys Thr Arg Ile Gln Val Arg Leu Gly Glu His Asn Ile
65                  70                  75                  80

Lys Val Leu Glu Gly Asn Glu Gln Phe Ile Asn Ala Ala Lys Ile Ile
                85                  90                  95

Arg His Pro Lys Tyr Asn Arg Asp Thr Leu Asp Asn Asp Ile Met Leu
            100                 105                 110

Ile Lys Leu Ser Ser Pro Ala Val Ile Asn Ala Arg Val Ser Thr Ile
        115                 120                 125

Ser Leu Pro Thr Thr Pro Pro Ala Ala Gly Thr Glu Cys Leu Ile Ser
    130                 135                 140

Gly Trp Gly Asn Thr Leu Ser Phe Gly Ala Asp Tyr Pro Asp Glu Leu
145                 150                 155                 160

Lys Cys Leu Asp Ala Pro Val Leu Thr Gln Ala Glu Cys Lys Ala Ser
                165                 170                 175

Tyr Pro Gly Lys Ile Thr Asn Ser Met Phe Cys Val Gly Phe Leu Glu
            180                 185                 190

Gly Gly Lys Asp Ser Cys Gln Arg Asp Ser Gly Gly Pro Val Val Cys
        195                 200                 205

Asn Gly Gln Leu Gln Gly Val Val Ser Trp Gly His Gly Cys Ala Trp
    210                 215                 220

Lys Asn Arg Pro Gly Val Tyr Thr Lys Val Tyr Asn Tyr Val Asp Trp
225                 230                 235                 240

Ile Lys Asp Thr Ile Ala Ala Asn Ser
                245


<210> SEQ ID NO 15
<211> LENGTH: 298
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

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

-continued

```
Pro Ala Val Pro Gln Glu Asn Gln Asp Gly Arg Tyr Ser Leu Thr Tyr
            20                  25                  30

Ile Tyr Thr Gly Leu Ser Lys His Val Glu Asp Val Pro Ala Phe Gln
        35                  40                  45

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

Asp Arg Lys Ser Gln Pro Met Gly Leu Trp Arg Gln Val Glu Gly Met
65                  70                  75                  80

Glu Asp Trp Lys Gln Asp Ser Gln Leu Gln Lys Ala Arg Glu Asp Ile
                85                  90                  95

Phe Met Glu Thr Leu Lys Asp Ile Val Glu Tyr Tyr Asn Asp Ser Asn
            100                 105                 110

Gly Ser His Val Leu Gln Gly Arg Phe Gly Cys Glu Ile Glu Asn Asn
        115                 120                 125

Arg Ser Ser Gly Ala Phe Trp Lys Tyr Tyr Tyr Asp Gly Lys Asp Tyr
    130                 135                 140

Ile Glu Phe Asn Lys Glu Ile Pro Ala Trp Val Pro Phe Asp Pro Ala
145                 150                 155                 160

Ala Gln Ile Thr Lys Gln Lys Trp Glu Ala Glu Pro Val Tyr Val Gln
                165                 170                 175

Arg Ala Lys Ala Tyr Leu Glu Glu Glu Cys Pro Ala Thr Leu Arg Lys
            180                 185                 190

Tyr Leu Lys Tyr Ser Lys Asn Ile Leu Asp Arg Gln Asp Pro Pro Ser
        195                 200                 205

Val Val Val Thr Ser His Gln Ala Pro Gly Glu Lys Lys Lys Leu Lys
    210                 215                 220

Cys Leu Ala Tyr Asp Phe Tyr Pro Gly Lys Ile Asp Val His Trp Thr
225                 230                 235                 240

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

Asn Gly Asn Gly Thr Tyr Gln Ser Trp Val Val Val Ala Val Pro Pro
            260                 265                 270

Gln Asp Thr Ala Pro Tyr Ser Cys His Val Gln His Ser Ser Leu Ala
        275                 280                 285

Gln Pro Leu Val Val Pro Trp Glu Ala Ser
    290                 295


<210> SEQ ID NO 16
<211> LENGTH: 1049
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Asp Trp Ser Phe Phe Arg Val Val Ala Val Leu Phe Ile Phe Leu
1               5                   10                  15

Val Val Val Glu Val Asn Ser Glu Phe Arg Ile Gln Val Arg Asp Tyr
            20                  25                  30

Asn Thr Lys Asn Gly Thr Ile Lys Trp His Ser Ile Arg Arg Gln Lys
        35                  40                  45

Arg Glu Trp Ile Lys Phe Ala Ala Ala Cys Arg Glu Gly Glu Asp Asn
    50                  55                  60

Ser Lys Arg Asn Pro Ile Ala Lys Ile His Ser Asp Cys Ala Ala Asn
65                  70                  75                  80
```

-continued

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

Tyr Gly Ile Phe Val Ile Asn Gln Lys Thr Gly Glu Ile Asn Ile Thr
            100                 105                 110

Ser Ile Val Asp Arg Glu Val Thr Pro Phe Phe Ile Ile Tyr Cys Arg
        115                 120                 125

Ala Leu Asn Ser Met Gly Gln Asp Leu Glu Arg Pro Leu Glu Leu Arg
    130                 135                 140

Val Arg Val Leu Asp Ile Asn Asp Asn Pro Pro Val Phe Ser Met Ala
145                 150                 155                 160

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

Met Ile Leu Asn Ala Thr Asp Ala Asp Glu Pro Asn Asn Leu Asn Ser
            180                 185                 190

Lys Ile Ala Phe Lys Ile Ile Arg Gln Glu Pro Ser Asp Ser Pro Met
        195                 200                 205

Phe Ile Ile Asn Arg Asn Thr Gly Glu Ile Arg Thr Met Asn Asn Phe
    210                 215                 220

Leu Asp Arg Glu Gln Tyr Gly Gln Tyr Ala Leu Ala Val Arg Gly Ser
225                 230                 235                 240

Asp Arg Asp Gly Gly Ala Asp Gly Met Ser Ala Glu Cys Glu Cys Asn
                245                 250                 255

Ile Lys Ile Leu Asp Val Asn Asp Asn Ile Pro Tyr Met Glu Gln Ser
            260                 265                 270

Ser Tyr Thr Ile Glu Ile Gln Glu Asn Thr Leu Asn Ser Asn Leu Leu
        275                 280                 285

Glu Ile Arg Val Ile Asp Leu Asp Glu Glu Phe Ser Ala Asn Trp Met
    290                 295                 300

Ala Val Ile Phe Phe Ile Ser Gly Asn Glu Gly Asn Trp Phe Glu Ile
305                 310                 315                 320

Glu Met Asn Glu Arg Thr Asn Val Gly Ile Leu Lys Val Val Lys Pro
                325                 330                 335

Leu Asp Tyr Glu Ala Met Gln Ser Leu Gln Leu Ser Ile Gly Val Arg
            340                 345                 350

Asn Lys Ala Glu Phe His His Ser Ile Met Ser Gln Tyr Lys Leu Lys
        355                 360                 365

Ala Ser Ala Ile Ser Val Thr Val Leu Asn Val Ile Glu Gly Pro Val
    370                 375                 380

Phe Arg Pro Gly Ser Lys Thr Tyr Val Val Thr Gly Asn Met Gly Ser
385                 390                 395                 400

Asn Asp Lys Val Gly Asp Phe Val Ala Thr Asp Leu Asp Thr Gly Arg
                405                 410                 415

Pro Ser Thr Thr Val Arg Tyr Val Met Gly Asn Asn Pro Ala Asp Leu
            420                 425                 430

Leu Ala Val Asp Ser Arg Thr Gly Lys Leu Thr Leu Lys Asn Lys Val
        435                 440                 445

Thr Lys Glu Gln Tyr Asn Met Leu Gly Gly Lys Tyr Gln Gly Thr Ile
    450                 455                 460

Leu Ser Ile Asp Asp Asn Leu Gln Arg Thr Cys Thr Gly Thr Ile Asn
465                 470                 475                 480

Ile Asn Ile Gln Ser Phe Gly Asn Asp Asp Arg Thr Asn Thr Glu Pro
```

-continued

```
               485                 490                 495

Asn Thr Lys Ile Thr Thr Asn Thr Gly Arg Gln Glu Ser Thr Ser Ser
            500                 505                 510

Thr Asn Tyr Asp Thr Ser Thr Thr Ser Thr Asp Ser Ser Gln Val Tyr
        515                 520                 525

Ser Ser Glu Pro Gly Asn Gly Ala Lys Asp Leu Leu Ser Asp Asn Val
    530                 535                 540

His Phe Gly Pro Ala Gly Ile Gly Leu Leu Ile Met Gly Phe Leu Val
545                 550                 555                 560

Leu Gly Leu Val Pro Phe Leu Met Ile Cys Cys Asp Cys Gly Gly Ala
                565                 570                 575

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

Ala Ile His Ser Trp Ala Val Glu Gly Pro Gln Pro Glu Pro Arg Asp
        595                 600                 605

Ile Thr Thr Val Ile Pro Gln Ile Pro Pro Asp Asn Ala Asn Ile Ile
    610                 615                 620

Glu Cys Ile Asp Asn Ser Gly Val Tyr Thr Asn Glu Tyr Gly Gly Arg
625                 630                 635                 640

Glu Met Gln Asp Leu Gly Gly Gly Glu Arg Met Thr Gly Phe Glu Leu
                645                 650                 655

Thr Glu Gly Val Lys Thr Ser Gly Met Pro Glu Ile Cys Gln Glu Tyr
            660                 665                 670

Ser Gly Thr Leu Arg Arg Asn Ser Met Arg Glu Cys Arg Glu Gly Gly
        675                 680                 685

Leu Asn Met Asn Phe Met Glu Ser Tyr Phe Cys Gln Lys Ala Tyr Ala
    690                 695                 700

Tyr Ala Asp Glu Asp Glu Gly Arg Pro Ser Asn Asp Cys Leu Leu Ile
705                 710                 715                 720

Tyr Asp Ile Glu Gly Val Gly Ser Pro Ala Gly Ser Val Gly Cys Cys
                725                 730                 735

Ser Phe Ile Gly Glu Asp Leu Asp Asp Ser Phe Leu Asp Thr Leu Gly
            740                 745                 750

Pro Lys Phe Lys Lys Leu Ala Asp Ile Ser Leu Gly Lys Glu Ser Tyr
        755                 760                 765

Pro Asp Leu Asp Pro Ser Trp Pro Pro Gln Ser Thr Glu Pro Val Cys
    770                 775                 780

Leu Pro Gln Glu Thr Glu Pro Val Val Ser Gly His Pro Pro Ile Ser
785                 790                 795                 800

Pro His Phe Gly Thr Thr Thr Val Ile Ser Glu Ser Thr Tyr Pro Ser
                805                 810                 815

Gly Pro Gly Val Leu His Pro Lys Pro Ile Leu Asp Pro Leu Gly Tyr
            820                 825                 830

Gly Asn Val Thr Val Thr Glu Ser Tyr Thr Thr Ser Asp Thr Leu Lys
        835                 840                 845

Pro Ser Val His Val His Asp Asn Arg Pro Ala Ser Asn Val Val Val
    850                 855                 860

Thr Glu Arg Val Val Gly Pro Ile Ser Gly Ala Asp Leu His Gly Met
865                 870                 875                 880

Leu Glu Met Pro Asp Leu Arg Asp Gly Ser Asn Val Ile Val Thr Glu
                885                 890                 895
```

-continued

```
Arg Val Ile Ala Pro Ser Ser Ser Leu Pro Thr Ser Leu Thr Ile His
            900                 905                 910

His Pro Arg Glu Ser Ser Asn Val Val Val Thr Glu Arg Val Ile Gln
        915                 920                 925

Pro Thr Ser Gly Met Ile Gly Ser Leu Ser Met His Pro Glu Leu Ala
    930                 935                 940

Asn Ala His Asn Val Ile Val Thr Glu Arg Val Val Ser Gly Ala Gly
945                 950                 955                 960

Val Thr Gly Ile Ser Gly Thr Thr Gly Ile Ser Gly Gly Ile Gly Ser
                965                 970                 975

Ser Gly Leu Val Gly Thr Ser Met Gly Ala Gly Ser Gly Ala Leu Ser
            980                 985                 990

Gly Ala Gly Ile Ser Gly Gly Gly  Ile Gly Leu Ser Ser  Leu Gly Gly
        995                 1000                 1005

Thr Ala  Ser Ile Gly His Met  Arg Ser Ser Ser Asp  His His Phe
    1010                1015                1020

Asn Gln  Thr Ile Gly Ser Ala  Ser Pro Ser Thr Ala  Arg Ser Arg
    1025                1030                1035

Ile Thr  Lys Tyr Ser Thr Val  Gln Tyr Ser Lys
    1040                1045


<210> SEQ ID NO 17
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Met Ser Asn Pro Arg Ser Leu Glu Glu Glu Lys Tyr Asp Met Ser Gly
1               5                   10                  15

Ala Arg Leu Ala Leu Ile Leu Cys Val Thr Lys Ala Arg Glu Gly Ser
            20                  25                  30

Glu Glu Asp Leu Asp Ala Leu Glu His Met Phe Arg Gln Leu Arg Phe
        35                  40                  45

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

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

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

Gly Glu Asp Gly Glu Met Val Lys Leu Glu Asn Leu Phe Glu Ala Leu
            100                 105                 110

Asn Asn Lys Asn Cys Gln Ala Leu Arg Ala Lys Pro Lys Val Tyr Ile
        115                 120                 125

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

Gly Asp Glu Ile Val Met Val Ile Lys Asp Ser Pro Gln Thr Ile Pro
145                 150                 155                 160

Thr Tyr Thr Asp Ala Leu His Val Tyr Ser Thr Val Glu Gly Tyr Ile
                165                 170                 175

Ala Tyr Arg His Asp Gln Lys Gly Ser Cys Phe Ile Gln Thr Leu Val
            180                 185                 190

Asp Val Phe Thr Lys Arg Lys Gly His Ile Leu Glu Leu Leu Thr Glu
        195                 200                 205
```

-continued

```
Val Thr Arg Arg Met Ala Glu Ala Glu Leu Val Gln Glu Gly Lys Ala
    210                 215                 220

Arg Lys Thr Asn Pro Glu Ile Gln Ser Thr Leu Arg Lys Arg Leu Tyr
225                 230                 235                 240

Leu Gln


<210> SEQ ID NO 18
<211> LENGTH: 2850
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Met Pro Lys Leu Leu Gln Gly Val Ile Thr Val Ile Asp Val Phe Tyr
1               5                   10                  15

Gln Tyr Ala Thr Gln His Gly Glu Tyr Asp Thr Leu Asn Lys Ala Glu
            20                  25                  30

Leu Lys Glu Leu Leu Glu Asn Glu Phe His Gln Ile Leu Lys Asn Pro
        35                  40                  45

Asn Asp Pro Asp Thr Val Asp Ile Ile Leu Gln Ser Leu Asp Arg Asp
    50                  55                  60

His Asn Lys Lys Val Asp Phe Thr Glu Tyr Leu Leu Met Ile Phe Lys
65                  70                  75                  80

Leu Val Gln Ala Arg Asn Lys Ile Ile Gly Lys Asp Tyr Cys Gln Val
                85                  90                  95

Ser Gly Ser Lys Leu Arg Asp Asp Thr His Gln His Gln Glu Glu Gln
            100                 105                 110

Glu Glu Thr Glu Lys Glu Glu Asn Lys Arg Gln Glu Ser Ser Phe Ser
        115                 120                 125

His Ser Ser Trp Ser Ala Gly Glu Asn Asp Ser Tyr Ser Arg Asn Val
    130                 135                 140

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

Phe Gln Arg Asp Phe Ser Gly Gln His Asn Ser Tyr Ser Gly Gln Ser
                165                 170                 175

Ser Ser Tyr Gly Glu Gln Asn Ser Asp Ser His Gln Ser Ser Gly Arg
            180                 185                 190

Gly Gln Cys Gly Ser Gly Ser Gly Gln Ser Pro Asn Tyr Gly Gln His
        195                 200                 205

Gly Ser Gly Ser Gly Gln Ser Ser Ser Asn Asp Thr His Gly Ser Gly
    210                 215                 220

Ser Gly Gln Ser Ser Gly Phe Ser Gln His Lys Ser Ser Ser Gly Gln
225                 230                 235                 240

Ser Ser Gly Tyr Ser Gln His Gly Ser Gly Ser Gly His Ser Ser Gly
                245                 250                 255

Tyr Gly Gln His Gly Ser Arg Ser Gly Gln Ser Ser Arg Gly Glu Arg
            260                 265                 270

His Arg Ser Ser Ser Gly Ser Ser Ser Ser Tyr Gly Gln His Gly Ser
        275                 280                 285

Gly Ser Arg Gln Ser Leu Gly His Gly Arg Gln Gly Ser Gly Ser Arg
    290                 295                 300

Gln Ser Pro Ser His Val Arg His Gly Ser Gly Ser Gly His Ser Ser
305                 310                 315                 320

Ser His Gly Gln His Gly Ser Gly Ser Ser Tyr Ser Tyr Ser Arg Gly
```

-continued

```
              325                 330                 335

His Tyr Glu Ser Gly Ser Gly Gln Thr Ser Gly Phe Gly Gln His Glu
            340                 345                 350

Ser Gly Ser Gly Gln Ser Ser Gly Tyr Ser Lys His Gly Ser Gly Ser
        355                 360                 365

Gly His Ser Ser Ser Gln Gly Gln His Gly Ser Thr Ser Gly Gln Ala
    370                 375                 380

Ser Ser Ser Gly Gln His Gly Ser Ser Ser Arg Gln Ser Ser Ser Tyr
385                 390                 395                 400

Gly Gln His Glu Ser Ala Ser Arg His Ser Ser Gly Arg Gly Gln His
                405                 410                 415

Ser Ser Gly Ser Gly Gln Ser Pro Gly His Gly Gln Arg Gly Ser Gly
            420                 425                 430

Ser Gly Gln Ser Pro Ser Ser Gly Gln His Gly Thr Gly Phe Gly Arg
        435                 440                 445

Ser Ser Ser Ser Gly Pro Tyr Val Ser Gly Ser Gly Tyr Ser Ser Gly
    450                 455                 460

Phe Gly His His Glu Ser Ser Ser Glu His Ser Ser Gly Tyr Thr Gln
465                 470                 475                 480

His Gly Ser Gly Ser Gly His Ser Ser Gly His Gly Gln His Gly Ser
                485                 490                 495

Arg Ser Gly Gln Ser Ser Arg Gly Glu Arg Gln Gly Ser Ser Ala Gly
            500                 505                 510

Ser Ser Ser Ser Tyr Gly Gln His Gly Ser Gly Ser Arg Gln Ser Leu
        515                 520                 525

Gly His Ser Arg His Gly Ser Gly Ser Gly Gln Ser Pro Ser Pro Ser
    530                 535                 540

Arg Gly Arg His Glu Ser Gly Ser Arg Gln Ser Ser Ser Tyr Gly Pro
545                 550                 555                 560

His Gly Tyr Gly Ser Gly Arg Ser Ser Ser Arg Gly Pro Tyr Glu Ser
                565                 570                 575

Gly Ser Gly His Ser Ser Gly Leu Gly His Gln Glu Ser Arg Ser Gly
            580                 585                 590

Gln Ser Ser Gly Tyr Gly Gln His Gly Ser Ser Ser Gly His Ser Ser
        595                 600                 605

Thr His Gly Gln His Gly Ser Thr Ser Gly Gln Ser Ser Ser Cys Gly
    610                 615                 620

Gln His Gly Ala Thr Ser Gly Gln Ser Ser Ser His Gly Gln His Gly
625                 630                 635                 640

Ser Gly Ser Ser Gln Ser Ser Arg Tyr Gly Gln Gln Gly Ser Gly Ser
                645                 650                 655

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

Ser Ser Tyr Gly Gln His Gly Ser Gly Ser Gly Trp Ser Ser Ser Asn
        675                 680                 685

Gly Pro His Gly Ser Val Ser Gly Gln Ser Ser Gly Phe Gly His Lys
    690                 695                 700

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

Ser His Ser Ser Gly Tyr Arg Lys His Gly Ser Arg Ser Gly Gln Ser
                725                 730                 735
```

-continued

```
Ser Arg Ser Glu Gln His Gly Ser Ser Ser Gly Leu Ser Ser Ser Tyr
           740                 745                 750

Gly Gln His Gly Ser Gly Ser His Gln Ser Ser Gly His Gly Arg Gln
       755                 760                 765

Gly Ser Gly Ser Gly His Ser Pro Ser Arg Val Arg His Gly Ser Ser
   770                 775                 780

Ser Gly His Ser Ser Ser His Gly Gln His Gly Ser Gly Thr Ser Cys
785                 790                 795                 800

Ser Ser Ser Cys Gly His Tyr Glu Ser Gly Ser Gly Gln Ala Ser Gly
               805                 810                 815

Phe Gly Gln His Glu Ser Gly Ser Gly Gln Gly Tyr Ser Gln His Gly
           820                 825                 830

Ser Ala Ser Gly His Phe Ser Ser Gln Gly Arg His Gly Ser Thr Ser
       835                 840                 845

Gly Gln Ser Ser Ser Ser Gly Gln His Asp Ser Ser Ser Gly Gln Ser
   850                 855                 860

Ser Ser Tyr Gly Gln His Glu Ser Ala Ser His His Ala Ser Gly Arg
865                 870                 875                 880

Gly Arg His Gly Ser Gly Ser Gly Gln Ser Pro Gly His Gly Gln Arg
               885                 890                 895

Gly Ser Gly Ser Gly Gln Ser Pro Ser Tyr Gly Arg His Gly Ser Gly
           900                 905                 910

Ser Gly Arg Ser Ser Ser Ser Gly Arg His Gly Ser Gly Ser Gly Gln
       915                 920                 925

Ser Ser Gly Phe Gly His Lys Ser Ser Ser Gly Gln Ser Ser Gly Tyr
   930                 935                 940

Thr Gln His Gly Ser Gly Ser Gly His Ser Ser Ser Tyr Glu Gln His
945                 950                 955                 960

Gly Ser Arg Ser Gly Gln Ser Ser Arg Ser Glu Gln His Gly Ser Ser
               965                 970                 975

Ser Gly Ser Ser Ser Ser Tyr Gly Gln His Gly Ser Gly Ser Arg Gln
           980                 985                 990

Ser Leu Gly His Gly Gln His Gly  Ser Gly Ser Gly Gln  Ser Pro Ser
       995                 1000                1005

Pro Ser  Arg Gly Arg His Gly  Ser Gly Ser Gly Gln  Ser Ser Ser
   1010                1015                1020

Tyr Gly  Pro Tyr Arg Ser Gly  Ser Gly Trp Ser Ser  Ser Arg Gly
   1025                1030                1035

Pro Tyr  Glu Ser Gly Ser Gly  His Ser Ser Gly Leu  Gly His Arg
   1040                1045                1050

Glu Ser  Arg Ser Gly Gln Ser  Ser Gly Tyr Gly Gln  His Gly Ser
   1055                1060                1065

Ser Ser  Gly His Ser Ser Thr  His Gly Gln His Gly  Ser Thr Ser
   1070                1075                1080

Gly Gln  Ser Ser Ser Cys Gly  Gln His Gly Ala Ser  Ser Gly Gln
   1085                1090                1095

Ser Ser  Ser His Gly Gln His  Gly Ser Gly Ser Ser  Gln Ser Ser
   1100                1105                1110

Gly Tyr  Gly Arg Gln Gly Ser  Gly Ser Gly Gln Ser  Pro Gly His
   1115                1120                1125

Gly Gln  Arg Gly Ser Gly Ser  Arg Gln Ser Pro Ser  Tyr Gly Arg
   1130                1135                1140
```

-continued

```
His Gly  Ser Gly Ser Gly Arg  Ser Ser Ser Ser Gly  Gln His Gly
    1145                1150                1155

Ser Gly  Leu Gly Glu Ser Ser  Gly Phe Gly His His  Glu Ser Ser
    1160                1165                1170

Ser Gly  Gln Ser Ser Ser Tyr  Ser Gln His Gly Ser  Gly Ser Gly
    1175                1180                1185

His Ser  Ser Gly Tyr Gly Gln  His Gly Ser Arg Ser  Gly Gln Ser
    1190                1195                1200

Ser Arg  Gly Glu Arg His Gly  Ser Ser Ser Gly Ser  Ser Ser His
    1205                1210                1215

Tyr Gly  Gln His Gly Ser Gly  Ser Arg Gln Ser Ser  Gly His Gly
    1220                1225                1230

Arg Gln  Gly Ser Gly Ser Gly  His Ser Pro Ser Arg  Gly Arg His
    1235                1240                1245

Gly Ser  Gly Leu Gly His Ser  Ser Ser His Gly Gln  His Gly Ser
    1250                1255                1260

Gly Ser  Gly Arg Ser Ser Ser  Arg Gly Pro Tyr Glu  Ser Arg Ser
    1265                1270                1275

Gly His  Ser Ser Val Phe Gly  Gln His Glu Ser Gly  Ser Gly His
    1280                1285                1290

Ser Ser  Ala Tyr Ser Gln His  Gly Ser Gly Ser Gly  His Phe Cys
    1295                1300                1305

Ser Gln  Gly Gln His Gly Ser  Thr Ser Gly Gln Ser  Ser Thr Phe
    1310                1315                1320

Asp Gln  Glu Gly Ser Ser Thr  Gly Gln Ser Ser Ser  Tyr Gly His
    1325                1330                1335

Arg Gly  Ser Gly Ser Ser Gln  Ser Ser Gly Tyr Gly  Arg His Gly
    1340                1345                1350

Ala Gly  Ser Gly Gln Ser Pro  Ser Arg Gly Arg His  Gly Ser Gly
    1355                1360                1365

Ser Gly  His Ser Ser Ser Tyr  Gly Gln His Gly Ser  Gly Ser Gly
    1370                1375                1380

Trp Ser  Ser Ser Ser Gly Arg  His Gly Ser Gly Ser  Gly Gln Ser
    1385                1390                1395

Ser Gly  Phe Gly His His Glu  Ser Ser Ser Trp Gln  Ser Ser Gly
    1400                1405                1410

Cys Thr  Gln His Gly Ser Gly  Ser Gly His Ser Ser  Ser Tyr Glu
    1415                1420                1425

Gln His  Gly Ser Arg Ser Gly  Gln Ser Ser Arg Gly  Glu Arg His
    1430                1435                1440

Gly Ser  Ser Ser Gly Ser Ser  Ser Ser Tyr Gly Gln  His Gly Ser
    1445                1450                1455

Gly Ser  Arg Gln Ser Leu Gly  His Gly Gln His Gly  Ser Gly Ser
    1460                1465                1470

Gly Gln  Ser Pro Ser Pro Ser  Arg Gly Arg His Gly  Ser Gly Ser
    1475                1480                1485

Gly Gln  Ser Ser Ser Tyr Ser  Pro Tyr Gly Ser Gly  Ser Gly Trp
    1490                1495                1500

Ser Ser  Ser Arg Gly Pro Tyr  Glu Ser Gly Ser Ser  His Ser Ser
    1505                1510                1515

Gly Leu  Gly His Arg Glu Ser  Arg Ser Gly Gln Ser  Ser Gly Tyr
```

-continued

```
    1520                1525                1530

Gly Gln  His Gly Ser Ser Ser  Gly His Ser Ser Thr  His Gly Gln
    1535                1540                1545

His Gly  Ser Thr Ser Gly Gln  Ser Ser Ser Cys Gly  Gln His Gly
    1550                1555                1560

Ala Ser  Ser Gly Gln Ser Ser  Ser His Gly Gln His  Gly Ser Gly
    1565                1570                1575

Ser Ser  Gln Ser Ser Gly Tyr  Gly Arg Gln Gly Ser  Gly Ser Gly
    1580                1585                1590

Gln Ser  Pro Gly His Gly Gln  Arg Gly Ser Gly Ser  Arg Gln Ser
    1595                1600                1605

Pro Ser  Tyr Gly Arg His Gly  Ser Gly Ser Gly Arg  Ser Ser Ser
    1610                1615                1620

Ser Gly  Gln His Gly Ser Gly  Leu Gly Glu Ser Ser  Gly Phe Gly
    1625                1630                1635

His His  Glu Ser Ser Ser Gly  Gln Ser Ser Ser Tyr  Ser Gln His
    1640                1645                1650

Gly Ser  Gly Ser Gly His Ser  Ser Gly Tyr Gly Gln  His Gly Ser
    1655                1660                1665

Arg Ser  Gly Gln Ser Ser Arg  Gly Glu Arg His Gly  Ser Ser Ser
    1670                1675                1680

Arg Ser  Ser Ser Arg Tyr Gly  Gln His Gly Ser Gly  Ser Arg Gln
    1685                1690                1695

Ser Ser  Gly His Gly Arg Gln  Gly Ser Gly Ser Gly  Gln Ser Pro
    1700                1705                1710

Ser Arg  Gly Arg His Gly Ser  Gly Leu Gly His Ser  Ser Ser His
    1715                1720                1725

Gly Gln  His Gly Ser Gly Ser  Gly Arg Ser Ser Ser  Arg Gly Pro
    1730                1735                1740

Tyr Glu  Ser Arg Ser Gly His  Ser Ser Val Phe Gly  Gln His Glu
    1745                1750                1755

Ser Gly  Ser Gly His Ser Ser  Ala Tyr Ser Gln His  Gly Ser Gly
    1760                1765                1770

Ser Gly  His Phe Cys Ser Gln  Gly Gln His Gly Ser  Thr Ser Gly
    1775                1780                1785

Gln Ser  Ser Thr Phe Asp Gln  Glu Gly Ser Ser Thr  Gly Gln Ser
    1790                1795                1800

Ser Ser  His Gly Gln His Gly  Ser Gly Ser Ser Gln  Ser Ser Ser
    1805                1810                1815

Tyr Gly  Gln Gln Gly Ser Gly  Ser Gly Gln Ser Pro  Ser Arg Gly
    1820                1825                1830

Arg His  Gly Ser Gly Ser Gly  His Ser Ser Ser Tyr  Gly Gln His
    1835                1840                1845

Gly Ser  Gly Ser Gly Trp Ser  Ser Ser Ser Gly Arg  His Gly Ser
    1850                1855                1860

Gly Ser  Gly Gln Ser Ser Gly  Phe Gly His His Glu  Ser Ser Ser
    1865                1870                1875

Trp Gln  Ser Ser Gly Tyr Thr  Gln His Gly Ser Gly  Ser Gly His
    1880                1885                1890

Ser Ser  Ser Tyr Glu Gln His  Gly Ser Arg Ser Gly  Gln Ser Ser
    1895                1900                1905
```

-continued

```
Arg Gly  Glu Gln His Gly Ser  Ser Ser Gly Ser Ser  Ser Ser Tyr
    1910                1915                1920

Gly Gln  His Gly Ser Gly Ser  Arg Gln Ser Leu Gly  His Gly Gln
    1925                1930                1935

His Gly  Ser Gly Ser Gly Gln  Ser Pro Ser Pro Ser  Arg Gly Arg
    1940                1945                1950

His Gly  Ser Gly Ser Gly Gln  Ser Ser Ser Tyr Gly  Pro Tyr Gly
    1955                1960                1965

Ser Gly  Ser Gly Trp Ser Ser  Ser Arg Gly Pro Tyr  Glu Ser Gly
    1970                1975                1980

Ser Gly  His Ser Ser Gly Leu  Gly His Arg Glu Ser  Arg Ser Gly
    1985                1990                1995

Gln Ser  Ser Gly Tyr Gly Gln  His Gly Ser Ser Ser  Gly His Ser
    2000                2005                2010

Ser Thr  His Gly Gln His Gly  Ser Ala Ser Gly Gln  Ser Ser Ser
    2015                2020                2025

Cys Gly  Gln His Gly Ala Ser  Ser Gly Gln Ser Ser  Ser His Gly
    2030                2035                2040

Gln His  Gly Ser Gly Ser Ser  Gln Ser Ser Gly Tyr  Gly Arg Gln
    2045                2050                2055

Gly Ser  Gly Ser Gly Gln Ser  Pro Gly His Gly Gln  Arg Gly Ser
    2060                2065                2070

Gly Ser  Arg Gln Ser Pro Ser  Tyr Gly Arg His Gly  Ser Gly Ser
    2075                2080                2085

Gly Arg  Ser Ser Ser Ser Gly  Gln His Gly Pro Gly  Leu Gly Glu
    2090                2095                2100

Ser Ser  Gly Phe Gly His His  Glu Ser Ser Ser Gly  Gln Ser Ser
    2105                2110                2115

Ser Tyr  Ser Gln His Gly Ser  Gly Ser Gly His Ser  Ser Gly Tyr
    2120                2125                2130

Gly Gln  His Gly Ser Arg Ser  Gly Gln Ser Ser Arg  Gly Glu Arg
    2135                2140                2145

His Gly  Ser Ser Ser Gly Ser  Ser Ser Arg Tyr Gly  Gln His Gly
    2150                2155                2160

Ser Gly  Ser Arg Gln Ser Ser  Gly His Gly Arg Gln  Gly Ser Gly
    2165                2170                2175

Ser Gly  His Ser Pro Ser Arg  Gly Arg His Gly Ser  Gly Ser Gly
    2180                2185                2190

His Ser  Ser Ser His Gly Gln  His Gly Ser Gly Ser  Gly Arg Ser
    2195                2200                2205

Ser Ser  Arg Gly Pro Tyr Glu  Ser Arg Ser Gly His  Ser Ser Val
    2210                2215                2220

Phe Gly  Gln His Glu Ser Gly  Ser Gly His Ser Ser  Ala Tyr Ser
    2225                2230                2235

Gln His  Gly Ser Gly Ser Gly  His Phe Cys Ser Gln  Gly Gln His
    2240                2245                2250

Gly Ser  Thr Ser Gly Gln Ser  Ser Thr Phe Asp Gln  Glu Gly Ser
    2255                2260                2265

Ser Thr  Gly Gln Ser Ser Ser  His Gly Gln His Gly  Ser Gly Ser
    2270                2275                2280

Ser Gln  Ser Ser Ser Tyr Gly  Gln Gln Gly Ser Gly  Ser Gly Gln
    2285                2290                2295
```

-continued

```
Ser Pro  Ser Arg Gly Arg His  Gly Ser Gly Ser Gly  His Ser Ser
    2300                2305                2310

Ser Tyr  Gly Gln His Gly Ser  Gly Ser Gly Trp Ser  Ser Ser Ser
    2315                2320                2325

Gly Arg  His Gly Ser Gly Ser  Gly Gln Ser Ser Gly  Phe Gly His
    2330                2335                2340

His Glu  Ser Ser Ser Trp Gln  Ser Ser Gly Tyr Thr  Gln His Gly
    2345                2350                2355

Ser Gly  Ser Gly His Ser Ser  Ser Tyr Glu Gln His  Gly Ser Arg
    2360                2365                2370

Ser Gly  Gln Ser Ser Arg Gly  Glu Arg His Gly Ser  Ser Ser Gly
    2375                2380                2385

Ser Ser  Ser Ser Tyr Gly Gln  His Gly Ser Gly Ser  Arg Gln Ser
    2390                2395                2400

Leu Gly  His Gly Gln His Gly  Ser Gly Ser Gly Gln  Ser Pro Ser
    2405                2410                2415

Pro Ser  Arg Gly Arg His Gly  Ser Gly Ser Gly Gln  Ser Ser Ser
    2420                2425                2430

Tyr Ser  Pro Tyr Gly Ser Gly  Ser Gly Trp Ser Ser  Ser Arg Gly
    2435                2440                2445

Pro Tyr  Glu Ser Gly Ser Gly  His Ser Ser Gly Leu  Gly His Arg
    2450                2455                2460

Glu Ser  Arg Ser Gly Gln Ser  Ser Gly Tyr Gly Gln  His Gly Ser
    2465                2470                2475

Ser Ser  Gly His Ser Ser Thr  His Gly Gln His Gly  Ser Thr Ser
    2480                2485                2490

Gly Gln  Ser Ser Ser Cys Gly  Gln His Gly Ala Ser  Ser Gly Gln
    2495                2500                2505

Ser Ser  Ser His Gly Gln His  Gly Ser Gly Ser Ser  Gln Ser Ser
    2510                2515                2520

Gly Tyr  Gly Arg Gln Gly Ser  Gly Ser Gly Gln Ser  Pro Gly His
    2525                2530                2535

Gly Gln  Arg Gly Ser Gly Ser  Arg Gln Ser Pro Ser  Tyr Gly Arg
    2540                2545                2550

His Gly  Ser Gly Ser Gly Arg  Ser Ser Ser Ser Gly  Gln His Gly
    2555                2560                2565

Ser Gly  Leu Gly Glu Ser Ser  Gly Phe Gly His His  Glu Ser Ser
    2570                2575                2580

Ser Gly  Gln Ser Ser Ser Tyr  Ser Gln His Gly Ser  Gly Ser Gly
    2585                2590                2595

His Ser  Ser Gly Tyr Gly Gln  His Gly Ser Arg Ser  Gly Gln Ser
    2600                2605                2610

Ser Arg  Gly Glu Arg His Gly  Ser Ser Ser Gly Ser  Ser Ser His
    2615                2620                2625

Tyr Gly  Gln His Gly Ser Gly  Ser Arg Gln Ser Ser  Gly His Gly
    2630                2635                2640

Arg Gln  Gly Ser Gly Ser Gly  Gln Ser Pro Ser Arg  Gly Arg His
    2645                2650                2655

Gly Ser  Gly Leu Gly His Ser  Ser Ser His Gly Gln  His Gly Ser
    2660                2665                2670

Gly Ser  Gly Arg Ser Ser Ser  Arg Gly Pro Tyr Glu  Ser Arg Leu
```

-continued

```
    2675                2680                2685

Gly His  Ser Ser Val Phe Gly  Gln His Glu Ser Gly  Ser Gly His
    2690                2695                2700

Ser Ser  Ala Tyr Ser Gln His  Gly Ser Gly Ser Gly  His Phe Cys
    2705                2710                2715

Ser Gln  Gly Gln His Gly Ser  Thr Ser Gly Gln Ser  Ser Thr Phe
    2720                2725                2730

Asp Gln  Glu Gly Ser Ser Thr  Gly Gln Ser Ser Ser  Tyr Gly His
    2735                2740                2745

Arg Gly  Ser Gly Ser Ser Gln  Ser Ser Gly Tyr Gly  Arg His Gly
    2750                2755                2760

Ala Gly  Ser Gly Gln Ser Leu  Ser His Gly Arg His  Gly Ser Gly
    2765                2770                2775

Ser Gly  Gln Ser Ser Ser Tyr  Gly Gln His Gly Ser  Gly Ser Gly
    2780                2785                2790

Gln Ser  Ser Gly Tyr Ser Gln  His Gly Ser Gly Ser  Gly Gln Asp
    2795                2800                2805

Gly Tyr  Ser Tyr Cys Lys Gly  Gly Ser Asn His Asp  Gly Gly Ser
    2810                2815                2820

Ser Gly  Ser Tyr Phe Leu Ser  Phe Pro Ser Ser Thr  Ser Pro Tyr
    2825                2830                2835

Glu Tyr  Val Gln Glu Gln Arg  Cys Tyr Phe Tyr Gln
    2840                2845                2850


<210> SEQ ID NO 19
<211> LENGTH: 427
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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

Leu Thr Gln Glu Ser Gln Ser Glu Glu Ile Asp Cys Asn Asp Lys Asp
            20                  25                  30

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

Gln Ser Asn Asn Gln Phe Val Leu Tyr Arg Ile Thr Glu Ala Thr Lys
    50                  55                  60

Thr Val Gly Ser Asp Thr Phe Tyr Ser Phe Lys Tyr Glu Ile Lys Glu
65                  70                  75                  80

Gly Asp Cys Pro Val Gln Ser Gly Lys Thr Trp Gln Asp Cys Glu Tyr
                85                  90                  95

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

Lys Arg Ser Ser Thr Lys Phe Ser Val Ala Thr Gln Thr Cys Gln Ile
        115                 120                 125

Thr Pro Ala Glu Gly Pro Val Val Thr Ala Gln Tyr Asp Cys Leu Gly
    130                 135                 140

Cys Val His Pro Ile Ser Thr Gln Ser Pro Asp Leu Glu Pro Ile Leu
145                 150                 155                 160

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

Phe Met Leu Asn Glu Val Lys Arg Ala Gln Arg Gln Val Val Ala Gly
```

-continued

```
            180                 185                 190

Leu Asn Phe Arg Ile Thr Tyr Ser Ile Val Gln Thr Asn Cys Ser Lys
        195                 200                 205

Glu Asn Phe Leu Phe Leu Thr Pro Asp Cys Lys Ser Leu Trp Asn Gly
    210                 215                 220

Asp Thr Gly Glu Cys Thr Asp Asn Ala Tyr Ile Asp Ile Gln Leu Arg
225                 230                 235                 240

Ile Ala Ser Phe Ser Gln Asn Cys Asp Ile Tyr Pro Gly Lys Asp Phe
                245                 250                 255

Val Gln Pro Pro Thr Lys Ile Cys Val Gly Cys Pro Arg Asp Ile Pro
            260                 265                 270

Thr Asn Ser Pro Glu Leu Glu Glu Thr Leu Thr His Thr Ile Thr Lys
        275                 280                 285

Leu Asn Ala Glu Asn Asn Ala Thr Phe Tyr Phe Lys Ile Asp Asn Val
    290                 295                 300

Lys Lys Ala Arg Val Gln Val Val Ala Gly Lys Lys Tyr Phe Ile Asp
305                 310                 315                 320

Phe Val Ala Arg Glu Thr Thr Cys Ser Lys Glu Ser Asn Glu Glu Leu
                325                 330                 335

Thr Glu Ser Cys Glu Thr Lys Lys Leu Gly Gln Ser Leu Asp Cys Asn
            340                 345                 350

Ala Glu Val Tyr Val Val Pro Trp Glu Lys Lys Ile Tyr Pro Thr Val
        355                 360                 365

Asn Cys Gln Pro Leu Gly Met Ile Ser Leu Met Lys Arg Pro Pro Gly
    370                 375                 380

Phe Ser Pro Phe Arg Ser Ser Arg Ile Gly Glu Ile Lys Glu Glu Thr
385                 390                 395                 400

Thr Ser His Leu Arg Ser Cys Glu Tyr Lys Gly Arg Pro Pro Lys Ala
                405                 410                 415

Gly Ala Glu Pro Ala Ser Glu Arg Glu Val Ser
            420                 425


<210> SEQ ID NO 20
<211> LENGTH: 418
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Gln Ala Leu Val Leu Leu Leu Cys Ile Gly Ala Leu Leu Gly His
1               5                   10                  15

Ser Ser Cys Gln Asn Pro Ala Ser Pro Pro Glu Glu Gly Ser Pro Asp
            20                  25                  30

Pro Asp Ser Thr Gly Ala Leu Val Glu Glu Glu Asp Pro Phe Phe Lys
        35                  40                  45

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

Leu Tyr Arg Val Arg Ser Ser Met Ser Pro Thr Thr Asn Val Leu Leu
65                  70                  75                  80

Ser Pro Leu Ser Val Ala Thr Ala Leu Ser Ala Leu Ser Leu Gly Ala
                85                  90                  95

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

Ile Ser Ser Pro Asp Ile His Gly Thr Tyr Lys Glu Leu Leu Asp Thr
```

-continued

```
        115                 120                 125

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

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

Ser Tyr Gly Thr Arg Pro Arg Val Leu Thr Gly Asn Pro Arg Leu Asp
                165                 170                 175

Leu Gln Glu Ile Asn Asn Trp Val Gln Ala Gln Met Lys Gly Lys Leu
            180                 185                 190

Ala Arg Ser Thr Lys Glu Ile Pro Asp Glu Ile Ser Ile Leu Leu Leu
        195                 200                 205

Gly Val Ala His Phe Lys Gly Gln Trp Val Thr Lys Phe Asp Ser Arg
    210                 215                 220

Lys Thr Ser Leu Glu Asp Phe Tyr Leu Asp Glu Glu Arg Thr Val Arg
225                 230                 235                 240

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

Ser Asp Leu Ser Cys Lys Ile Ala Gln Leu Pro Leu Thr Gly Ser Met
            260                 265                 270

Ser Ile Ile Phe Phe Leu Pro Leu Lys Val Thr Gln Asn Leu Thr Leu
        275                 280                 285

Ile Glu Glu Ser Leu Thr Ser Glu Phe Ile His Asp Ile Asp Arg Glu
    290                 295                 300

Leu Lys Thr Val Gln Ala Val Leu Thr Val Pro Lys Leu Lys Leu Ser
305                 310                 315                 320

Tyr Glu Gly Glu Val Thr Lys Ser Leu Gln Glu Met Lys Leu Gln Ser
                325                 330                 335

Leu Phe Asp Ser Pro Asp Phe Ser Lys Ile Thr Gly Lys Pro Ile Lys
            340                 345                 350

Leu Thr Gln Val Glu His Arg Ala Gly Phe Glu Trp Asn Glu Asp Gly
        355                 360                 365

Ala Gly Thr Thr Pro Ser Pro Gly Leu Gln Pro Ala His Leu Thr Phe
    370                 375                 380

Pro Leu Asp Tyr His Leu Asn Gln Pro Phe Ile Phe Val Leu Arg Asp
385                 390                 395                 400

Thr Asp Thr Gly Ala Leu Leu Phe Ile Gly Lys Ile Leu Asp Pro Arg
                405                 410                 415

Gly Pro


<210> SEQ ID NO 21
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Met Ser Asn Thr Gln Ala Glu Arg Ser Ile Ile Gly Met Ile Asp Met
1               5                   10                  15

Phe His Lys Tyr Thr Arg Arg Asp Asp Lys Ile Glu Lys Pro Ser Leu
            20                  25                  30

Leu Thr Met Met Lys Glu Asn Phe Pro Asn Phe Leu Ser Ala Cys Asp
        35                  40                  45

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

-continued

Asn Glu Asp Lys Lys Ile Asp Phe Ser Glu Phe Leu Ser Leu Leu Gly
65 70 75 80

Asp Ile Ala Thr Asp Tyr His Lys Gln Ser His Gly Ala Ala Pro Cys
85 90 95

Ser Gly Gly Ser Gln
100

<210> SEQ ID NO 22
<211> LENGTH: 93
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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

His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp
20 25 30

Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys
35 40 45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly
50 55 60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val
65 70 75 80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu
85 90

<210> SEQ ID NO 23
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

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

Asn Thr Phe His Gln Tyr Ser Val Lys Leu Gly His Pro Asp Thr Leu
20 25 30

Asn Gln Gly Glu Phe Lys Glu Leu Val Arg Lys Asp Leu Gln Asn Phe
35 40 45

Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu
50 55 60

Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe Ile
65 70 75 80

Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His Glu
85 90 95

Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu Gly
100 105 110

Thr Pro

<210> SEQ ID NO 24
<211> LENGTH: 202
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Met Ser Ser Val Glu Lys Glu Thr Lys Thr Gln Cys Val Arg Ile Ala
1 5 10 15

-continued

```
Thr Lys Ala Ala Ala Thr Glu Glu Pro Glu Val Ile Pro Asp Pro Ala
            20                  25                  30

Lys Gln Thr Asp Arg Val Val Lys Ile Ala Gly Ile Ser Ala Gly Ile
        35                  40                  45

Leu Val Phe Ile Leu Leu Leu Leu Val Val Ile Leu Ile Val Lys Lys
    50                  55                  60

Arg Arg Ser Tyr Tyr Ser Tyr Ser Tyr Tyr Leu Lys Leu Ala Lys Lys
65                  70                  75                  80

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

Asn Ala Met Asp Arg Ser Tyr Ala Asp Gln Ser Thr Leu His Ala Glu
            100                 105                 110

Asp Pro Leu Ser Ile Thr Phe Met Asp Gln His Asn Phe Ser Pro Arg
        115                 120                 125

Leu Pro Asn Asp Pro Leu Val Pro Thr Ala Val Leu Asp Glu Asn His
    130                 135                 140

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

Cys Glu Gly Thr Glu Ser Pro Tyr Gln Thr Gly Gln Leu His Pro Ala
                165                 170                 175

Ile Arg Val Ala Asp Leu Leu Gln His Ile Asn Leu Met Lys Thr Ser
            180                 185                 190

Asp Ser Tyr Gly Phe Lys Glu Glu Tyr Glu
        195                 200


<210> SEQ ID NO 25
<211> LENGTH: 484
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Met Ser Arg Ser Thr Gln Glu Leu Leu Gly Tyr His Cys Arg Leu Gln
1               5                   10                  15

Asp Lys Leu Gln Glu Gln Glu Gly Ser Leu Ala Ala Glu Gly Arg His
            20                  25                  30

Ser Leu Ala Ser Ala Ala Asp His Met Lys Val Val Pro Ser Leu Leu
        35                  40                  45

Leu Ser Val Leu Leu Ala Gln Val Trp Leu Val Pro Gly Leu Ala Pro
    50                  55                  60

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

Val Val Gln Ala Pro Lys Glu Glu Glu Glu Asp Glu Gln Glu Ala Ser
                85                  90                  95

Glu Glu Lys Ala Ser Glu Glu Glu Lys Ala Trp Leu Met Ala Ser Arg
            100                 105                 110

Gln Gln Leu Ala Lys Glu Thr Ser Asn Phe Gly Phe Ser Leu Leu Arg
        115                 120                 125

Lys Ile Ser Met Arg His Asp Gly Asn Met Val Phe Ser Pro Phe Gly
    130                 135                 140

Met Ser Leu Ala Met Thr Gly Leu Met Leu Gly Ala Thr Gly Pro Thr
145                 150                 155                 160

Glu Thr Gln Ile Lys Arg Gly Leu His Leu Gln Ala Leu Lys Pro Thr
                165                 170                 175
```

-continued

```
Lys Pro Gly Leu Leu Pro Ser Leu Phe Lys Gly Leu Arg Glu Thr Leu
            180                 185                 190

Ser Arg Asn Leu Glu Leu Gly Leu Thr Gln Gly Ser Phe Ala Phe Ile
        195                 200                 205

His Lys Asp Phe Asp Val Lys Glu Thr Phe Phe Asn Leu Ser Lys Arg
    210                 215                 220

Tyr Phe Asp Thr Glu Cys Val Pro Met Asn Phe Arg Asn Ala Ser Gln
225                 230                 235                 240

Ala Lys Arg Leu Met Asn His Tyr Ile Asn Lys Glu Thr Arg Gly Lys
                245                 250                 255

Ile Pro Lys Leu Phe Asp Glu Ile Asn Pro Glu Thr Lys Leu Ile Leu
            260                 265                 270

Val Asp Tyr Ile Leu Phe Lys Gly Lys Trp Leu Thr Pro Phe Asp Pro
        275                 280                 285

Val Phe Thr Glu Val Asp Thr Phe His Leu Asp Lys Tyr Lys Thr Ile
    290                 295                 300

Lys Val Pro Met Met Tyr Gly Ala Gly Lys Phe Ala Ser Thr Phe Asp
305                 310                 315                 320

Lys Asn Phe Arg Cys His Val Leu Lys Leu Pro Tyr Gln Gly Asn Ala
                325                 330                 335

Thr Met Leu Val Val Leu Met Glu Lys Met Gly Asp His Leu Ala Leu
            340                 345                 350

Glu Asp Tyr Leu Thr Thr Asp Leu Val Glu Thr Trp Leu Arg Asn Met
        355                 360                 365

Lys Thr Arg Asn Met Glu Val Phe Phe Pro Lys Phe Lys Leu Asp Gln
    370                 375                 380

Lys Tyr Glu Met His Glu Leu Leu Arg Gln Met Gly Ile Arg Arg Ile
385                 390                 395                 400

Phe Ser Pro Phe Ala Asp Leu Ser Glu Leu Ser Ala Thr Gly Arg Asn
                405                 410                 415

Leu Gln Val Ser Arg Val Leu Gln Arg Thr Val Ile Glu Val Asp Glu
            420                 425                 430

Arg Gly Thr Glu Ala Val Ala Gly Ile Leu Ser Glu Ile Thr Ala Tyr
        435                 440                 445

Ser Met Pro Pro Val Ile Lys Val Asp Arg Pro Phe His Phe Met Ile
    450                 455                 460

Tyr Glu Glu Thr Ser Gly Met Leu Leu Phe Leu Gly Arg Val Val Asn
465                 470                 475                 480

Pro Thr Leu Leu


<210> SEQ ID NO 26
<211> LENGTH: 228
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Met Pro Gly Ala Gly Asp Gly Gly Lys Ala Pro Ala Arg Trp Leu Gly
1               5                   10                  15

Thr Gly Leu Leu Gly Leu Phe Leu Leu Pro Val Thr Leu Ser Leu Glu
            20                  25                  30

Val Ser Val Gly Lys Ala Thr Asp Ile Tyr Ala Val Asn Gly Thr Glu
        35                  40                  45
```

-continued

Ile Leu Leu Pro Cys Thr Phe Ser Ser Cys Phe Gly Phe Glu Asp Leu
50 55 60

His Phe Arg Trp Thr Tyr Asn Ser Ser Asp Ala Phe Lys Ile Leu Ile
65 70 75 80

Glu Gly Thr Val Lys Asn Glu Lys Ser Asp Pro Lys Val Thr Leu Lys
85 90 95

Asp Asp Asp Arg Ile Thr Leu Val Gly Ser Thr Lys Glu Lys Met Asn
100 105 110

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

Tyr Thr Cys His Val Lys Asn Pro Lys Glu Asn Asn Leu Gln His His
130 135 140

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

Thr Val Thr Leu Ile Ile Leu Ala Val Val Gly Gly Val Ile Gly Leu
165 170 175

Leu Ile Leu Ile Leu Leu Ile Lys Lys Leu Ile Ile Phe Ile Leu Lys
180 185 190

Lys Thr Arg Glu Lys Lys Lys Glu Cys Leu Val Ser Ser Ser Gly Asn
195 200 205

Asp Asn Thr Glu Asn Gly Leu Pro Gly Ser Lys Ala Glu Glu Lys Pro
210 215 220

Pro Ser Lys Val
225

<210> SEQ ID NO 27
<211> LENGTH: 2214
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Met Ala Thr Arg Ser Ser Arg Arg Glu Ser Arg Leu Pro Phe Leu Phe
1 5 10 15

Thr Leu Val Ala Leu Leu Pro Pro Gly Ala Leu Cys Glu Val Trp Thr
20 25 30

Gln Arg Leu His Gly Gly Ser Ala Pro Leu Pro Gln Asp Arg Gly Phe
35 40 45

Leu Val Val Gln Gly Asp Pro Arg Glu Leu Arg Leu Trp Ala Arg Gly
50 55 60

Asp Ala Arg Gly Ala Ser Arg Ala Asp Glu Lys Pro Leu Arg Arg Lys
65 70 75 80

Arg Ser Ala Ala Leu Gln Pro Glu Pro Ile Lys Val Tyr Gly Gln Val
85 90 95

Ser Leu Asn Asp Ser His Asn Gln Met Val Val His Trp Ala Gly Glu
100 105 110

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

Arg Pro Lys Ser Ser Asp Val Tyr Val Ser Tyr Asp Tyr Gly Lys Ser
130 135 140

Phe Lys Lys Ile Ser Asp Lys Leu Asn Phe Gly Leu Gly Asn Arg Ser
145 150 155 160

Glu Ala Val Ile Ala Gln Phe Tyr His Ser Pro Ala Asp Asn Lys Arg
165 170 175

-continued

```
Tyr Ile Phe Ala Asp Ala Tyr Ala Gln Tyr Leu Trp Ile Thr Phe Asp
            180                 185                 190

Phe Cys Asn Thr Leu Gln Gly Phe Ser Ile Pro Phe Arg Ala Ala Asp
        195                 200                 205

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

Ser His Pro Asn Lys Gln Leu Trp Lys Ser Asp Asp Phe Gly Gln Thr
225                 230                 235                 240

Trp Ile Met Ile Gln Glu His Val Lys Ser Phe Ser Trp Gly Ile Asp
                245                 250                 255

Pro Tyr Asp Lys Pro Asn Thr Ile Tyr Ile Glu Arg His Glu Pro Ser
            260                 265                 270

Gly Tyr Ser Thr Val Phe Arg Ser Thr Asp Phe Phe Gln Ser Arg Glu
        275                 280                 285

Asn Gln Glu Val Ile Leu Glu Glu Val Arg Asp Phe Gln Leu Arg Asp
    290                 295                 300

Lys Tyr Met Phe Ala Thr Lys Val Val His Leu Leu Gly Ser Glu Gln
305                 310                 315                 320

Gln Ser Ser Val Gln Leu Trp Val Ser Phe Gly Arg Lys Pro Met Arg
                325                 330                 335

Ala Ala Gln Phe Val Thr Arg His Pro Ile Asn Glu Tyr Tyr Ile Ala
            340                 345                 350

Asp Ala Ser Glu Asp Gln Val Phe Val Cys Val Ser His Ser Asn Asn
        355                 360                 365

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

Ser Leu Glu Asn Val Leu Tyr Tyr Ser Pro Gly Gly Ala Gly Ser Asp
385                 390                 395                 400

Thr Leu Val Arg Tyr Phe Ala Asn Glu Pro Phe Ala Asp Phe His Arg
                405                 410                 415

Val Glu Gly Leu Gln Gly Val Tyr Ile Ala Thr Leu Ile Asn Gly Ser
            420                 425                 430

Met Asn Glu Glu Asn Met Arg Ser Val Ile Thr Phe Asp Lys Gly Gly
        435                 440                 445

Thr Trp Glu Phe Leu Gln Ala Pro Ala Phe Thr Gly Tyr Gly Glu Lys
    450                 455                 460

Ile Asn Cys Glu Leu Ser Gln Gly Cys Ser Leu His Leu Ala Gln Arg
465                 470                 475                 480

Leu Ser Gln Leu Leu Asn Leu Gln Leu Arg Arg Met Pro Ile Leu Ser
                485                 490                 495

Lys Glu Ser Ala Pro Gly Leu Ile Ile Ala Thr Gly Ser Val Gly Lys
            500                 505                 510

Asn Leu Ala Ser Lys Thr Asn Val Tyr Ile Ser Ser Ser Ala Gly Ala
        515                 520                 525

Arg Trp Arg Glu Ala Leu Pro Gly Pro His Tyr Tyr Thr Trp Gly Asp
    530                 535                 540

His Gly Gly Ile Ile Thr Ala Ile Ala Gln Gly Met Glu Thr Asn Glu
545                 550                 555                 560

Leu Lys Tyr Ser Thr Asn Glu Gly Glu Thr Trp Lys Thr Phe Ile Phe
                565                 570                 575

Ser Glu Lys Pro Val Phe Val Tyr Gly Leu Leu Thr Glu Pro Gly Glu
            580                 585                 590
```

-continued

```
Lys Ser Thr Val Phe Thr Ile Phe Gly Ser Asn Lys Glu Asn Val His
        595                 600                 605

Ser Trp Leu Ile Leu Gln Val Asn Ala Thr Asp Ala Leu Gly Val Pro
    610                 615                 620

Cys Thr Glu Asn Asp Tyr Lys Leu Trp Ser Pro Ser Asp Glu Arg Gly
625                 630                 635                 640

Asn Glu Cys Leu Leu Gly His Lys Thr Val Phe Lys Arg Arg Thr Pro
                645                 650                 655

His Ala Thr Cys Phe Asn Gly Glu Asp Phe Asp Arg Pro Val Val Val
            660                 665                 670

Ser Asn Cys Ser Cys Thr Arg Glu Asp Tyr Glu Cys Asp Phe Gly Phe
        675                 680                 685

Lys Met Ser Glu Asp Leu Ser Leu Glu Val Cys Val Pro Asp Pro Glu
    690                 695                 700

Phe Ser Gly Lys Ser Tyr Ser Pro Pro Val Pro Cys Pro Val Gly Ser
705                 710                 715                 720

Thr Tyr Arg Arg Thr Arg Gly Tyr Arg Lys Ile Ser Gly Asp Thr Cys
                725                 730                 735

Ser Gly Gly Asp Val Glu Ala Arg Leu Glu Gly Glu Leu Val Pro Cys
            740                 745                 750

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

Ile Tyr Arg Tyr Asp Leu Ala Ser Gly Ala Thr Glu Gln Leu Pro Leu
    770                 775                 780

Thr Gly Leu Arg Ala Ala Val Ala Leu Asp Phe Asp Tyr Glu His Asn
785                 790                 795                 800

Cys Leu Tyr Trp Ser Asp Leu Ala Leu Asp Val Ile Gln Arg Leu Cys
                805                 810                 815

Leu Asn Gly Ser Thr Gly Gln Glu Val Ile Ile Asn Ser Gly Leu Glu
            820                 825                 830

Thr Val Glu Ala Leu Ala Phe Glu Pro Leu Ser Gln Leu Leu Tyr Trp
        835                 840                 845

Val Asp Ala Gly Phe Lys Lys Ile Glu Val Ala Asn Pro Asp Gly Asp
    850                 855                 860

Phe Arg Leu Thr Ile Val Asn Ser Ser Val Leu Asp Arg Pro Arg Ala
865                 870                 875                 880

Leu Val Leu Val Pro Gln Glu Gly Val Met Phe Trp Thr Asp Trp Gly
                885                 890                 895

Asp Leu Lys Pro Gly Ile Tyr Arg Ser Asn Met Asp Gly Ser Ala Ala
            900                 905                 910

Tyr His Leu Val Ser Glu Asp Val Lys Trp Pro Asn Gly Ile Ser Val
        915                 920                 925

Asp Asp Gln Trp Ile Tyr Trp Thr Asp Ala Tyr Leu Glu Cys Ile Glu
    930                 935                 940

Arg Ile Thr Phe Ser Gly Gln Gln Arg Ser Val Ile Leu Asp Asn Leu
945                 950                 955                 960

Pro His Pro Tyr Ala Ile Ala Val Phe Lys Asn Glu Ile Tyr Trp Asp
                965                 970                 975

Asp Trp Ser Gln Leu Ser Ile Phe Arg Ala Ser Lys Tyr Ser Gly Ser
            980                 985                 990

Gln Met Glu Ile Leu Ala Asn Gln  Leu Thr Gly Leu Met  Asp Met Lys
```

-continued

```
        995                 1000                1005

Ile Phe  Tyr Lys Gly Lys Asn  Thr Gly Ser Asn Ala  Cys Val Pro
    1010                1015                1020

Arg Pro  Cys Ser Leu Leu Cys  Leu Pro Lys Ala Asn  Asn Ser Arg
    1025                1030                1035

Ser Cys  Arg Cys Pro Glu Asp  Val Ser Ser Ser Val  Leu Pro Ser
    1040                1045                1050

Gly Asp  Leu Met Cys Asp Cys  Pro Gln Gly Tyr Gln  Leu Lys Asn
    1055                1060                1065

Asn Thr  Cys Val Lys Glu Glu  Asn Thr Cys Leu Arg  Asn Gln Tyr
    1070                1075                1080

Arg Cys  Ser Asn Gly Asn Cys  Ile Asn Ser Ile Trp  Trp Cys Asp
    1085                1090                1095

Phe Asp  Asn Asp Cys Gly Asp  Met Ser Asp Glu Arg  Asn Cys Pro
    1100                1105                1110

Thr Thr  Ile Cys Asp Leu Asp  Thr Gln Phe Arg Cys  Gln Glu Ser
    1115                1120                1125

Gly Thr  Cys Ile Pro Leu Ser  Tyr Lys Cys Asp Leu  Glu Asp Asp
    1130                1135                1140

Cys Gly  Asp Asn Ser Asp Glu  Ser His Cys Glu Met  His Gln Cys
    1145                1150                1155

Arg Ser  Asp Glu Tyr Asn Cys  Ser Ser Gly Met Cys  Ile Arg Ser
    1160                1165                1170

Ser Trp  Val Cys Asp Gly Asp  Asn Asp Cys Arg Asp  Trp Ser Asp
    1175                1180                1185

Glu Ala  Asn Cys Thr Ala Ile  Tyr His Thr Cys Glu  Ala Ser Asn
    1190                1195                1200

Phe Gln  Cys Arg Asn Gly His  Cys Ile Pro Gln Arg  Trp Ala Cys
    1205                1210                1215

Asp Gly  Asp Thr Asp Cys Gln  Asp Gly Ser Asp Glu  Asp Pro Val
    1220                1225                1230

Asn Cys  Glu Lys Lys Cys Asn  Gly Phe Arg Cys Pro  Asn Gly Thr
    1235                1240                1245

Cys Ile  Pro Ser Ser Lys His  Cys Asp Gly Leu Arg  Asp Cys Ser
    1250                1255                1260

Asp Gly  Ser Asp Glu Gln His  Cys Glu Pro Leu Cys  Thr His Phe
    1265                1270                1275

Met Asp  Phe Val Cys Lys Asn  Arg Gln Gln Cys Leu  Phe His Ser
    1280                1285                1290

Met Val  Cys Asp Gly Ile Ile  Gln Cys Arg Asp Gly  Ser Asp Glu
    1295                1300                1305

Asp Ala  Ala Phe Ala Gly Cys  Ser Gln Asp Pro Glu  Phe His Lys
    1310                1315                1320

Val Cys  Asp Glu Phe Gly Phe  Gln Cys Gln Asn Gly  Val Cys Ile
    1325                1330                1335

Ser Leu  Ile Trp Lys Cys Asp  Gly Met Asp Asp Cys  Gly Asp Tyr
    1340                1345                1350

Ser Asp  Glu Ala Asn Cys Glu  Asn Pro Thr Glu Ala  Pro Asn Cys
    1355                1360                1365

Ser Arg  Tyr Phe Gln Phe Arg  Cys Glu Asn Gly His  Cys Ile Pro
    1370                1375                1380
```

-continued

```
Asn Arg  Trp Lys Cys Asp Arg  Glu Asn Asp Cys Gly  Asp Trp Ser
    1385                1390                1395

Asp Glu  Lys Asp Cys Gly Asp  Ser His Ile Leu Pro  Phe Ser Thr
    1400                1405                1410

Pro Gly  Pro Ser Thr Cys Leu  Pro Asn Tyr Tyr Arg  Cys Ser Ser
    1415                1420                1425

Gly Thr  Cys Val Met Asp Thr  Trp Val Cys Asp Gly  Tyr Arg Asp
    1430                1435                1440

Cys Ala  Asp Gly Ser Asp Glu  Glu Ala Cys Pro Leu  Leu Ala Asn
    1445                1450                1455

Val Thr  Ala Ala Ser Thr Pro  Thr Gln Leu Gly Arg  Cys Asp Arg
    1460                1465                1470

Phe Glu  Phe Glu Cys His Gln  Pro Lys Thr Cys Ile  Pro Asn Trp
    1475                1480                1485

Lys Arg  Cys Asp Gly His Gln  Asp Cys Gln Asp Gly  Arg Asp Glu
    1490                1495                1500

Ala Asn  Cys Pro Thr His Ser  Thr Leu Thr Cys Met  Ser Arg Glu
    1505                1510                1515

Phe Gln  Cys Glu Asp Gly Glu  Ala Cys Ile Val Leu  Ser Glu Arg
    1520                1525                1530

Cys Asp  Gly Phe Leu Asp Cys  Ser Asp Glu Ser Asp  Glu Lys Ala
    1535                1540                1545

Cys Ser  Asp Glu Leu Thr Val  Tyr Lys Val Gln Asn  Leu Gln Trp
    1550                1555                1560

Thr Ala  Asp Phe Ser Gly Asp  Val Thr Leu Thr Trp  Met Arg Pro
    1565                1570                1575

Lys Lys  Met Pro Ser Ala Ser  Cys Val Tyr Asn Val  Tyr Tyr Arg
    1580                1585                1590

Val Val  Gly Glu Ser Ile Trp  Lys Thr Leu Glu Thr  His Ser Asn
    1595                1600                1605

Lys Thr  Asn Thr Val Leu Lys  Val Leu Lys Pro Asp  Thr Thr Tyr
    1610                1615                1620

Gln Val  Lys Val Gln Val Gln  Cys Leu Ser Lys Ala  His Asn Thr
    1625                1630                1635

Asn Asp  Phe Val Thr Leu Arg  Thr Pro Glu Gly Leu  Pro Asp Ala
    1640                1645                1650

Pro Arg  Asn Leu Gln Leu Ser  Leu Pro Arg Glu Ala  Glu Gly Val
    1655                1660                1665

Ile Val  Gly His Trp Ala Pro  Pro Ile His Thr His  Gly Leu Ile
    1670                1675                1680

Arg Glu  Tyr Ile Val Glu Tyr  Ser Arg Ser Gly Ser  Lys Met Trp
    1685                1690                1695

Ala Ser  Gln Arg Ala Ala Ser  Asn Phe Thr Glu Ile  Lys Asn Leu
    1700                1705                1710

Leu Val  Asn Thr Leu Tyr Thr  Val Arg Val Ala Ala  Val Thr Ser
    1715                1720                1725

Arg Gly  Ile Gly Asn Trp Ser  Asp Ser Lys Ser Ile  Thr Thr Ile
    1730                1735                1740

Lys Gly  Lys Val Ile Pro Pro  Pro Asp Ile His Ile  Asp Ser Tyr
    1745                1750                1755

Gly Glu  Asn Tyr Leu Ser Phe  Thr Leu Thr Met Glu  Ser Asp Ile
    1760                1765                1770
```

-continued

```
Lys Val  Asn Gly Tyr Val Val  Asn Leu Phe Trp Ala  Phe Asp Thr
    1775                1780                1785

His Lys  Gln Glu Arg Arg Thr  Leu Asn Phe Arg Gly  Ser Ile Leu
    1790                1795                1800

Ser His  Lys Val Gly Asn Leu  Thr Ala His Thr Ser  Tyr Glu Ile
    1805                1810                1815

Ser Ala  Trp Ala Lys Thr Asp  Leu Gly Asp Ser Pro  Leu Ala Phe
    1820                1825                1830

Glu His  Val Met Thr Arg Gly  Val Arg Pro Pro Ala  Pro Ser Leu
    1835                1840                1845

Lys Ala  Lys Ala Ile Asn Gln  Thr Ala Val Glu Cys  Thr Trp Thr
    1850                1855                1860

Gly Pro  Arg Asn Val Val Tyr  Gly Ile Phe Tyr Ala  Thr Ser Phe
    1865                1870                1875

Leu Asp  Leu Tyr Arg Asn Pro  Lys Ser Leu Thr Thr  Ser Leu His
    1880                1885                1890

Asn Lys  Thr Val Ile Val Ser  Lys Asp Glu Gln Tyr  Leu Phe Leu
    1895                1900                1905

Val Arg  Val Val Val Pro Tyr  Gln Gly Pro Ser Ser  Asp Tyr Val
    1910                1915                1920

Val Val  Lys Met Ile Pro Asp  Ser Arg Leu Pro Pro  Arg His Leu
    1925                1930                1935

His Val  Val His Thr Gly Lys  Thr Ser Val Val Ile  Lys Trp Glu
    1940                1945                1950

Ser Pro  Tyr Asp Ser Pro Asp  Gln Asp Leu Leu Tyr  Ala Ile Ala
    1955                1960                1965

Val Lys  Asp Leu Ile Arg Lys  Thr Asp Arg Ser Tyr  Lys Val Lys
    1970                1975                1980

Ser Arg  Asn Ser Thr Val Glu  Tyr Thr Leu Asn Lys  Leu Glu Pro
    1985                1990                1995

Gly Gly  Lys Tyr His Ile Ile  Val Gln Leu Gly Asn  Met Ser Lys
    2000                2005                2010

Asp Ser  Ser Ile Lys Ile Thr  Thr Val Ser Leu Ser  Ala Pro Asp
    2015                2020                2025

Ala Leu  Lys Ile Ile Thr Glu  Asn Asp His Val Leu  Leu Phe Trp
    2030                2035                2040

Lys Ser  Leu Ala Leu Lys Glu  Lys His Phe Asn Glu  Ser Arg Gly
    2045                2050                2055

Tyr Glu  Ile His Met Phe Asp  Ser Ala Met Asn Ile  Thr Ala Tyr
    2060                2065                2070

Leu Gly  Asn Thr Thr Asp Asn  Phe Phe Lys Ile Ser  Asn Leu Lys
    2075                2080                2085

Met Gly  His Asn Tyr Thr Phe  Thr Val Gln Ala Arg  Cys Leu Phe
    2090                2095                2100

Gly Asn  Gln Ile Cys Gly Glu  Pro Ala Ile Leu Leu  Tyr Asp Glu
    2105                2110                2115

Leu Gly  Ser Gly Ala Asp Ala  Ser Ala Thr Gln Ala  Ala Arg Ser
    2120                2125                2130

Thr Asp  Val Ala Ala Val Val  Val Pro Ile Leu Phe  Leu Ile Leu
    2135                2140                2145

Leu Ser  Leu Gly Val Gly Phe  Ala Ile Leu Tyr Thr  Lys His Arg
```

-continued

```
    2150                2155                2160

Arg Leu  Gln Ser Ser Phe Thr  Ala Phe Ala Asn Ser  His Tyr Ser
    2165                2170                2175

Ser Arg  Leu Gly Ser Ala Ile  Phe Ser Ser Gly Asp  Asp Leu Gly
    2180                2185                2190

Glu Asp  Asp Glu Asp Ala Pro  Met Ile Thr Gly Phe  Ser Asp Asp
    2195                2200                2205

Val Pro  Met Val Ile Ala
    2210
```

<210> SEQ ID NO 28
<211> LENGTH: 168
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

```
Met Arg Ser Phe Leu Leu Val Trp Lys Leu Phe Arg Arg Lys Asp Met
1               5                   10                  15

Lys His Gln Arg Lys Thr Ala Thr Glu Phe Lys Thr Thr Glu Glu Gly
            20                  25                  30

Glu Thr Arg Gln Asp Gly Lys Asp Gly Ser Leu Thr Tyr Arg Ala Asp
        35                  40                  45

Thr Cys Ser Pro Cys Pro Glu Ala Gly Gly Pro Pro Ser Ser Ser Ile
    50                  55                  60

Ala Ser Gly Ser Ser Ile Ser Val Gly Asn Ser Pro Ser His Ser His
65                  70                  75                  80

Ser His Thr Ser Arg Arg Cys Gly Gly Ser Ser Arg Ser Arg Glu Cys
                85                  90                  95

Cys Ser Ser Leu His Ser Ser Arg Gly Ser Arg Gly Ser Ser Trp Ser
            100                 105                 110

Ser Ser Pro Pro Gly Ser Thr Cys Arg Trp Cys Ser Cys His Ser His
        115                 120                 125

His His Ser His His Arg Ser His His Arg Ser His His Cys Ser His
    130                 135                 140

His His Ser His His His Ser Gly His His Ser His His Asn Phe His
145                 150                 155                 160

Asn His Ser Asn Pro Trp Cys Gln
                165
```

<210> SEQ ID NO 29
<211> LENGTH: 527
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

```
Met Ala Asp Ser Arg Asp Pro Ala Ser Asp Gln Met Gln His Trp Lys
1               5                   10                  15

Glu Gln Arg Ala Ala Gln Lys Ala Asp Val Leu Thr Thr Gly Ala Gly
            20                  25                  30

Asn Pro Val Gly Asp Lys Leu Asn Val Ile Thr Val Gly Pro Arg Gly
        35                  40                  45

Pro Leu Leu Val Gln Asp Val Val Phe Thr Asp Glu Met Ala His Phe
    50                  55                  60

Asp Arg Glu Arg Ile Pro Glu Arg Val Val His Ala Lys Gly Ala Gly
65                  70                  75                  80
```

-continued

```
Ala Phe Gly Tyr Phe Glu Val Thr His Asp Ile Thr Lys Tyr Ser Lys
                85                  90                  95

Ala Lys Val Phe Glu His Ile Gly Lys Lys Thr Pro Ile Ala Val Arg
            100                 105                 110

Phe Ser Thr Val Ala Gly Glu Ser Gly Ser Ala Asp Thr Val Arg Asp
        115                 120                 125

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

Leu Val Gly Asn Asn Thr Pro Ile Phe Phe Ile Arg Asp Pro Ile Leu
145                 150                 155                 160

Phe Pro Ser Phe Ile His Ser Gln Lys Arg Asn Pro Gln Thr His Leu
                165                 170                 175

Lys Asp Pro Asp Met Val Trp Asp Phe Trp Ser Leu Arg Pro Glu Ser
            180                 185                 190

Leu His Gln Val Ser Phe Leu Phe Ser Asp Arg Gly Ile Pro Asp Gly
        195                 200                 205

His Arg His Met Asn Gly Tyr Gly Ser His Thr Phe Lys Leu Val Asn
    210                 215                 220

Ala Asn Gly Glu Ala Val Tyr Cys Lys Phe His Tyr Lys Thr Asp Gln
225                 230                 235                 240

Gly Ile Lys Asn Leu Ser Val Glu Asp Ala Ala Arg Leu Ser Gln Glu
                245                 250                 255

Asp Pro Asp Tyr Gly Ile Arg Asp Leu Phe Asn Ala Ile Ala Thr Gly
            260                 265                 270

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

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

His Lys Asp Tyr Pro Leu Ile Pro Val Gly Lys Leu Val Leu Asn Arg
305                 310                 315                 320

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

Ser Asn Met Pro Pro Gly Ile Glu Ala Ser Pro Asp Lys Met Leu Gln
            340                 345                 350

Gly Arg Leu Phe Ala Tyr Pro Asp Thr His Arg His Arg Leu Gly Pro
        355                 360                 365

Asn Tyr Leu His Ile Pro Val Asn Cys Pro Tyr Arg Ala Arg Val Ala
    370                 375                 380

Asn Tyr Gln Arg Asp Gly Pro Met Cys Met Gln Asp Asn Gln Gly Gly
385                 390                 395                 400

Ala Pro Asn Tyr Tyr Pro Asn Ser Phe Gly Ala Pro Glu Gln Gln Pro
                405                 410                 415

Ser Ala Leu Glu His Ser Ile Gln Tyr Ser Gly Glu Val Arg Arg Phe
            420                 425                 430

Asn Thr Ala Asn Asp Asp Asn Val Thr Gln Val Arg Ala Phe Tyr Val
        435                 440                 445

Asn Val Leu Asn Glu Glu Gln Arg Lys Arg Leu Cys Glu Asn Ile Ala
    450                 455                 460

Gly His Leu Lys Asp Ala Gln Ile Phe Ile Gln Lys Lys Ala Val Lys
465                 470                 475                 480

Asn Phe Thr Glu Val His Pro Asp Tyr Gly Ser His Ile Gln Ala Leu
```

-continued

```
                485                 490                 495

Leu Asp Lys Tyr Asn Ala Glu Lys Pro Lys Asn Ala Ile His Thr Phe
            500                 505                 510

Val Gln Ser Gly Ser His Leu Ala Ala Arg Glu Lys Ala Asn Leu
        515                 520                 525


<210> SEQ ID NO 30
<211> LENGTH: 175
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Met Asn Ile His Ile His Thr Cys Met His Ile Tyr Thr His Ala His
1               5                   10                  15

Thr His Ala His Ile His Thr Cys Ile His Thr His Thr His Met His
            20                  25                  30

Thr His Thr Leu Thr Tyr Thr His Ile His Met His Thr His Thr Gln
        35                  40                  45

Thr His Ile Tyr Thr Gln Ala His Ile His Ser Cys Thr Gln Ile Asn
    50                  55                  60

Ile Tyr Thr Tyr Ala Tyr Thr Leu Thr Cys Thr Gln Thr His Thr His
65                  70                  75                  80

Ile Cys Thr His Ala His Thr Leu Thr Tyr Thr His Ile His Thr Cys
                85                  90                  95

Thr Tyr Lys Arg Thr Tyr Ile Gln Gly His Ile His Thr His Met His
            100                 105                 110

Thr Tyr Thr Cys Thr Cys Thr His Thr His Lys His Ile His Ala His
        115                 120                 125

Ile His Ile His Thr His Thr His Ile Tyr Thr His Thr Asp Ala Tyr
    130                 135                 140

Thr His Met Asp Thr Tyr Thr His Thr Tyr Pro His Thr His Ile Cys
145                 150                 155                 160

Ile His Ser His Thr His Ala His Thr Tyr Thr His Ile Arg Thr
                165                 170                 175


<210> SEQ ID NO 31
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Met Ala Arg Leu Leu Gln Ala Ser Cys Leu Leu Ser Leu Leu Leu Ala
1               5                   10                  15

Gly Phe Val Ser Gln Ser Arg Gly Gln Glu Lys Ser Lys Met Asp Cys
            20                  25                  30

His Gly Gly Ile Ser Gly Thr Ile Tyr Glu Tyr Gly Ala Leu Thr Ile
        35                  40                  45

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

Leu Phe Val Asn Val Ala Ser Tyr Cys Gly Leu Thr Gly Gln Tyr Ile
65                  70                  75                  80

Glu Leu Asn Ala Leu Gln Glu Glu Leu Ala Pro Phe Gly Leu Val Ile
                85                  90                  95

Leu Gly Phe Pro Cys Asn Gln Phe Gly Lys Gln Glu Pro Gly Glu Asn
            100                 105                 110
```

-continued

```
Ser Glu Ile Leu Pro Thr Leu Lys Tyr Val Arg Pro Gly Gly Gly Phe
        115                 120                 125

Val Pro Asn Phe Gln Leu Phe Glu Lys Gly Asp Val Asn Gly Glu Lys
    130                 135                 140

Glu Gln Lys Phe Tyr Thr Phe Leu Lys Asn Ser Cys Pro Pro Thr Ser
145                 150                 155                 160

Glu Leu Leu Gly Thr Ser Asp Arg Leu Phe Trp Glu Pro Met Lys Val
                165                 170                 175

His Asp Ile Arg Trp Asn Phe Glu Lys Phe Leu Val Gly Pro Asp Gly
            180                 185                 190

Ile Pro Ile Met Arg Trp His His Arg Thr Thr Val Ser Asn Val Lys
        195                 200                 205

Met Asp Ile Leu Ser Tyr Met Arg Arg Gln Ala Ala Leu Gly Val Lys
    210                 215                 220

Arg Lys
225


<210> SEQ ID NO 32
<211> LENGTH: 655
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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

Gly Pro Phe Leu Leu Leu Leu Leu Leu Leu Leu Leu Leu Pro Arg Gly
            20                  25                  30

Phe Gln Pro Gln Pro Gly Gly Asn Arg Thr Glu Ser Pro Glu Pro Asn
        35                  40                  45

Ala Thr Ala Thr Pro Ala Ile Pro Thr Ile Leu Val Thr Ser Val Thr
    50                  55                  60

Ser Glu Thr Pro Ala Thr Ser Ala Pro Glu Ala Glu Gly Pro Gln Ser
65                  70                  75                  80

Gly Gly Leu Pro Pro Pro Pro Arg Ala Val Pro Ser Ser Ser Ser Pro
                85                  90                  95

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

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

His Arg Lys Trp Cys Ala Thr Thr His Asn Tyr Asp Arg Asp Arg Ala
    130                 135                 140

Trp Gly Tyr Cys Val Glu Ala Thr Pro Pro Pro Gly Gly Pro Ala Ala
145                 150                 155                 160

Leu Asp Pro Cys Ala Ser Gly Pro Cys Leu Asn Gly Gly Ser Cys Ser
                165                 170                 175

Asn Thr Gln Asp Pro Gln Ser Tyr His Cys Ser Cys Pro Arg Ala Phe
            180                 185                 190

Thr Gly Lys Asp Cys Gly Thr Glu Lys Cys Phe Asp Glu Thr Arg Tyr
        195                 200                 205

Glu Tyr Leu Glu Gly Gly Asp Arg Trp Ala Arg Val Arg Gln Gly His
    210                 215                 220

Val Glu Gln Cys Glu Cys Phe Gly Gly Arg Thr Trp Cys Glu Gly Thr
225                 230                 235                 240
```

-continued

```
Arg His Thr Ala Cys Leu Ser Ser Pro Cys Leu Asn Gly Gly Thr Cys
                245                 250                 255

His Leu Ile Val Ala Thr Gly Thr Thr Val Cys Ala Cys Pro Pro Gly
            260                 265                 270

Phe Ala Gly Arg Leu Cys Asn Ile Glu Pro Asp Glu Arg Cys Phe Leu
        275                 280                 285

Gly Asn Gly Thr Gly Tyr Arg Gly Val Ala Ser Thr Ser Ala Ser Gly
    290                 295                 300

Leu Ser Cys Leu Ala Trp Asn Ser Asp Leu Leu Tyr Gln Glu Leu His
305                 310                 315                 320

Val Asp Ser Val Gly Ala Ala Ala Leu Leu Gly Leu Gly Pro His Ala
                325                 330                 335

Tyr Cys Arg Asn Pro Asp Asn Asp Glu Arg Pro Trp Cys Tyr Val Val
            340                 345                 350

Lys Asp Ser Ala Leu Ser Trp Glu Tyr Cys Arg Leu Glu Ala Cys Glu
        355                 360                 365

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

Glu Pro Ala Ser Pro Gly Arg Gln Ala Cys Gly Arg Arg His Lys Lys
385                 390                 395                 400

Arg Thr Phe Leu Arg Pro Arg Ile Ile Gly Gly Ser Ser Ser Leu Pro
                405                 410                 415

Gly Ser His Pro Trp Leu Ala Ala Ile Tyr Ile Gly Asp Ser Phe Cys
            420                 425                 430

Ala Gly Ser Leu Val His Thr Cys Trp Val Val Ser Ala Ala His Cys
        435                 440                 445

Phe Ser His Ser Pro Pro Arg Asp Ser Val Ser Val Val Leu Gly Gln
    450                 455                 460

His Phe Phe Asn Arg Thr Thr Asp Val Thr Gln Thr Phe Gly Ile Glu
465                 470                 475                 480

Lys Tyr Ile Pro Tyr Thr Leu Tyr Ser Val Phe Asn Pro Ser Asp His
                485                 490                 495

Asp Leu Val Leu Ile Arg Leu Lys Lys Lys Gly Asp Arg Cys Ala Thr
            500                 505                 510

Arg Ser Gln Phe Val Gln Pro Ile Cys Leu Pro Glu Pro Gly Ser Thr
        515                 520                 525

Phe Pro Ala Gly His Lys Cys Gln Ile Ala Gly Trp Gly His Leu Asp
    530                 535                 540

Glu Asn Val Ser Gly Tyr Ser Ser Ser Leu Arg Glu Ala Leu Val Pro
545                 550                 555                 560

Leu Val Ala Asp His Lys Cys Ser Ser Pro Glu Val Tyr Gly Ala Asp
                565                 570                 575

Ile Ser Pro Asn Met Leu Cys Ala Gly Tyr Phe Asp Cys Lys Ser Asp
            580                 585                 590

Ala Cys Gln Gly Asp Ser Gly Gly Pro Leu Ala Cys Glu Lys Asn Gly
        595                 600                 605

Val Ala Tyr Leu Tyr Gly Ile Ile Ser Trp Gly Asp Gly Cys Gly Arg
    610                 615                 620

Leu His Lys Pro Gly Val Tyr Thr Arg Val Ala Asn Tyr Val Asp Trp
625                 630                 635                 640

Ile Asn Asp Arg Ile Arg Pro Pro Arg Arg Leu Val Ala Pro Ser
```

-continued

645 650 655

<210> SEQ ID NO 33
<211> LENGTH: 697
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Met Leu Arg Gly Pro Cys Ser Pro Leu Asn Asp Phe Gln Val Leu Arg
1 5 10 15

Gly Thr Glu Leu Gln His Leu Leu His Ala Val Val Pro Gly Pro Trp
20 25 30

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

Leu Met Asp Cys Arg Ala Phe His Tyr Asn Val Ser Ser His Gly Cys
50 55 60

Gln Leu Leu Pro Trp Thr Gln His Ser Pro His Thr Arg Leu Arg Arg
65 70 75 80

Ser Gly Arg Cys Asp Leu Phe Gln Lys Lys Asp Tyr Val Arg Thr Cys
85 90 95

Ile Met Asn Asn Gly Val Gly Tyr Arg Gly Thr Met Ala Thr Thr Val
100 105 110

Gly Gly Leu Pro Cys Gln Ala Trp Ser His Lys Phe Pro Asn Asp His
115 120 125

Lys Tyr Thr Pro Thr Leu Arg Asn Gly Leu Glu Glu Asn Phe Cys Arg
130 135 140

Asn Pro Asp Gly Asp Pro Gly Gly Pro Trp Cys Tyr Thr Thr Asp Pro
145 150 155 160

Ala Val Arg Phe Gln Ser Cys Gly Ile Lys Ser Cys Arg Glu Ala Ala
165 170 175

Cys Val Trp Cys Asn Gly Glu Glu Tyr Arg Gly Ala Val Asp Arg Thr
180 185 190

Glu Ser Gly Arg Glu Cys Gln Arg Trp Asp Leu Gln His Pro His Gln
195 200 205

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

Tyr Cys Arg Asn Pro Asp Gly Ser Glu Arg Pro Trp Cys Tyr Thr Thr
225 230 235 240

Asp Pro Gln Ile Glu Arg Glu Phe Cys Asp Leu Pro Arg Cys Gly Ser
245 250 255

Glu Ala Gln Pro Arg Gln Glu Ala Thr Thr Val Ser Cys Phe Arg Gly
260 265 270

Lys Gly Glu Gly Tyr Arg Gly Thr Ala Asn Thr Thr Thr Ala Gly Val
275 280 285

Pro Cys Gln Arg Trp Asp Ala Gln Ile Pro His Gln His Arg Phe Thr
290 295 300

Pro Glu Lys Tyr Ala Cys Lys Asp Leu Arg Glu Asn Phe Cys Arg Asn
305 310 315 320

Pro Asp Gly Ser Glu Ala Pro Trp Cys Phe Thr Leu Arg Pro Gly Met
325 330 335

Arg Ala Ala Phe Cys Tyr Gln Ile Arg Arg Cys Thr Asp Asp Val Arg
340 345 350

Pro Gln Asp Cys Tyr His Gly Ala Gly Glu Gln Tyr Arg Gly Thr Val

-continued

```
        355                 360                 365

Ser Lys Thr Arg Lys Gly Val Gln Cys Gln Arg Trp Ser Ala Glu Thr
    370                 375                 380

Pro His Lys Pro Gln Phe Thr Phe Thr Ser Glu Pro His Ala Gln Leu
385                 390                 395                 400

Glu Glu Asn Phe Cys Arg Asn Pro Asp Gly Asp Ser His Gly Pro Trp
                405                 410                 415

Cys Tyr Thr Met Asp Pro Arg Thr Pro Phe Asp Tyr Cys Ala Leu Arg
            420                 425                 430

Arg Cys Ala Asp Asp Gln Pro Pro Ser Ile Leu Asp Pro Pro Asp Gln
        435                 440                 445

Val Gln Phe Glu Lys Cys Gly Lys Arg Val Asp Arg Leu Asp Gln Arg
    450                 455                 460

Arg Ser Lys Leu Arg Val Val Gly Gly His Pro Gly Asn Ser Pro Trp
465                 470                 475                 480

Thr Val Ser Leu Arg Asn Arg Gln Gly Gln His Phe Cys Gly Gly Ser
                485                 490                 495

Leu Val Lys Glu Gln Trp Ile Leu Thr Ala Arg Gln Cys Phe Ser Ser
            500                 505                 510

Cys His Met Pro Leu Thr Gly Tyr Glu Val Trp Leu Gly Thr Leu Phe
        515                 520                 525

Gln Asn Pro Gln His Gly Glu Pro Ser Leu Gln Arg Val Pro Val Ala
    530                 535                 540

Lys Met Val Cys Gly Pro Ser Gly Ser Gln Leu Val Leu Leu Lys Leu
545                 550                 555                 560

Glu Arg Ser Val Thr Leu Asn Gln Arg Val Ala Leu Ile Cys Leu Pro
                565                 570                 575

Pro Glu Trp Tyr Val Val Pro Pro Gly Thr Lys Cys Glu Ile Ala Gly
            580                 585                 590

Trp Gly Glu Thr Lys Gly Thr Gly Asn Asp Thr Val Leu Asn Val Ala
        595                 600                 605

Leu Leu Asn Val Ile Ser Asn Gln Glu Cys Asn Ile Lys His Arg Gly
    610                 615                 620

Arg Val Arg Glu Ser Glu Met Cys Thr Glu Gly Leu Leu Ala Pro Val
625                 630                 635                 640

Gly Ala Cys Glu Gly Asp Tyr Gly Gly Pro Leu Ala Cys Phe Thr His
                645                 650                 655

Asn Cys Trp Val Leu Glu Gly Ile Ile Ile Pro Asn Arg Val Cys Ala
            660                 665                 670

Arg Ser Arg Trp Pro Ala Val Phe Thr Arg Val Ser Val Phe Val Asp
        675                 680                 685

Trp Ile His Lys Val Met Arg Leu Gly
    690                 695


<210> SEQ ID NO 34
<211> LENGTH: 240
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Met Thr Pro His Arg Leu Leu Pro Pro Leu Leu Leu Leu Leu Ala Leu
1               5                   10                  15

Leu Leu Ala Ala Ser Pro Gly Gly Ala Leu Ala Arg Cys Pro Gly Cys
```

-continued

```
            20                  25                  30

Gly Gln Gly Val Gln Ala Gly Cys Pro Gly Gly Cys Val Glu Glu Glu
        35                  40                  45

Asp Gly Gly Ser Pro Ala Glu Gly Cys Ala Glu Ala Glu Gly Cys Leu
    50                  55                  60

Arg Arg Glu Gly Gln Glu Cys Gly Val Tyr Thr Pro Asn Cys Ala Pro
65                  70                  75                  80

Gly Leu Gln Cys His Pro Pro Lys Asp Asp Glu Ala Pro Leu Arg Ala
                85                  90                  95

Leu Leu Leu Gly Arg Gly Arg Cys Leu Pro Ala Arg Ala Pro Ala Val
            100                 105                 110

Ala Glu Glu Asn Pro Lys Glu Ser Lys Pro Gln Ala Gly Thr Ala Arg
        115                 120                 125

Pro Gln Asp Val Asn Arg Arg Asp Gln Gln Arg Asn Pro Gly Thr Ser
    130                 135                 140

Thr Thr Pro Ser Gln Pro Asn Ser Ala Gly Val Gln Asp Thr Glu Met
145                 150                 155                 160

Gly Pro Cys Arg Arg His Leu Asp Ser Val Leu Gln Gln Leu Gln Thr
                165                 170                 175

Glu Val Tyr Arg Gly Ala Gln Thr Leu Tyr Val Pro Asn Cys Asp His
            180                 185                 190

Arg Gly Phe Tyr Arg Lys Arg Gln Cys Arg Ser Ser Gln Gly Gln Arg
        195                 200                 205

Arg Gly Pro Cys Trp Cys Val Asp Arg Met Gly Lys Ser Leu Pro Gly
    210                 215                 220

Ser Pro Asp Gly Asn Gly Ser Ser Ser Cys Pro Thr Gly Ser Ser Gly
225                 230                 235                 240


<210> SEQ ID NO 35
<211> LENGTH: 88
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

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

Tyr Thr Met Leu Lys Glu Val Thr Cys Asp Val Cys Val Cys Val Arg
            20                  25                  30

Ala Arg Ala Cys Thr Cys Met Cys Met Cys Val Cys Glu Cys Met Asp
        35                  40                  45

Val Cys Val Arg Leu Tyr Thr Met Leu Lys Glu Val Thr Cys Asp Met
    50                  55                  60

Cys Val Cys Ala Arg Thr Cys Val His Val Cys Val Ser Ala Trp Met
65                  70                  75                  80

Cys Val Cys Thr Cys Thr Gln Cys
                85


<210> SEQ ID NO 36
<211> LENGTH: 1439
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Met Asp Thr Thr Ala Ala Ala Ala Leu Pro Ala Phe Val Ala Leu Leu
1               5                   10                  15
```

-continued

```
Leu Leu Ser Pro Trp Pro Leu Leu Gly Ser Ala Gln Gly Gln Phe Ser
            20                  25                  30

Ala Gly Gly Cys Thr Phe Asp Asp Gly Pro Gly Ala Cys Asp Tyr His
        35                  40                  45

Gln Asp Leu Tyr Asp Asp Phe Glu Trp Val His Val Ser Ala Gln Glu
    50                  55                  60

Pro His Tyr Leu Pro Pro Glu Met Pro Gln Gly Ser Tyr Met Ile Val
65                  70                  75                  80

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

Thr Met Lys Glu Asn Asp Thr His Cys Ile Asp Phe Ser Tyr Leu Leu
            100                 105                 110

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

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

Thr Gly Arg Asp Trp Leu Arg Ala Glu Leu Ala Val Ser Thr Phe Trp
145                 150                 155                 160

Pro Asn Glu Tyr Gln Val Ile Phe Glu Ala Glu Val Ser Gly Gly Arg
                165                 170                 175

Ser Gly Tyr Ile Ala Ile Asp Asp Ile Gln Val Leu Ser Tyr Pro Cys
            180                 185                 190

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

Gly Gln Asn Ala Thr Phe Gln Cys Ile Ala Thr Gly Arg Asp Ala Val
    210                 215                 220

His Asn Lys Leu Trp Leu Gln Arg Arg Asn Gly Glu Asp Ile Pro Val
225                 230                 235                 240

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

Leu Gln Glu Val Thr Lys Thr Asp Gln Asp Leu Tyr Arg Cys Val Thr
            260                 265                 270

Gln Ser Glu Arg Gly Ser Gly Val Ser Asn Phe Ala Gln Leu Ile Val
        275                 280                 285

Arg Glu Pro Pro Arg Pro Ile Ala Pro Pro Gln Leu Leu Gly Val Gly
    290                 295                 300

Pro Thr Tyr Leu Leu Ile Gln Leu Asn Ala Asn Ser Ile Ile Gly Asp
305                 310                 315                 320

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

Trp Thr Glu Thr His Ala Val Asn Ala Pro Thr Tyr Lys Leu Trp His
            340                 345                 350

Leu Asp Pro Asp Thr Glu Tyr Glu Ile Arg Val Leu Leu Thr Arg Pro
        355                 360                 365

Gly Glu Gly Gly Thr Gly Leu Pro Gly Pro Pro Leu Ile Thr Arg Thr
    370                 375                 380

Lys Cys Ala Glu Pro Met Arg Thr Pro Lys Thr Leu Lys Ile Ala Glu
385                 390                 395                 400

Ile Gln Ala Arg Arg Ile Ala Val Asp Trp Glu Ser Leu Gly Tyr Asn
                405                 410                 415

Ile Thr Arg Cys His Thr Phe Asn Val Thr Ile Cys Tyr His Tyr Phe
```

-continued

```
           420                 425                 430

Arg Gly His Asn Glu Ser Lys Ala Asp Cys Leu Asp Met Asp Pro Lys
        435                 440                 445

Ala Pro Gln His Val Val Asn His Leu Pro Pro Tyr Thr Asn Val Ser
    450                 455                 460

Leu Lys Met Ile Leu Thr Asn Pro Glu Gly Arg Lys Glu Ser Glu Glu
465                 470                 475                 480

Thr Ile Ile Gln Thr Asp Glu Asp Val Pro Gly Pro Val Pro Val Lys
                485                 490                 495

Ser Leu Gln Gly Thr Ser Phe Glu Asn Lys Ile Phe Leu Asn Trp Lys
            500                 505                 510

Glu Pro Leu Asp Pro Asn Gly Ile Ile Thr Gln Tyr Glu Ile Ser Tyr
        515                 520                 525

Ser Ser Ile Arg Ser Phe Asp Pro Ala Val Pro Val Ala Gly Pro Pro
    530                 535                 540

Gln Thr Val Ser Asn Leu Trp Asn Ser Thr His His Val Phe Met His
545                 550                 555                 560

Leu His Pro Gly Thr Thr Tyr Gln Phe Phe Ile Arg Ala Ser Thr Val
                565                 570                 575

Lys Gly Phe Gly Pro Ala Thr Ala Ile Asn Val Thr Thr Asn Ile Ser
            580                 585                 590

Ala Pro Thr Leu Pro Asp Tyr Glu Gly Val Asp Ala Ser Leu Asn Glu
        595                 600                 605

Thr Ala Thr Thr Ile Thr Val Leu Leu Arg Pro Ala Gln Ala Lys Gly
    610                 615                 620

Ala Pro Ile Ser Ala Tyr Gln Ile Val Val Glu Glu Leu His Pro His
625                 630                 635                 640

Arg Thr Lys Arg Glu Ala Gly Ala Met Glu Cys Tyr Gln Val Pro Val
                645                 650                 655

Thr Tyr Gln Asn Ala Met Ser Gly Gly Ala Pro Tyr Tyr Phe Ala Ala
            660                 665                 670

Glu Leu Pro Pro Gly Asn Leu Pro Glu Pro Ala Pro Phe Thr Val Gly
        675                 680                 685

Asp Asn Arg Thr Tyr Gln Gly Phe Trp Asn Pro Pro Leu Ala Pro Arg
    690                 695                 700

Lys Gly Tyr Asn Ile Tyr Phe Gln Ala Met Ser Ser Val Glu Lys Glu
705                 710                 715                 720

Thr Lys Thr Gln Cys Val Arg Ile Ala Thr Lys Ala Ala Thr Glu Glu
                725                 730                 735

Pro Glu Val Ile Pro Asp Pro Ala Lys Gln Thr Asp Arg Val Val Lys
            740                 745                 750

Ile Ala Gly Ile Ser Ala Gly Ile Leu Val Phe Ile Leu Leu Leu Leu
        755                 760                 765

Val Val Ile Leu Ile Val Lys Lys Ser Lys Leu Ala Lys Lys Arg Lys
    770                 775                 780

Asp Ala Met Gly Asn Thr Arg Gln Glu Met Thr His Met Val Asn Ala
785                 790                 795                 800

Met Asp Arg Ser Tyr Ala Asp Gln Ser Thr Leu His Ala Glu Asp Pro
                805                 810                 815

Leu Ser Ile Thr Phe Met Asp Gln His Asn Phe Ser Pro Arg Tyr Glu
            820                 825                 830
```

-continued

```
Asn His Ser Ala Thr Ala Glu Ser Ser Arg Leu Leu Asp Val Pro Arg
        835                 840                 845

Tyr Leu Cys Glu Gly Thr Glu Ser Pro Tyr Gln Thr Gly Gln Leu His
    850                 855                 860

Pro Ala Ile Arg Val Ala Asp Leu Leu Gln His Ile Asn Leu Met Lys
865                 870                 875                 880

Thr Ser Asp Ser Tyr Gly Phe Lys Glu Glu Tyr Glu Ser Phe Phe Glu
                885                 890                 895

Gly Gln Ser Ala Ser Trp Asp Val Ala Lys Lys Asp Gln Asn Arg Ala
            900                 905                 910

Lys Asn Arg Tyr Gly Asn Ile Ile Ala Tyr Asp His Ser Arg Val Ile
        915                 920                 925

Leu Gln Pro Val Glu Asp Asp Pro Ser Ser Asp Tyr Ile Asn Ala Asn
    930                 935                 940

Tyr Ile Asp Gly Tyr Gln Arg Pro Ser His Tyr Ile Ala Thr Gln Gly
945                 950                 955                 960

Pro Val His Glu Thr Val Tyr Asp Phe Trp Arg Met Ile Trp Gln Glu
                965                 970                 975

Gln Ser Ala Cys Ile Val Met Val Thr Asn Leu Val Glu Val Gly Arg
            980                 985                 990

Val Lys Cys Tyr Lys Tyr Trp Pro  Asp Asp Thr Glu Val  Tyr Gly Asp
        995                 1000                1005

Phe Lys  Val Thr Cys Val Glu  Met Glu Pro Leu Ala  Glu Tyr Val
    1010                1015                1020

Val Arg  Thr Phe Thr Leu Glu  Arg Arg Gly Tyr Asn  Glu Ile Arg
    1025                1030                1035

Glu Val  Lys Gln Phe His Phe  Thr Gly Trp Pro Asp  His Gly Val
    1040                1045                1050

Pro Tyr  His Ala Thr Gly Leu  Leu Ser Phe Ile Arg  Arg Val Lys
    1055                1060                1065

Leu Ser  Asn Pro Pro Ser Ala  Gly Pro Ile Val Val  His Cys Ser
    1070                1075                1080

Ala Gly  Ala Gly Arg Thr Gly  Cys Tyr Ile Val Ile  Asp Ile Met
    1085                1090                1095

Leu Asp  Met Ala Glu Arg Glu  Gly Val Val Asp Ile  Tyr Asn Cys
    1100                1105                1110

Val Lys  Ala Leu Arg Ser Arg  Arg Ile Asn Met Val  Gln Thr Glu
    1115                1120                1125

Glu Gln  Tyr Ile Phe Ile His  Asp Ala Ile Leu Glu  Ala Cys Leu
    1130                1135                1140

Cys Gly  Glu Thr Ala Ile Pro  Val Cys Glu Phe Lys  Ala Ala Tyr
    1145                1150                1155

Phe Asp  Met Ile Arg Ile Asp  Ser Gln Thr Asn Ser  Ser His Leu
    1160                1165                1170

Lys Asp  Glu Phe Gln Thr Leu  Asn Ser Val Thr Pro  Arg Leu Gln
    1175                1180                1185

Ala Glu  Asp Cys Ser Ile Ala  Cys Leu Pro Arg Asn  His Asp Lys
    1190                1195                1200

Asn Arg  Phe Met Asp Met Leu  Pro Pro Asp Arg Cys  Leu Pro Phe
    1205                1210                1215

Leu Ile  Thr Ile Asp Gly Glu  Ser Ser Asn Tyr Ile  Asn Ala Ala
    1220                1225                1230
```

-continued

```
Leu Met  Asp Ser Tyr Arg Gln  Pro Ala Ala Phe Ile  Val Thr Gln
    1235                1240                1245

Tyr Pro  Leu Pro Asn Thr Val  Lys Asp Phe Trp Arg  Leu Val Tyr
    1250                1255                1260

Asp Tyr  Gly Cys Thr Ser Ile  Val Met Leu Asn Glu  Val Asp Leu
    1265                1270                1275

Ser Gln  Gly Cys Pro Gln Tyr  Trp Pro Glu Glu Gly  Met Leu Arg
    1280                1285                1290

Tyr Gly  Pro Ile Gln Val Glu  Cys Met Ser Cys Ser  Met Asp Cys
    1295                1300                1305

Asp Val  Ile Asn Arg Ile Phe  Arg Ile Cys Asn Leu  Thr Arg Pro
    1310                1315                1320

Gln Glu  Gly Tyr Leu Met Val  Gln Gln Phe Gln Tyr  Leu Gly Trp
    1325                1330                1335

Ala Ser  His Arg Glu Val Pro  Gly Ser Lys Arg Ser  Phe Leu Lys
    1340                1345                1350

Leu Ile  Leu Gln Val Glu Lys  Trp Gln Glu Glu Cys  Glu Glu Gly
    1355                1360                1365

Glu Gly  Arg Thr Ile Ile His  Cys Leu Asn Gly Gly  Gly Arg Ser
    1370                1375                1380

Gly Met  Phe Cys Ala Ile Gly  Ile Val Val Glu Met  Val Lys Arg
    1385                1390                1395

Gln Asn  Val Val Asp Val Phe  His Ala Val Lys Thr  Leu Arg Asn
    1400                1405                1410

Ser Lys  Pro Asn Met Val Glu  Ala Pro Glu Gln Tyr  Arg Phe Cys
    1415                1420                1425

Tyr Asp  Val Ala Leu Glu Tyr  Leu Glu Ser Ser
    1430                1435


<210> SEQ ID NO 37
<211> LENGTH: 1272
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Met Val Ala Ala Ala Ala Ala Thr Glu Ala Arg Leu Arg Arg Arg Thr
1               5                  10                  15

Ala Ala Thr Ala Ala Leu Ala Gly Arg Ser Gly Gly Pro His Trp Asp
            20                  25                  30

Trp Asp Val Thr Arg Ala Gly Arg Pro Gly Leu Gly Ala Gly Leu Arg
        35                  40                  45

Leu Pro Arg Leu Leu Ser Pro Pro Leu Arg Pro Arg Leu Leu Leu Leu
    50                  55                  60

Leu Leu Leu Leu Ser Pro Pro Leu Leu Leu Leu Leu Leu Pro Cys Glu
65                  70                  75                  80

Ala Glu Ala Ala Ala Ala Ala Ala Ala Val Ser Gly Ser Ala Ala Ala
                85                  90                  95

Glu Ala Lys Glu Cys Asp Arg Pro Cys Val Asn Gly Gly Arg Cys Asn
            100                 105                 110

Pro Gly Thr Gly Gln Cys Val Cys Pro Ala Gly Trp Val Gly Glu Gln
        115                 120                 125

Cys Gln His Cys Gly Gly Arg Phe Arg Leu Thr Gly Ser Ser Gly Phe
    130                 135                 140
```

-continued

```
Val Thr Asp Gly Pro Gly Asn Tyr Lys Tyr Lys Thr Lys Cys Thr Trp
145                 150                 155                 160

Leu Ile Glu Gly Gln Pro Asn Arg Ile Met Arg Leu Arg Phe Asn His
                165                 170                 175

Phe Ala Thr Glu Cys Ser Trp Asp His Leu Tyr Val Tyr Asp Gly Asp
            180                 185                 190

Ser Ile Tyr Ala Pro Leu Val Ala Ala Phe Ser Gly Leu Ile Val Pro
        195                 200                 205

Glu Arg Asp Gly Asn Glu Thr Val Pro Glu Val Val Ala Thr Ser Gly
    210                 215                 220

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

Phe Asn Ile Thr Tyr Ser Phe Asp Met Cys Pro Asn Asn Cys Ser Gly
                245                 250                 255

Arg Gly Glu Cys Lys Ile Ser Asn Ser Ser Asp Thr Val Glu Cys Glu
            260                 265                 270

Cys Ser Glu Asn Trp Lys Gly Glu Ala Cys Asp Ile Pro His Cys Thr
        275                 280                 285

Asp Asn Cys Gly Phe Pro His Arg Gly Ile Cys Asn Ser Ser Asp Val
    290                 295                 300

Arg Gly Cys Ser Cys Phe Ser Asp Trp Gln Gly Pro Gly Cys Ser Val
305                 310                 315                 320

Pro Val Pro Ala Asn Gln Ser Phe Trp Thr Arg Glu Glu Tyr Ser Asn
                325                 330                 335

Leu Lys Leu Pro Arg Ala Ser His Lys Ala Val Val Asn Gly Asn Ile
            340                 345                 350

Met Trp Val Val Gly Gly Tyr Met Phe Asn His Ser Asp Tyr Asn Met
        355                 360                 365

Val Leu Ala Tyr Asp Leu Ala Ser Arg Glu Trp Leu Pro Leu Asn Arg
    370                 375                 380

Ser Val Asn Asn Val Val Val Arg Tyr Gly His Ser Leu Ala Leu Tyr
385                 390                 395                 400

Lys Asp Lys Ile Tyr Met Tyr Gly Gly Lys Ile Asp Ser Thr Gly Asn
                405                 410                 415

Val Thr Asn Glu Leu Arg Val Phe His Ile His Asn Glu Ser Trp Val
            420                 425                 430

Leu Leu Thr Pro Lys Ala Lys Glu Gln Tyr Ala Val Val Gly His Ser
        435                 440                 445

Ala His Ile Val Thr Leu Lys Asn Gly Arg Val Val Met Leu Val Ile
    450                 455                 460

Phe Gly His Cys Pro Leu Tyr Gly Tyr Ile Ser Asn Val Gln Glu Tyr
465                 470                 475                 480

Asp Leu Asp Lys Asn Thr Trp Ser Ile Leu His Thr Gln Gly Ala Leu
                485                 490                 495

Val Gln Gly Gly Tyr Gly His Ser Ser Val Tyr Asp His Arg Thr Arg
            500                 505                 510

Ala Leu Tyr Val His Gly Gly Tyr Lys Ala Phe Ser Ala Asn Lys Tyr
        515                 520                 525

Arg Leu Ala Asp Asp Leu Tyr Arg Tyr Asp Val Asp Thr Gln Met Trp
    530                 535                 540

Thr Ile Leu Lys Asp Ser Arg Phe Phe Arg Tyr Leu His Thr Ala Val
```

-continued

```
545                 550                 555                 560

Ile Val Ser Gly Thr Met Leu Val Phe Gly Gly Asn Thr His Asn Asp
                565                 570                 575

Thr Ser Met Ser His Gly Ala Lys Cys Phe Ser Ser Asp Phe Met Ala
            580                 585                 590

Tyr Asp Ile Ala Cys Asp Arg Trp Ser Val Leu Pro Arg Pro Asp Leu
        595                 600                 605

His His Asp Val Asn Arg Phe Gly His Ser Ala Val Leu His Asn Ser
    610                 615                 620

Thr Met Tyr Val Phe Gly Gly Phe Asn Ser Leu Leu Leu Ser Asp Ile
625                 630                 635                 640

Leu Val Phe Thr Ser Glu Gln Cys Asp Ala His Arg Ser Glu Ala Ala
                645                 650                 655

Cys Leu Ala Ala Gly Pro Gly Ile Arg Cys Val Trp Asn Thr Gly Ser
            660                 665                 670

Ser Gln Cys Ile Ser Trp Ala Leu Ala Thr Asp Glu Gln Glu Glu Lys
        675                 680                 685

Leu Lys Ser Glu Cys Phe Ser Lys Arg Thr Leu Asp His Asp Arg Cys
    690                 695                 700

Asp Gln His Thr Asp Cys Tyr Ser Cys Thr Ala Asn Thr Asn Asp Cys
705                 710                 715                 720

His Trp Cys Asn Asp His Cys Val Pro Arg Asn His Ser Cys Ser Glu
                725                 730                 735

Gly Gln Ile Ser Ile Phe Arg Tyr Glu Asn Cys Pro Lys Asp Asn Pro
            740                 745                 750

Met Tyr Tyr Cys Asn Lys Lys Thr Ser Cys Arg Ser Cys Ala Leu Asp
        755                 760                 765

Gln Asn Cys Gln Trp Glu Pro Arg Asn Gln Glu Cys Ile Ala Leu Pro
    770                 775                 780

Glu Asn Ile Cys Gly Ile Gly Trp His Leu Val Gly Asn Ser Cys Leu
785                 790                 795                 800

Lys Ile Thr Thr Ala Lys Glu Asn Tyr Asp Asn Ala Lys Leu Phe Cys
                805                 810                 815

Arg Asn His Asn Ala Leu Leu Ala Ser Leu Thr Thr Gln Lys Lys Val
            820                 825                 830

Glu Phe Val Leu Lys Gln Leu Arg Ile Met Gln Ser Ser Gln Ser Met
        835                 840                 845

Ser Lys Leu Thr Leu Thr Pro Trp Val Gly Leu Arg Lys Ile Asn Val
    850                 855                 860

Ser Tyr Trp Cys Trp Glu Asp Met Ser Pro Phe Thr Asn Ser Leu Leu
865                 870                 875                 880

Gln Trp Met Pro Ser Glu Pro Ser Asp Ala Gly Phe Cys Gly Ile Leu
                885                 890                 895

Ser Glu Pro Ser Thr Arg Gly Leu Lys Ala Ala Thr Cys Ile Asn Pro
            900                 905                 910

Leu Asn Gly Ser Val Cys Glu Arg Pro Ala Asn His Ser Ala Lys Gln
        915                 920                 925

Cys Arg Thr Pro Cys Ala Leu Arg Thr Ala Cys Gly Asp Cys Thr Ser
    930                 935                 940

Gly Ser Ser Glu Cys Met Trp Cys Ser Asn Met Lys Gln Cys Val Asp
945                 950                 955                 960
```

-continued

```
Ser Asn Ala Tyr Val Ala Ser Phe Pro Phe Gly Gln Cys Met Glu Trp
               965                 970                 975

Tyr Thr Met Ser Thr Cys Pro Pro Glu Asn Cys Ser Gly Tyr Cys Thr
            980                 985                 990

Cys Ser His Cys Leu Glu Gln Pro  Gly Cys Gly Trp Cys  Thr Asp Pro
        995                 1000                1005

Ser Asn  Thr Gly Lys Gly Lys  Cys Ile Glu Gly Ser  Tyr Lys Gly
    1010                1015                1020

Pro Val  Lys Met Pro Ser Gln  Ala Pro Thr Gly Asn  Phe Tyr Pro
    1025                1030                1035

Gln Pro  Leu Leu Asn Ser Ser  Met Cys Leu Glu Asp  Ser Arg Tyr
    1040                1045                1050

Asn Trp  Ser Phe Ile His Cys  Pro Ala Cys Gln Cys  Asn Gly His
    1055                1060                1065

Ser Lys  Cys Ile Asn Gln Ser  Ile Cys Glu Lys Cys  Glu Asn Leu
    1070                1075                1080

Thr Thr  Gly Lys His Cys Glu  Thr Cys Ile Ser Gly  Phe Tyr Gly
    1085                1090                1095

Asp Pro  Thr Asn Gly Gly Lys  Cys Gln Pro Cys Lys  Cys Asn Gly
    1100                1105                1110

His Ala  Ser Leu Cys Asn Thr  Asn Thr Gly Lys Cys  Phe Cys Thr
    1115                1120                1125

Thr Lys  Gly Val Lys Gly Asp  Glu Cys Gln Leu Cys  Glu Val Glu
    1130                1135                1140

Asn Arg  Tyr Gln Gly Asn Pro  Leu Arg Gly Thr Cys  Tyr Tyr Thr
    1145                1150                1155

Leu Leu  Ile Asp Tyr Gln Phe  Thr Phe Ser Leu Ser  Gln Glu Asp
    1160                1165                1170

Asp Arg  Tyr Tyr Thr Ala Ile  Asn Phe Val Ala Thr  Pro Asp Glu
    1175                1180                1185

Gln Asn  Arg Asp Leu Asp Met  Phe Ile Asn Ala Ser  Lys Asn Phe
    1190                1195                1200

Asn Leu  Asn Ile Thr Trp Ala  Ala Ser Phe Ser Ala  Gly Thr Gln
    1205                1210                1215

Ala Gly  Glu Glu Met Pro Val  Val Ser Lys Thr Asn  Ile Lys Glu
    1220                1225                1230

Tyr Lys  Asp Ser Phe Ser Asn  Glu Lys Phe Asp Phe  Arg Asn His
    1235                1240                1245

Pro Asn  Ile Thr Phe Phe Val  Tyr Val Ser Asn Phe  Thr Trp Pro
    1250                1255                1260

Ile Lys  Ile Gln Val Gln Thr  Glu Gln
    1265                1270


<210> SEQ ID NO 38
<211> LENGTH: 289
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

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

Asp Asp Thr Asp Ala Val Glu Ile Ala Ile Asp Asn Thr Ala Phe Met
            20                  25                  30
```

-continued

```
Asp Glu Phe Phe Ser Glu Ile Glu Glu Thr Arg Leu Asn Ile Asp Lys
        35                  40                  45

Ile Ser Glu His Val Glu Glu Ala Lys Lys Leu Tyr Ser Ile Ile Leu
    50                  55                  60

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

Thr Thr Glu Ile Lys Lys Arg Ala Asn Asn Val Arg Asn Lys Leu Lys
                85                  90                  95

Ser Met Glu Lys His Ile Glu Glu Asp Glu Val Arg Ser Ser Ala Asp
            100                 105                 110

Leu Arg Ile Arg Lys Ser Gln His Ser Val Leu Ser Arg Lys Phe Val
        115                 120                 125

Glu Val Met Thr Lys Tyr Asn Glu Ala Gln Val Asp Phe Arg Glu Arg
    130                 135                 140

Ser Lys Gly Arg Ile Gln Arg Gln Leu Glu Ile Thr Gly Lys Lys Thr
145                 150                 155                 160

Thr Asp Glu Glu Leu Glu Glu Met Leu Glu Ser Gly Asn Pro Ala Ile
                165                 170                 175

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

Glu Ile Glu Gly Arg His Lys Asp Ile Val Arg Leu Glu Ser Ser Ile
        195                 200                 205

Lys Glu Leu His Asp Met Phe Met Asp Ile Ala Met Leu Val Glu Asn
    210                 215                 220

Gln Gly Glu Met Leu Asp Asn Ile Glu Leu Asn Val Met His Thr Val
225                 230                 235                 240

Asp His Val Glu Lys Ala Arg Asp Glu Thr Lys Lys Ala Val Lys Tyr
                245                 250                 255

Gln Ser Gln Ala Arg Lys Lys Leu Ile Ile Ile Ile Val Leu Val Val
            260                 265                 270

Val Leu Leu Gly Ile Leu Ala Leu Ile Ile Gly Leu Ser Val Gly Leu
        275                 280                 285

Asn
```

<210> SEQ ID NO 39
<211> LENGTH: 666
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

```
Met Arg Lys Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser
1               5                   10                  15

Pro Ile Gln Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val
            20                  25                  30

Thr Leu Asp Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys
        35                  40                  45

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

Thr His Tyr Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln
65                  70                  75                  80

Leu Asn Glu Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg
                85                  90                  95

Thr Ala Gly Trp Asn Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn
```

-continued

```
           100                 105                 110

Trp Thr Gly Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe
        115                 120                 125

Ser Ala Ser Cys Val Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu
    130                 135                 140

Cys Arg Leu Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser
145                 150                 155                 160

Gln Glu Pro Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp
                165                 170                 175

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

Leu Ser Asp Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp
        195                 200                 205

Asn Thr Arg Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg
    210                 215                 220

Val Pro Ser His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp
225                 230                 235                 240

Ala Ile Trp Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp
                245                 250                 255

Lys Ser Pro Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp
            260                 265                 270

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

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

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

Val Trp Cys Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp
                325                 330                 335

Ser Gly Leu Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr
            340                 345                 350

Glu Asp Cys Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser
        355                 360                 365

Leu Asp Gly Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro
    370                 375                 380

Val Leu Ala Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro
385                 390                 395                 400

Asn Cys Val Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val
                405                 410                 415

Arg Arg Ser Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys
            420                 425                 430

Ser Cys His Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met
        435                 440                 445

Gly Leu Leu Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe
    450                 455                 460

Ser Gln Ser Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala
465                 470                 475                 480

Leu Cys Ile Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser
                485                 490                 495

Asn Glu Arg Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu
            500                 505                 510
```

-continued

```
Asn Ala Gly Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn
        515                 520                 525

Thr Asp Gly Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala
    530                 535                 540

Asp Phe Ala Leu Leu Cys Leu Asp Gly Lys Arg Lys Pro Val Thr Glu
545                 550                 555                 560

Ala Arg Ser Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser
                565                 570                 575

Arg Met Asp Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln
            580                 585                 590

Ala Lys Phe Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu
        595                 600                 605

Phe Gln Ser Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys
    610                 615                 620

Leu Ala Arg Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro
625                 630                 635                 640

Gln Tyr Val Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro
                645                 650                 655

Leu Leu Glu Ala Cys Glu Phe Leu Arg Lys
            660                 665


<210> SEQ ID NO 40
<211> LENGTH: 4655
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Met Asp Arg Gly Pro Ala Ala Val Ala Cys Thr Leu Leu Leu Ala Leu
1               5                   10                  15

Val Ala Cys Leu Ala Pro Ala Ser Gly Gln Glu Cys Asp Ser Ala His
            20                  25                  30

Phe Arg Cys Gly Ser Gly His Cys Ile Pro Ala Asp Trp Arg Cys Asp
        35                  40                  45

Gly Thr Lys Asp Cys Ser Asp Asp Ala Asp Glu Ile Gly Cys Ala Val
    50                  55                  60

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

Ile Pro Asn Ser Trp Val Cys Asp Gln Asp Gln Asp Cys Asp Asp Gly
                85                  90                  95

Ser Asp Glu Arg Gln Asp Cys Ser Gln Ser Thr Cys Ser Ser His Gln
            100                 105                 110

Ile Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp
        115                 120                 125

His Val Arg Asp Cys Pro Asp Gly Ala Asp Glu Asn Asp Cys Gln Tyr
    130                 135                 140

Pro Thr Cys Glu Gln Leu Thr Cys Asp Asn Gly Ala Cys Tyr Asn Thr
145                 150                 155                 160

Ser Gln Lys Cys Asp Trp Lys Val Asp Cys Arg Asp Ser Ser Asp Glu
                165                 170                 175

Ile Asn Cys Thr Glu Ile Cys Leu His Asn Glu Phe Ser Cys Gly Asn
            180                 185                 190

Gly Glu Cys Ile Pro Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys
        195                 200                 205
```

-continued

```
Gln Asp Gly Ser Asp Glu His Ala Cys Asn Tyr Pro Thr Cys Gly Gly
    210                 215                 220

Tyr Gln Phe Thr Cys Pro Ser Gly Arg Cys Ile Tyr Gln Asn Trp Val
225                 230                 235                 240

Cys Asp Gly Glu Asp Asp Cys Lys Asp Asn Gly Asp Glu Asp Gly Cys
                245                 250                 255

Glu Ser Gly Pro His Asp Val His Lys Cys Ser Pro Arg Glu Trp Ser
            260                 265                 270

Cys Pro Glu Ser Gly Arg Cys Ile Ser Ile Tyr Lys Val Cys Asp Gly
        275                 280                 285

Ile Leu Asp Cys Pro Gly Arg Glu Asp Glu Asn Asn Thr Ser Thr Gly
    290                 295                 300

Lys Tyr Cys Ser Met Thr Leu Cys Ser Ala Leu Asn Cys Gln Tyr Gln
305                 310                 315                 320

Cys His Glu Thr Pro Tyr Gly Gly Ala Cys Phe Cys Pro Pro Gly Tyr
                325                 330                 335

Ile Ile Asn His Asn Asp Ser Arg Thr Cys Val Glu Phe Asp Asp Cys
            340                 345                 350

Gln Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Ser Arg Pro Gly Arg
        355                 360                 365

His Leu Cys His Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln Tyr
    370                 375                 380

Cys Lys Ala Asn Asp Ser Phe Gly Glu Ala Ser Ile Ile Phe Ser Asn
385                 390                 395                 400

Gly Arg Asp Leu Leu Ile Gly Asp Ile His Gly Arg Ser Phe Arg Ile
                405                 410                 415

Leu Val Glu Ser Gln Asn Arg Gly Val Ala Val Gly Val Ala Phe His
            420                 425                 430

Tyr His Leu Gln Arg Val Phe Trp Thr Asp Thr Val Gln Asn Lys Val
        435                 440                 445

Phe Ser Val Asp Ile Asn Gly Leu Asn Ile Gln Glu Val Leu Asn Val
    450                 455                 460

Ser Val Glu Thr Pro Glu Asn Leu Ala Val Asp Trp Val Asn Asn Lys
465                 470                 475                 480

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

Asp Gly Ser Tyr Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro
            500                 505                 510

Arg Gly Ile Ala Val Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp
        515                 520                 525

Trp Glu Ser Leu Ser Gly Glu Pro Lys Leu Glu Arg Ala Phe Met Asp
    530                 535                 540

Gly Ser Asn Arg Lys Asp Leu Val Lys Thr Lys Leu Gly Trp Pro Ala
545                 550                 555                 560

Gly Val Thr Leu Asp Met Ile Ser Lys Arg Val Tyr Trp Val Asp Ser
                565                 570                 575

Arg Phe Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys
            580                 585                 590

Thr Val Val His Gly Gly Ser Leu Ile Pro His Pro Phe Gly Val Ser
        595                 600                 605

Leu Phe Glu Gly Gln Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val
    610                 615                 620
```

-continued

```
Leu Lys Ala Asn Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr Tyr Gln
625                 630                 635                 640

Ala Ser Leu Arg Pro Tyr Gly Val Thr Val Tyr His Ser Leu Arg Gln
                645                 650                 655

Pro Tyr Ala Thr Asn Pro Cys Lys Asp Asn Asn Gly Gly Cys Glu Gln
            660                 665                 670

Val Cys Val Leu Ser His Arg Thr Asp Asn Asp Gly Leu Gly Phe Arg
        675                 680                 685

Cys Lys Cys Thr Phe Gly Phe Gln Leu Asp Thr Asp Glu Arg His Cys
    690                 695                 700

Ile Ala Val Gln Asn Phe Leu Ile Phe Ser Ser Gln Val Ala Ile Arg
705                 710                 715                 720

Gly Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val
                725                 730                 735

Ser Gly Asn Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln Asp
            740                 745                 750

Ser Thr Ile Phe Phe Ser Asp Met Ser Lys His Met Ile Phe Lys Gln
        755                 760                 765

Lys Ile Asp Gly Thr Gly Arg Glu Ile Leu Ala Ala Asn Arg Val Glu
    770                 775                 780

Asn Val Glu Ser Leu Ala Phe Asp Trp Ile Ser Lys Asn Leu Tyr Trp
785                 790                 795                 800

Thr Asp Ser His Tyr Lys Ser Ile Ser Val Met Arg Leu Ala Asp Lys
                805                 810                 815

Thr Arg Arg Thr Val Val Gln Tyr Leu Asn Asn Pro Arg Ser Val Val
            820                 825                 830

Val His Pro Phe Ala Gly Tyr Leu Phe Phe Thr Asp Trp Phe Arg Pro
        835                 840                 845

Ala Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Leu Pro Val
    850                 855                 860

Ile Asn Thr Thr Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ala
865                 870                 875                 880

Ala Ser Arg Leu Tyr Trp Val Asp Ala Tyr Phe Asp Lys Ile Glu His
                885                 890                 895

Ser Thr Phe Asp Gly Leu Asp Arg Arg Arg Leu Gly His Ile Glu Gln
            900                 905                 910

Met Thr His Pro Phe Gly Leu Ala Ile Phe Gly Glu His Leu Phe Phe
        915                 920                 925

Thr Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ala Asp Gly
    930                 935                 940

Gly Glu Met Thr Val Ile Arg Ser Gly Ile Ala Tyr Ile Leu His Leu
945                 950                 955                 960

Lys Ser Tyr Asp Val Asn Ile Gln Thr Gly Ser Asn Ala Cys Asn Gln
                965                 970                 975

Pro Thr His Pro Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro
            980                 985                 990

Asn Phe Gln Arg Val Cys Gly Cys  Pro Tyr Gly Met Arg  Leu Ala Ser
        995                 1000                1005

Asn His  Leu Thr Cys Glu Gly  Asp Pro Thr Asn Glu  Pro Pro Thr
    1010                1015                1020

Glu Gln  Cys Gly Leu Phe Ser  Phe Pro Cys Lys Asn  Gly Arg Cys
```

-continued

```
    1025                1030                1035

Val Pro  Asn Tyr Tyr Leu Cys  Asp Gly Val Asp Asp  Cys His Asp
    1040                1045                1050

Asn Ser  Asp Glu Gln Leu Cys  Gly Thr Leu Asn Asn  Thr Cys Ser
    1055                1060                1065

Ser Ser  Ala Phe Thr Cys Gly  His Gly Glu Cys Ile  Pro Ala His
    1070                1075                1080

Trp Arg  Cys Asp Lys Arg Asn  Asp Cys Val Asp Gly  Ser Asp Glu
    1085                1090                1095

His Asn  Cys Pro Thr His Ala  Pro Ala Ser Cys Leu  Asp Thr Gln
    1100                1105                1110

Tyr Thr  Cys Asp Asn His Gln  Cys Ile Ser Lys Asn  Trp Val Cys
    1115                1120                1125

Asp Thr  Asp Asn Asp Cys Gly  Asp Gly Ser Asp Glu  Lys Asn Cys
    1130                1135                1140

Asn Ser  Thr Glu Thr Cys Gln  Pro Ser Gln Phe Asn  Cys Pro Asn
    1145                1150                1155

His Arg  Cys Ile Asp Leu Ser  Phe Val Cys Asp Gly  Asp Lys Asp
    1160                1165                1170

Cys Val  Asp Gly Ser Asp Glu  Val Gly Cys Val Leu  Asn Cys Thr
    1175                1180                1185

Ala Ser  Gln Phe Lys Cys Ala  Ser Gly Asp Lys Cys  Ile Gly Val
    1190                1195                1200

Thr Asn  Arg Cys Asp Gly Val  Phe Asp Cys Ser Asp  Asn Ser Asp
    1205                1210                1215

Glu Ala  Gly Cys Pro Thr Arg  Pro Pro Gly Met Cys  His Ser Asp
    1220                1225                1230

Glu Phe  Gln Cys Gln Glu Asp  Gly Ile Cys Ile Pro  Asn Phe Trp
    1235                1240                1245

Glu Cys  Asp Gly His Pro Asp  Cys Leu Tyr Gly Ser  Asp Glu His
    1250                1255                1260

Asn Ala  Cys Val Pro Lys Thr  Cys Pro Ser Ser Tyr  Phe His Cys
    1265                1270                1275

Asp Asn  Gly Asn Cys Ile His  Arg Ala Trp Leu Cys  Asp Arg Asp
    1280                1285                1290

Asn Asp  Cys Gly Asp Met Ser  Asp Glu Lys Asp Cys  Pro Thr Gln
    1295                1300                1305

Pro Phe  Arg Cys Pro Ser Trp  Gln Trp Gln Cys Leu  Gly His Asn
    1310                1315                1320

Ile Cys  Val Asn Leu Ser Val  Val Cys Asp Gly Ile  Phe Asp Cys
    1325                1330                1335

Pro Asn  Gly Thr Asp Glu Ser  Pro Leu Cys Asn Gly  Asn Ser Cys
    1340                1345                1350

Ser Asp  Phe Asn Gly Gly Cys  Thr His Glu Cys Val  Gln Glu Pro
    1355                1360                1365

Phe Gly  Ala Lys Cys Leu Cys  Pro Leu Gly Phe Leu  Leu Ala Asn
    1370                1375                1380

Asp Ser  Lys Thr Cys Glu Asp  Ile Asp Glu Cys Asp  Ile Leu Gly
    1385                1390                1395

Ser Cys  Ser Gln His Cys Tyr  Asn Met Arg Gly Ser  Phe Arg Cys
    1400                1405                1410
```

-continued

```
Ser Cys  Asp Thr Gly Tyr Met  Leu Glu Ser Asp Gly  Arg Thr Cys
    1415                1420                1425

Lys Val  Thr Ala Ser Glu Ser  Leu Leu Leu Leu Val  Ala Ser Gln
    1430                1435                1440

Asn Lys  Ile Ile Ala Asp Ser  Val Thr Ser Gln Val  His Asn Ile
    1445                1450                1455

Tyr Ser  Leu Val Glu Asn Gly  Ser Tyr Ile Val Ala  Val Asp Phe
    1460                1465                1470

Asp Ser  Ile Ser Gly Arg Ile  Phe Trp Ser Asp Ala  Thr Gln Gly
    1475                1480                1485

Lys Thr  Trp Ser Ala Phe Gln  Asn Gly Thr Asp Arg  Arg Val Val
    1490                1495                1500

Phe Asp  Ser Ser Ile Ile Leu  Thr Glu Thr Ile Ala  Ile Asp Trp
    1505                1510                1515

Val Gly  Arg Asn Leu Tyr Trp  Thr Asp Tyr Ala Leu  Glu Thr Ile
    1520                1525                1530

Glu Val  Ser Lys Ile Asp Gly  Ser His Arg Thr Val  Leu Ile Ser
    1535                1540                1545

Lys Asn  Leu Thr Asn Pro Arg  Gly Leu Ala Leu Asp  Pro Arg Met
    1550                1555                1560

Asn Glu  His Leu Leu Phe Trp  Ser Asp Trp Gly His  His Pro Arg
    1565                1570                1575

Ile Glu  Arg Ala Ser Met Asp  Gly Ser Met Arg Thr  Val Ile Val
    1580                1585                1590

Gln Asp  Lys Ile Phe Trp Pro  Cys Gly Leu Thr Ile  Asp Tyr Pro
    1595                1600                1605

Asn Arg  Leu Leu Tyr Phe Met  Asp Ser Tyr Leu Asp  Tyr Met Asp
    1610                1615                1620

Phe Cys  Asp Tyr Asn Gly His  His Arg Arg Gln Val  Ile Ala Ser
    1625                1630                1635

Asp Leu  Ile Ile Arg His Pro  Tyr Ala Leu Thr Leu  Phe Glu Asp
    1640                1645                1650

Ser Val  Tyr Trp Thr Asp Arg  Ala Thr Arg Arg Val  Met Arg Ala
    1655                1660                1665

Asn Lys  Trp His Gly Gly Asn  Gln Ser Val Val Met  Tyr Asn Ile
    1670                1675                1680

Gln Trp  Pro Leu Gly Ile Val  Ala Val His Pro Ser  Lys Gln Pro
    1685                1690                1695

Asn Ser  Val Asn Pro Cys Ala  Phe Ser Arg Cys Ser  His Leu Cys
    1700                1705                1710

Leu Leu  Ser Ser Gln Gly Pro  His Phe Tyr Ser Cys  Val Cys Pro
    1715                1720                1725

Ser Gly  Trp Ser Leu Ser Pro  Asp Leu Leu Asn Cys  Leu Arg Asp
    1730                1735                1740

Asp Gln  Pro Phe Leu Ile Thr  Val Arg Gln His Ile  Ile Phe Gly
    1745                1750                1755

Ile Ser  Leu Asn Pro Glu Val  Lys Ser Asn Asp Ala  Met Val Pro
    1760                1765                1770

Ile Ala  Gly Ile Gln Asn Gly  Leu Asp Val Glu Phe  Asp Asp Ala
    1775                1780                1785

Glu Gln  Tyr Ile Tyr Trp Val  Glu Asn Pro Gly Glu  Ile His Arg
    1790                1795                1800
```

-continued

```
Val Lys  Thr Asp Gly Thr Asn  Arg Thr Val Phe Ala  Ser Ile Ser
    1805                1810                1815

Met Val  Gly Pro Ser Met Asn  Leu Ala Leu Asp Trp  Ile Ser Arg
    1820                1825                1830

Asn Leu  Tyr Ser Thr Asn Pro  Arg Thr Gln Ser Ile  Glu Val Leu
    1835                1840                1845

Thr Leu  His Gly Asp Ile Arg  Tyr Arg Lys Thr Leu  Ile Ala Asn
    1850                1855                1860

Asp Gly  Thr Ala Leu Gly Val  Gly Phe Pro Ile Gly  Ile Thr Val
    1865                1870                1875

Asp Pro  Ala Arg Gly Lys Leu  Tyr Trp Ser Asp Gln  Gly Thr Asp
    1880                1885                1890

Ser Gly  Val Pro Ala Lys Ile  Ala Ser Ala Asn Met  Asp Gly Thr
    1895                1900                1905

Ser Val  Lys Thr Leu Phe Thr  Gly Asn Leu Glu His  Leu Glu Cys
    1910                1915                1920

Val Thr  Leu Asp Ile Glu Glu  Gln Lys Leu Tyr Trp  Ala Val Thr
    1925                1930                1935

Gly Arg  Gly Val Ile Glu Arg  Gly Asn Val Asp Gly  Thr Asp Arg
    1940                1945                1950

Met Ile  Leu Val His Gln Leu  Ser His Pro Trp Gly  Ile Ala Val
    1955                1960                1965

His Asp  Ser Phe Leu Tyr Tyr  Thr Asp Glu Gln Tyr  Glu Val Ile
    1970                1975                1980

Glu Arg  Val Asp Lys Ala Thr  Gly Ala Asn Lys Ile  Val Leu Arg
    1985                1990                1995

Asp Asn  Val Pro Asn Leu Arg  Gly Leu Gln Val Tyr  His Arg Arg
    2000                2005                2010

Asn Ala  Ala Glu Ser Ser Asn  Gly Cys Ser Asn Asn  Met Asn Ala
    2015                2020                2025

Cys Gln  Gln Ile Cys Leu Pro  Val Pro Gly Gly Leu  Phe Ser Cys
    2030                2035                2040

Ala Cys  Ala Thr Gly Phe Lys  Leu Asn Pro Asp Asn  Arg Ser Cys
    2045                2050                2055

Ser Pro  Tyr Asn Ser Phe Ile  Val Val Ser Met Leu  Ser Ala Ile
    2060                2065                2070

Arg Gly  Phe Ser Leu Glu Leu  Ser Asp His Ser Glu  Thr Met Val
    2075                2080                2085

Pro Val  Ala Gly Gln Gly Arg  Asn Ala Leu His Val  Asp Val Asp
    2090                2095                2100

Val Ser  Ser Gly Phe Ile Tyr  Trp Cys Asp Phe Ser  Ser Ser Val
    2105                2110                2115

Ala Ser  Asp Asn Ala Ile Arg  Arg Ile Lys Pro Asp  Gly Ser Ser
    2120                2125                2130

Leu Met  Asn Ile Val Thr His  Gly Ile Gly Glu Asn  Gly Val Arg
    2135                2140                2145

Gly Ile  Ala Val Asp Trp Val  Ala Gly Asn Leu Tyr  Phe Thr Asn
    2150                2155                2160

Ala Phe  Val Ser Glu Thr Leu  Ile Glu Val Leu Arg  Ile Asn Thr
    2165                2170                2175

Thr Tyr  Arg Arg Val Leu Leu  Lys Val Thr Val Asp  Met Pro Arg
```

-continued

```
    2180                2185                2190

His Ile  Val Val Asp Pro Lys  Asn Arg Tyr Leu Phe  Trp Ala Asp
    2195                2200                2205

Tyr Gly  Gln Arg Pro Lys Ile  Glu Arg Ser Phe Leu  Asp Cys Thr
    2210                2215                2220

Asn Arg  Thr Val Leu Val Ser  Glu Gly Ile Val Thr  Pro Arg Gly
    2225                2230                2235

Leu Ala  Val Asp Arg Ser Asp  Gly Tyr Val Tyr Trp  Val Asp Asp
    2240                2245                2250

Ser Leu  Asp Ile Ile Ala Arg  Ile Arg Ile Asn Gly  Glu Asn Ser
    2255                2260                2265

Glu Val  Ile Arg Tyr Gly Ser  Arg Tyr Pro Thr Pro  Tyr Gly Ile
    2270                2275                2280

Thr Val  Phe Glu Asn Ser Ile  Ile Trp Val Asp Arg  Asn Leu Lys
    2285                2290                2295

Lys Ile  Phe Gln Ala Ser Lys  Glu Pro Glu Asn Thr  Glu Pro Pro
    2300                2305                2310

Thr Val  Ile Arg Asp Asn Ile  Asn Trp Leu Arg Asp  Val Thr Ile
    2315                2320                2325

Phe Asp  Lys Gln Val Gln Pro  Arg Ser Pro Ala Glu  Val Asn Asn
    2330                2335                2340

Asn Pro  Cys Leu Glu Asn Asn  Gly Gly Cys Ser His  Leu Cys Phe
    2345                2350                2355

Ala Leu  Pro Gly Leu His Thr  Pro Lys Cys Asp Cys  Ala Phe Gly
    2360                2365                2370

Thr Leu  Gln Ser Asp Gly Lys  Asn Cys Ala Ile Ser  Thr Glu Asn
    2375                2380                2385

Phe Leu  Ile Phe Ala Leu Ser  Asn Ser Leu Arg Ser  Leu His Leu
    2390                2395                2400

Asp Pro  Glu Asn His Ser Pro  Pro Phe Gln Thr Ile  Asn Val Glu
    2405                2410                2415

Arg Thr  Val Met Ser Leu Asp  Tyr Asp Ser Val Ser  Asp Arg Ile
    2420                2425                2430

Tyr Phe  Thr Gln Asn Leu Ala  Ser Gly Val Gly Gln  Ile Ser Tyr
    2435                2440                2445

Ala Thr  Leu Ser Ser Gly Ile  His Thr Pro Thr Val  Ile Ala Ser
    2450                2455                2460

Gly Ile  Gly Thr Ala Asp Gly  Ile Ala Phe Asp Trp  Ile Thr Arg
    2465                2470                2475

Arg Ile  Tyr Tyr Ser Asp Tyr  Leu Asn Gln Met Ile  Asn Ser Met
    2480                2485                2490

Ala Glu  Asp Gly Ser Asn Arg  Thr Val Ile Ala Arg  Val Pro Lys
    2495                2500                2505

Pro Arg  Ala Ile Val Leu Asp  Pro Cys Gln Gly Tyr  Leu Tyr Trp
    2510                2515                2520

Ala Asp  Trp Asp Thr His Ala  Lys Ile Glu Arg Ala  Thr Leu Gly
    2525                2530                2535

Gly Asn  Phe Arg Val Pro Ile  Val Asn Ser Ser Leu  Val Met Pro
    2540                2545                2550

Ser Gly  Leu Thr Leu Asp Tyr  Glu Glu Asp Leu Leu  Tyr Trp Val
    2555                2560                2565
```

-continued

```
Asp Ala  Ser Leu Gln Arg Ile  Glu Arg Ser Thr Leu  Thr Gly Val
    2570                2575                2580

Asp Arg  Glu Val Ile Val Asn  Ala Ala Val His Ala  Phe Gly Leu
    2585                2590                2595

Thr Leu  Tyr Gly Gln Tyr Ile  Tyr Trp Thr Asp Leu  Tyr Thr Gln
    2600                2605                2610

Arg Ile  Tyr Arg Ala Asn Lys  Tyr Asp Gly Ser Gly  Gln Ile Ala
    2615                2620                2625

Met Thr  Thr Asn Leu Leu Ser  Gln Pro Arg Gly Ile  Asn Thr Val
    2630                2635                2640

Val Lys  Asn Gln Lys Gln Gln  Cys Asn Asn Pro Cys  Glu Gln Phe
    2645                2650                2655

Asn Gly  Gly Cys Ser His Ile  Cys Ala Pro Gly Pro  Asn Gly Ala
    2660                2665                2670

Glu Cys  Gln Cys Pro His Glu  Gly Asn Trp Tyr Leu  Ala Asn Asn
    2675                2680                2685

Arg Lys  His Cys Ile Val Asp  Asn Gly Glu Arg Cys  Gly Ala Ser
    2690                2695                2700

Ser Phe  Thr Cys Ser Asn Gly  Arg Cys Ile Ser Glu  Glu Trp Lys
    2705                2710                2715

Cys Asp  Asn Asp Asn Asp Cys  Gly Asp Gly Ser Asp  Glu Met Glu
    2720                2725                2730

Ser Val  Cys Ala Leu His Thr  Cys Ser Pro Thr Ala  Phe Thr Cys
    2735                2740                2745

Ala Asn  Gly Arg Cys Val Gln  Tyr Ser Tyr Arg Cys  Asp Tyr Tyr
    2750                2755                2760

Asn Asp  Cys Gly Asp Gly Ser  Asp Glu Ala Gly Cys  Leu Phe Arg
    2765                2770                2775

Asp Cys  Asn Ala Thr Thr Glu  Phe Met Cys Asn Asn  Arg Arg Cys
    2780                2785                2790

Ile Pro  Arg Glu Phe Ile Cys  Asn Gly Val Asp Asn  Cys His Asp
    2795                2800                2805

Asn Asn  Thr Ser Asp Glu Lys  Asn Cys Pro Asp Arg  Thr Cys Gln
    2810                2815                2820

Ser Gly  Tyr Thr Lys Cys His  Asn Ser Asn Ile Cys  Ile Pro Arg
    2825                2830                2835

Val Tyr  Leu Cys Asp Gly Asp  Asn Asp Cys Gly Asp  Asn Ser Asp
    2840                2845                2850

Glu Asn  Pro Thr Tyr Cys Thr  Thr His Thr Cys Ser  Ser Ser Glu
    2855                2860                2865

Phe Gln  Cys Ala Ser Gly Arg  Cys Ile Pro Gln His  Trp Tyr Cys
    2870                2875                2880

Asp Gln  Glu Thr Asp Cys Phe  Asp Ala Ser Asp Glu  Pro Ala Ser
    2885                2890                2895

Cys Gly  His Ser Glu Arg Thr  Cys Leu Ala Asp Glu  Phe Lys Cys
    2900                2905                2910

Asp Gly  Gly Arg Cys Ile Pro  Ser Glu Trp Ile Cys  Asp Gly Asp
    2915                2920                2925

Asn Asp  Cys Gly Asp Met Ser  Asp Glu Asp Lys Arg  His Gln Cys
    2930                2935                2940

Gln Asn  Gln Asn Cys Ser Asp  Ser Glu Phe Leu Cys  Val Asn Asp
    2945                2950                2955
```

-continued

```
Arg Pro  Pro Asp Arg Arg Cys  Ile Pro Gln Ser Trp  Val Cys Asp
    2960                2965                2970

Gly Asp  Val Asp Cys Thr Asp  Gly Tyr Asp Glu Asn  Gln Asn Cys
    2975                2980                2985

Thr Arg  Arg Thr Cys Ser Glu  Asn Glu Phe Thr Cys  Gly Tyr Gly
    2990                2995                3000

Leu Cys  Ile Pro Lys Ile Phe  Arg Cys Asp Arg His  Asn Asp Cys
    3005                3010                3015

Gly Asp  Tyr Ser Asp Glu Arg  Gly Cys Leu Tyr Gln  Thr Cys Gln
    3020                3025                3030

Gln Asn  Gln Phe Thr Cys Gln  Asn Gly Arg Cys Ile  Ser Lys Thr
    3035                3040                3045

Phe Val  Cys Asp Glu Asp Asn  Asp Cys Gly Asp Gly  Ser Asp Glu
    3050                3055                3060

Leu Met  His Leu Cys His Thr  Pro Glu Pro Thr Cys  Pro Pro His
    3065                3070                3075

Glu Phe  Lys Cys Asp Asn Gly  Arg Cys Ile Glu Met  Met Lys Leu
    3080                3085                3090

Cys Asn  His Leu Asp Asp Cys  Leu Asp Asn Ser Asp  Glu Lys Gly
    3095                3100                3105

Cys Gly  Ile Asn Glu Cys His  Asp Pro Ser Ile Ser  Gly Cys Asp
    3110                3115                3120

His Asn  Cys Thr Asp Thr Leu  Thr Ser Phe Tyr Cys  Ser Cys Arg
    3125                3130                3135

Pro Gly  Tyr Lys Leu Met Ser  Asp Lys Arg Thr Cys  Val Asp Ile
    3140                3145                3150

Asp Glu  Cys Thr Glu Met Pro  Phe Val Cys Ser Gln  Lys Cys Glu
    3155                3160                3165

Asn Val  Ile Gly Ser Tyr Ile  Cys Lys Cys Ala Pro  Gly Tyr Leu
    3170                3175                3180

Arg Glu  Pro Asp Gly Lys Thr  Cys Arg Gln Asn Ser  Asn Ile Glu
    3185                3190                3195

Pro Tyr  Leu Ile Phe Ser Asn  Arg Tyr Tyr Leu Arg  Asn Leu Thr
    3200                3205                3210

Ile Asp  Gly Tyr Phe Tyr Ser  Leu Ile Leu Glu Gly  Leu Asp Asn
    3215                3220                3225

Val Val  Ala Leu Asp Phe Asp  Arg Val Glu Lys Arg  Leu Tyr Trp
    3230                3235                3240

Ile Asp  Thr Gln Arg Gln Val  Ile Glu Arg Met Phe  Leu Asn Lys
    3245                3250                3255

Thr Asn  Lys Glu Thr Ile Ile  Asn His Arg Leu Pro  Ala Ala Glu
    3260                3265                3270

Ser Leu  Ala Val Asp Trp Val  Ser Arg Lys Leu Tyr  Trp Leu Asp
    3275                3280                3285

Ala Arg  Leu Asp Gly Leu Phe  Val Ser Asp Leu Asn  Gly Gly His
    3290                3295                3300

Arg Arg  Met Leu Ala Gln His  Cys Val Asp Ala Asn  Asn Thr Phe
    3305                3310                3315

Cys Phe  Asp Asn Pro Arg Gly  Leu Ala Leu His Pro  Gln Tyr Gly
    3320                3325                3330

Tyr Leu  Tyr Trp Ala Asp Trp  Gly His Arg Ala Tyr  Ile Gly Arg
```

-continued

```
    3335                3340                3345

Val Gly  Met Asp Gly Thr Asn  Lys Ser Val Ile Ile  Ser Thr Lys
    3350                3355                3360

Leu Glu  Trp Pro Asn Gly Ile  Thr Ile Asp Tyr Thr  Asn Asp Leu
    3365                3370                3375

Leu Tyr  Trp Ala Asp Ala His  Leu Gly Tyr Ile Glu  Tyr Ser Asp
    3380                3385                3390

Leu Glu  Gly His His Arg His  Thr Val Tyr Asp Gly  Ala Leu Pro
    3395                3400                3405

His Pro  Phe Ala Ile Thr Ile  Phe Glu Asp Thr Ile  Tyr Trp Thr
    3410                3415                3420

Asp Trp  Asn Thr Arg Thr Val  Glu Lys Gly Asn Lys  Tyr Asp Gly
    3425                3430                3435

Ser Asn  Arg Gln Thr Leu Val  Asn Thr Thr His Arg  Pro Phe Asp
    3440                3445                3450

Ile His  Val Tyr His Pro Tyr  Arg Gln Pro Ile Val  Ser Asn Pro
    3455                3460                3465

Cys Gly  Thr Asn Asn Gly Gly  Cys Ser His Leu Cys  Leu Ile Lys
    3470                3475                3480

Pro Gly  Gly Lys Gly Phe Thr  Cys Glu Cys Pro Asp  Asp Phe Arg
    3485                3490                3495

Thr Leu  Gln Leu Ser Gly Ser  Thr Tyr Cys Met Pro  Met Cys Ser
    3500                3505                3510

Ser Thr  Gln Phe Leu Cys Ala  Asn Asn Glu Lys Cys  Ile Pro Ile
    3515                3520                3525

Trp Trp  Lys Cys Asp Gly Gln  Lys Asp Cys Ser Asp  Gly Ser Asp
    3530                3535                3540

Glu Leu  Ala Leu Cys Pro Gln  Arg Phe Cys Arg Leu  Gly Gln Phe
    3545                3550                3555

Gln Cys  Ser Asp Gly Asn Cys  Thr Ser Pro Gln Thr  Leu Cys Asn
    3560                3565                3570

Ala His  Gln Asn Cys Pro Asp  Gly Ser Asp Glu Asp  Arg Leu Leu
    3575                3580                3585

Cys Glu  Asn His His Cys Asp  Ser Asn Glu Trp Gln  Cys Ala Asn
    3590                3595                3600

Lys Arg  Cys Ile Pro Glu Ser  Trp Gln Cys Asp Thr  Phe Asn Asp
    3605                3610                3615

Cys Glu  Asp Asn Ser Asp Glu  Asp Ser Ser His Cys  Ala Ser Arg
    3620                3625                3630

Thr Cys  Arg Pro Gly Gln Phe  Arg Cys Ala Asn Gly  Arg Cys Ile
    3635                3640                3645

Pro Gln  Ala Trp Lys Cys Asp  Val Asp Asn Asp Cys  Gly Asp His
    3650                3655                3660

Ser Asp  Glu Pro Ile Glu Glu  Cys Met Ser Ser Ala  His Leu Cys
    3665                3670                3675

Asp Asn  Phe Thr Glu Phe Ser  Cys Lys Thr Asn Tyr  Arg Cys Ile
    3680                3685                3690

Pro Lys  Trp Ala Val Cys Asn  Gly Val Asp Asp Cys  Arg Asp Asn
    3695                3700                3705

Ser Asp  Glu Gln Gly Cys Glu  Glu Arg Thr Cys His  Pro Val Gly
    3710                3715                3720
```

-continued

```
Asp Phe  Arg Cys Lys Asn His  His Cys Ile Pro Leu  Arg Trp Gln
    3725                3730                3735

Cys Asp  Gly Gln Asn Asp Cys  Gly Asp Asn Ser Asp  Glu Glu Asn
    3740                3745                3750

Cys Ala  Pro Arg Glu Cys Thr  Glu Ser Glu Phe Arg  Cys Val Asn
    3755                3760                3765

Gln Gln  Cys Ile Pro Ser Arg  Trp Ile Cys Asp His  Tyr Asn Asp
    3770                3775                3780

Cys Gly  Asp Asn Ser Asp Glu  Arg Asp Cys Glu Met  Arg Thr Cys
    3785                3790                3795

His Pro  Glu Tyr Phe Gln Cys  Thr Ser Gly His Cys  Val His Ser
    3800                3805                3810

Glu Leu  Lys Cys Asp Gly Ser  Ala Asp Cys Leu Asp  Ala Ser Asp
    3815                3820                3825

Glu Ala  Asp Cys Pro Thr Arg  Phe Pro Asp Gly Ala  Tyr Cys Gln
    3830                3835                3840

Ala Thr  Met Phe Glu Cys Lys  Asn His Val Cys Ile  Pro Pro Tyr
    3845                3850                3855

Trp Lys  Cys Asp Gly Asp Asp  Asp Cys Gly Asp Gly  Ser Asp Glu
    3860                3865                3870

Glu Leu  His Leu Cys Leu Asp  Val Pro Cys Asn Ser  Pro Asn Arg
    3875                3880                3885

Phe Arg  Cys Asp Asn Asn Arg  Cys Ile Tyr Ser His  Glu Val Cys
    3890                3895                3900

Asn Gly  Val Asp Asp Cys Gly  Asp Gly Thr Asp Glu  Thr Glu Glu
    3905                3910                3915

His Cys  Arg Lys Pro Thr Pro  Lys Pro Cys Thr Glu  Tyr Glu Tyr
    3920                3925                3930

Lys Cys  Gly Asn Gly His Cys  Ile Pro His Asp Asn  Val Cys Asp
    3935                3940                3945

Asp Ala  Asp Asp Cys Gly Asp  Trp Ser Asp Glu Leu  Gly Cys Asn
    3950                3955                3960

Lys Gly  Lys Glu Arg Thr Cys  Ala Glu Asn Ile Cys  Glu Gln Asn
    3965                3970                3975

Cys Thr  Gln Leu Asn Glu Gly  Gly Phe Ile Cys Ser  Cys Thr Ala
    3980                3985                3990

Gly Phe  Glu Thr Asn Val Phe  Asp Arg Thr Ser Cys  Leu Asp Ile
    3995                4000                4005

Asn Glu  Cys Glu Gln Phe Gly  Thr Cys Pro Gln His  Cys Arg Asn
    4010                4015                4020

Thr Lys  Gly Ser Tyr Glu Cys  Val Cys Ala Asp Gly  Phe Thr Ser
    4025                4030                4035

Met Ser  Asp Arg Pro Gly Lys  Arg Cys Ala Ala Glu  Gly Ser Ser
    4040                4045                4050

Pro Leu  Leu Leu Leu Pro Asp  Asn Val Arg Ile Arg  Lys Tyr Asn
    4055                4060                4065

Leu Ser  Ser Glu Arg Phe Ser  Glu Tyr Leu Gln Asp  Glu Glu Tyr
    4070                4075                4080

Ile Gln  Ala Val Asp Tyr Asp  Trp Asp Pro Lys Asp  Ile Gly Leu
    4085                4090                4095

Ser Val  Val Tyr Tyr Thr Val  Arg Gly Glu Gly Ser  Arg Phe Gly
    4100                4105                4110
```

-continued

```
Ala Ile  Lys Arg Ala Tyr Ile  Pro Asn Phe Glu Ser  Gly Arg Asn
    4115                4120                4125

Asn Leu  Val Gln Glu Val Asp  Leu Lys Leu Lys Tyr  Val Met Gln
    4130                4135                4140

Pro Asp  Gly Ile Ala Val Asp  Trp Val Gly Arg His  Ile Tyr Trp
    4145                4150                4155

Ser Asp  Val Lys Asn Lys Arg  Ile Glu Val Ala Lys  Leu Asp Gly
    4160                4165                4170

Arg Tyr  Arg Lys Trp Leu Ile  Ser Thr Asp Leu Asp  Gln Pro Ala
    4175                4180                4185

Ala Ile  Ala Val Asn Pro Lys  Leu Gly Leu Met Phe  Trp Thr Asp
    4190                4195                4200

Trp Gly  Lys Glu Pro Lys Ile  Glu Ser Ala Trp Met  Asn Gly Glu
    4205                4210                4215

Asp Arg  Asn Ile Leu Val Phe  Glu Asp Leu Gly Trp  Pro Thr Gly
    4220                4225                4230

Leu Ser  Ile Asp Tyr Leu Asn  Asn Asp Arg Ile Tyr  Trp Ser Asp
    4235                4240                4245

Phe Lys  Glu Asp Val Ile Glu  Thr Ile Lys Tyr Asp  Gly Thr Asp
    4250                4255                4260

Arg Arg  Val Ile Ala Lys Glu  Ala Met Asn Pro Tyr  Ser Leu Asp
    4265                4270                4275

Ile Phe  Glu Asp Gln Leu Tyr  Trp Ile Ser Lys Glu  Lys Gly Glu
    4280                4285                4290

Val Trp  Lys Gln Asn Lys Phe  Gly Gln Gly Lys Lys  Glu Lys Thr
    4295                4300                4305

Leu Val  Val Asn Pro Trp Leu  Thr Gln Val Arg Ile  Phe His Gln
    4310                4315                4320

Leu Arg  Tyr Asn Lys Ser Val  Pro Asn Leu Cys Lys  Gln Ile Cys
    4325                4330                4335

Ser His  Leu Cys Leu Leu Arg  Pro Gly Gly Tyr Ser  Cys Ala Cys
    4340                4345                4350

Pro Gln  Gly Ser Ser Phe Ile  Glu Gly Ser Thr Thr  Glu Cys Asp
    4355                4360                4365

Ala Ala  Ile Glu Leu Pro Ile  Asn Leu Pro Pro Pro  Cys Arg Cys
    4370                4375                4380

Met His  Gly Gly Asn Cys Tyr  Phe Asp Glu Thr Asp  Leu Pro Lys
    4385                4390                4395

Cys Lys  Cys Pro Ser Gly Tyr  Thr Gly Lys Tyr Cys  Glu Met Ala
    4400                4405                4410

Phe Ser  Lys Gly Ile Ser Pro  Gly Thr Thr Ala Val  Ala Val Leu
    4415                4420                4425

Leu Thr  Ile Leu Leu Ile Val  Val Ile Gly Ala Leu  Ala Ile Ala
    4430                4435                4440

Gly Phe  Phe His Tyr Arg Arg  Thr Gly Ser Leu Leu  Pro Ala Leu
    4445                4450                4455

Pro Lys  Leu Pro Ser Leu Ser  Ser Leu Val Lys Pro  Ser Glu Asn
    4460                4465                4470

Gly Asn  Gly Val Thr Phe Arg  Ser Gly Ala Asp Leu  Asn Met Asp
    4475                4480                4485

Ile Gly  Val Ser Gly Phe Gly  Pro Glu Thr Ala Ile  Asp Arg Ser
```

-continued

```
    4490                4495                4500

Met Ala  Met Ser Glu Asp Phe  Val Met Glu Met Gly  Lys Gln Pro
    4505                4510                4515

Ile Ile  Phe Glu Asn Pro Met  Tyr Ser Ala Arg Asp  Ser Ala Val
    4520                4525                4530

Lys Val  Val Gln Pro Ile Gln  Val Thr Val Ser Glu  Asn Val Asp
    4535                4540                4545

Asn Lys  Asn Tyr Gly Ser Pro  Ile Asn Pro Ser Glu  Ile Val Pro
    4550                4555                4560

Glu Thr  Asn Pro Thr Ser Pro  Ala Ala Asp Gly Thr  Gln Val Thr
    4565                4570                4575

Lys Trp  Asn Leu Phe Lys Arg  Lys Ser Lys Gln Thr  Thr Asn Phe
    4580                4585                4590

Glu Asn  Pro Ile Tyr Ala Gln  Met Glu Asn Glu Gln  Lys Glu Ser
    4595                4600                4605

Val Ala  Ala Thr Pro Pro Pro  Ser Pro Ser Leu Pro  Ala Lys Pro
    4610                4615                4620

Lys Pro  Pro Ser Arg Arg Asp  Pro Thr Pro Thr Tyr  Ser Ala Thr
    4625                4630                4635

Glu Asp  Thr Phe Lys Asp Thr  Ala Asn Leu Val Lys  Glu Asp Ser
    4640                4645                4650

Glu Val
    4655


    <210> SEQ ID NO 41
<211> LENGTH: 4544
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Met Leu Thr Pro Pro Leu Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu
1               5                   10                  15

Val Ala Ala Ala Ile Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln Phe
            20                  25                  30

Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys Asp
        35                  40                  45

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

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

Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Val Gln
                85                  90                  95

Asp Cys Met Asp Gly Ser Asp Glu Gly Pro His Cys Arg Glu Leu Gln
            100                 105                 110

Gly Asn Cys Ser Arg Leu Gly Cys Gln His His Cys Val Pro Thr Leu
        115                 120                 125

Asp Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala Asp
    130                 135                 140

Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr Cys
145                 150                 155                 160

Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Ile Cys Gly Cys Val
                165                 170                 175

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

-continued

```
           180                 185                 190

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

Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr Pro
    210                 215                 220

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

Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln Leu
                245                 250                 255

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

Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile Asp
        275                 280                 285

Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg Ile
    290                 295                 300

Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp Leu
305                 310                 315                 320

Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly Lys
                325                 330                 335

Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys Asp
            340                 345                 350

Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val Phe
        355                 360                 365

Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp Ala
    370                 375                 380

Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys Gly
385                 390                 395                 400

Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly Leu
                405                 410                 415

Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala Asn
            420                 425                 430

Ala Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser Thr
        435                 440                 445

Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His Ile
    450                 455                 460

Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu Asn
465                 470                 475                 480

Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu Ala
                485                 490                 495

Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser Leu
            500                 505                 510

Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe Leu
        515                 520                 525

Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met Gly
    530                 535                 540

Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met Asn
545                 550                 555                 560

Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe Ala
                565                 570                 575

Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu
            580                 585                 590
```

-continued

```
Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val Ala
        595                 600                 605

Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro Lys
    610                 615                 620

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

Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val Asp
                645                 650                 655

Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro Lys
            660                 665                 670

Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser His
        675                 680                 685

Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly Leu
    690                 695                 700

Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe Tyr
705                 710                 715                 720

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

Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His Gly
            740                 745                 750

Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg Leu
        755                 760                 765

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

Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln Gln
785                 790                 795                 800

Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser Ser
                805                 810                 815

Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu Asp
            820                 825                 830

Gln Val Leu Asp Ala Asp Gly Val Thr Cys Leu Ala Asn Pro Ser Tyr
        835                 840                 845

Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser
    850                 855                 860

Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu
865                 870                 875                 880

Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro
                885                 890                 895

Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp
            900                 905                 910

Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn
        915                 920                 925

Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala
    930                 935                 940

Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp
945                 950                 955                 960

Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys
                965                 970                 975

Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile
            980                 985                 990

Asn Trp Arg Cys Asp Asn Asp Asn  Asp Cys Gly Asp Asn  Ser Asp Glu
        995                 1000                1005
```

-continued

```
Ala Gly  Cys Ser His Ser Cys  Ser Ser Thr Gln Phe  Lys Cys Asn
    1010                1015                1020

Ser Gly  Arg Cys Ile Pro Glu  His Trp Thr Cys Asp  Gly Asp Asn
    1025                1030                1035

Asp Cys  Gly Asp Tyr Ser Asp  Glu Thr His Ala Asn  Cys Thr Asn
    1040                1045                1050

Gln Ala  Thr Arg Pro Pro Gly  Gly Cys His Thr Asp  Glu Phe Gln
    1055                1060                1065

Cys Arg  Leu Asp Gly Leu Cys  Ile Pro Leu Arg Trp  Arg Cys Asp
    1070                1075                1080

Gly Asp  Thr Asp Cys Met Asp  Ser Ser Asp Glu Lys  Ser Cys Glu
    1085                1090                1095

Gly Val  Thr His Val Cys Asp  Pro Ser Val Lys Phe  Gly Cys Lys
    1100                1105                1110

Asp Ser  Ala Arg Cys Ile Ser  Lys Ala Trp Val Cys  Asp Gly Asp
    1115                1120                1125

Asn Asp  Cys Glu Asp Asn Ser  Asp Glu Glu Asn Cys  Glu Ser Leu
    1130                1135                1140

Ala Cys  Arg Pro Pro Ser His  Pro Cys Ala Asn Asn  Thr Ser Val
    1145                1150                1155

Cys Leu  Pro Pro Asp Lys Leu  Cys Asp Gly Asn Asp  Asp Cys Gly
    1160                1165                1170

Asp Gly  Ser Asp Glu Gly Glu  Leu Cys Asp Gln Cys  Ser Leu Asn
    1175                1180                1185

Asn Gly  Gly Cys Ser His Asn  Cys Ser Val Ala Pro  Gly Glu Gly
    1190                1195                1200

Ile Val  Cys Ser Cys Pro Leu  Gly Met Glu Leu Gly  Pro Asp Asn
    1205                1210                1215

His Thr  Cys Gln Ile Gln Ser  Tyr Cys Ala Lys His  Leu Lys Cys
    1220                1225                1230

Ser Gln  Lys Cys Asp Gln Asn  Lys Phe Ser Val Lys  Cys Ser Cys
    1235                1240                1245

Tyr Glu  Gly Trp Val Leu Glu  Pro Asp Gly Glu Ser  Cys Arg Ser
    1250                1255                1260

Leu Asp  Pro Phe Lys Pro Phe  Ile Ile Phe Ser Asn  Arg His Glu
    1265                1270                1275

Ile Arg  Arg Ile Asp Leu His  Lys Gly Asp Tyr Ser  Val Leu Val
    1280                1285                1290

Pro Gly  Leu Arg Asn Thr Ile  Ala Leu Asp Phe His  Leu Ser Gln
    1295                1300                1305

Ser Ala  Leu Tyr Trp Thr Asp  Val Val Glu Asp Lys  Ile Tyr Arg
    1310                1315                1320

Gly Lys  Leu Leu Asp Asn Gly  Ala Leu Thr Ser Phe  Glu Val Val
    1325                1330                1335

Ile Gln  Tyr Gly Leu Ala Thr  Pro Glu Gly Leu Ala  Val Asp Trp
    1340                1345                1350

Ile Ala  Gly Asn Ile Tyr Trp  Val Glu Ser Asn Leu  Asp Gln Ile
    1355                1360                1365

Glu Val  Ala Lys Leu Asp Gly  Thr Leu Arg Thr Thr  Leu Leu Ala
    1370                1375                1380

Gly Asp  Ile Glu His Pro Arg  Ala Ile Ala Leu Asp  Pro Arg Asp
```

-continued

```
    1385                1390                1395

Gly Ile  Leu Phe Trp Thr Asp  Trp Asp Ala Ser Leu  Pro Arg Ile
    1400                1405                1410

Glu Ala  Ala Ser Met Ser Gly  Ala Gly Arg Arg Thr  Val His Arg
    1415                1420                1425

Glu Thr  Gly Ser Gly Gly Trp  Pro Asn Gly Leu Thr  Val Asp Tyr
    1430                1435                1440

Leu Glu  Lys Arg Ile Leu Trp  Ile Asp Ala Arg Ser  Asp Ala Ile
    1445                1450                1455

Tyr Ser  Ala Arg Tyr Asp Gly  Ser Gly His Met Glu  Val Leu Arg
    1460                1465                1470

Gly His  Glu Phe Leu Ser His  Pro Phe Ala Val Thr  Leu Tyr Gly
    1475                1480                1485

Gly Glu  Val Tyr Trp Thr Asp  Trp Arg Thr Asn Thr  Leu Ala Lys
    1490                1495                1500

Ala Asn  Lys Trp Thr Gly His  Asn Val Thr Val Val  Gln Arg Thr
    1505                1510                1515

Asn Thr  Gln Pro Phe Asp Leu  Gln Val Tyr His Pro  Ser Arg Gln
    1520                1525                1530

Pro Met  Ala Pro Asn Pro Cys  Glu Ala Asn Gly Gly  Gln Gly Pro
    1535                1540                1545

Cys Ser  His Leu Cys Leu Ile  Asn Tyr Asn Arg Thr  Val Ser Cys
    1550                1555                1560

Ala Cys  Pro His Leu Met Lys  Leu His Lys Asp Asn  Thr Thr Cys
    1565                1570                1575

Tyr Glu  Phe Lys Lys Phe Leu  Leu Tyr Ala Arg Gln  Met Glu Ile
    1580                1585                1590

Arg Gly  Val Asp Leu Asp Ala  Pro Tyr Tyr Asn Tyr  Ile Ile Ser
    1595                1600                1605

Phe Thr  Val Pro Asp Ile Asp  Asn Val Thr Val Leu  Asp Tyr Asp
    1610                1615                1620

Ala Arg  Glu Gln Arg Val Tyr  Trp Ser Asp Val Arg  Thr Gln Ala
    1625                1630                1635

Ile Lys  Arg Ala Phe Ile Asn  Gly Thr Gly Val Glu  Thr Val Val
    1640                1645                1650

Ser Ala  Asp Leu Pro Asn Ala  His Gly Leu Ala Val  Asp Trp Val
    1655                1660                1665

Ser Arg  Asn Leu Phe Trp Thr  Ser Tyr Asp Thr Asn  Lys Lys Gln
    1670                1675                1680

Ile Asn  Val Ala Arg Leu Asp  Gly Ser Phe Lys Asn  Ala Val Val
    1685                1690                1695

Gln Gly  Leu Glu Gln Pro His  Gly Leu Val Val His  Pro Leu Arg
    1700                1705                1710

Gly Lys  Leu Tyr Trp Thr Asp  Gly Asp Asn Ile Ser  Met Ala Asn
    1715                1720                1725

Met Asp  Gly Ser Asn Arg Thr  Leu Leu Phe Ser Gly  Gln Lys Gly
    1730                1735                1740

Pro Val  Gly Leu Ala Ile Asp  Phe Pro Glu Ser Lys  Leu Tyr Trp
    1745                1750                1755

Ile Ser  Ser Gly Asn His Thr  Ile Asn Arg Cys Asn  Leu Asp Gly
    1760                1765                1770
```

-continued

```
Ser Gly  Leu Glu Val Ile Asp  Ala Met Arg Ser Gln  Leu Gly Lys
    1775                1780                1785

Ala Thr  Ala Leu Ala Ile Met  Gly Asp Lys Leu Trp  Trp Ala Asp
    1790                1795                1800

Gln Val  Ser Glu Lys Met Gly  Thr Cys Ser Lys Ala  Asp Gly Ser
    1805                1810                1815

Gly Ser  Val Val Leu Arg Asn  Ser Thr Thr Leu Val  Met His Met
    1820                1825                1830

Lys Val  Tyr Asp Glu Ser Ile  Gln Leu Asp His Lys  Gly Thr Asn
    1835                1840                1845

Pro Cys  Ser Val Asn Asn Gly  Asp Cys Ser Gln Leu  Cys Leu Pro
    1850                1855                1860

Thr Ser  Glu Thr Thr Arg Ser  Cys Met Cys Thr Ala  Gly Tyr Ser
    1865                1870                1875

Leu Arg  Ser Gly Gln Gln Ala  Cys Glu Gly Val Gly  Ser Phe Leu
    1880                1885                1890

Leu Tyr  Ser Val His Glu Gly  Ile Arg Gly Ile Pro  Leu Asp Pro
    1895                1900                1905

Asn Asp  Lys Ser Asp Ala Leu  Val Pro Val Ser Gly  Thr Ser Leu
    1910                1915                1920

Ala Val  Gly Ile Asp Phe His  Ala Glu Asn Asp Thr  Ile Tyr Trp
    1925                1930                1935

Val Asp  Met Gly Leu Ser Thr  Ile Ser Arg Ala Lys  Arg Asp Gln
    1940                1945                1950

Thr Trp  Arg Glu Asp Val Val  Thr Asn Gly Ile Gly  Arg Val Glu
    1955                1960                1965

Gly Ile  Ala Val Asp Trp Ile  Ala Gly Asn Ile Tyr  Trp Thr Asp
    1970                1975                1980

Gln Gly  Phe Asp Val Ile Glu  Val Ala Arg Leu Asn  Gly Ser Phe
    1985                1990                1995

Arg Tyr  Val Val Ile Ser Gln  Gly Leu Asp Lys Pro  Arg Ala Ile
    2000                2005                2010

Thr Val  His Pro Glu Lys Gly  Tyr Leu Phe Trp Thr  Glu Trp Gly
    2015                2020                2025

Gln Tyr  Pro Arg Ile Glu Arg  Ser Arg Leu Asp Gly  Thr Glu Arg
    2030                2035                2040

Val Val  Leu Val Asn Val Ser  Ile Ser Trp Pro Asn  Gly Ile Ser
    2045                2050                2055

Val Asp  Tyr Gln Asp Gly Lys  Leu Tyr Trp Cys Asp  Ala Arg Thr
    2060                2065                2070

Asp Lys  Ile Glu Arg Ile Asp  Leu Glu Thr Gly Glu  Asn Arg Glu
    2075                2080                2085

Val Val  Leu Ser Ser Asn Asn  Met Asp Met Phe Ser  Val Ser Val
    2090                2095                2100

Phe Glu  Asp Phe Ile Tyr Trp  Ser Asp Arg Thr His  Ala Asn Gly
    2105                2110                2115

Ser Ile  Lys Arg Gly Ser Lys  Asp Asn Ala Thr Asp  Ser Val Pro
    2120                2125                2130

Leu Arg  Thr Gly Ile Gly Val  Gln Leu Lys Asp Ile  Lys Val Phe
    2135                2140                2145

Asn Arg  Asp Arg Gln Lys Gly  Thr Asn Val Cys Ala  Val Ala Asn
    2150                2155                2160
```

-continued

```
Gly Gly  Cys Gln Gln Leu Cys  Leu Tyr Arg Gly Arg  Gly Gln Arg
    2165                2170                2175

Ala Cys  Ala Cys Ala His Gly  Met Leu Ala Glu Asp  Gly Ala Ser
    2180                2185                2190

Cys Arg  Glu Tyr Ala Gly Tyr  Leu Leu Tyr Ser Glu  Arg Thr Ile
    2195                2200                2205

Leu Lys  Ser Ile His Leu Ser  Asp Glu Arg Asn Leu  Asn Ala Pro
    2210                2215                2220

Val Gln  Pro Phe Glu Asp Pro  Glu His Met Lys Asn  Val Ile Ala
    2225                2230                2235

Leu Ala  Phe Asp Tyr Arg Ala  Gly Thr Ser Pro Gly  Thr Pro Asn
    2240                2245                2250

Arg Ile  Phe Phe Ser Asp Ile  His Phe Gly Asn Ile  Gln Gln Ile
    2255                2260                2265

Asn Asp  Asp Gly Ser Arg Arg  Ile Thr Ile Val Glu  Asn Val Gly
    2270                2275                2280

Ser Val  Glu Gly Leu Ala Tyr  His Arg Gly Trp Asp  Thr Leu Tyr
    2285                2290                2295

Trp Thr  Ser Tyr Thr Thr Ser  Thr Ile Thr Arg His  Thr Val Asp
    2300                2305                2310

Gln Thr  Arg Pro Gly Ala Phe  Glu Arg Glu Thr Val  Ile Thr Met
    2315                2320                2325

Ser Gly  Asp Asp His Pro Arg  Ala Phe Val Leu Asp  Glu Cys Gln
    2330                2335                2340

Asn Leu  Met Phe Trp Thr Asn  Trp Asn Glu Gln His  Pro Ser Ile
    2345                2350                2355

Met Arg  Ala Ala Leu Ser Gly  Ala Asn Val Leu Thr  Leu Ile Glu
    2360                2365                2370

Lys Asp  Ile Arg Thr Pro Asn  Gly Leu Ala Ile Asp  His Arg Ala
    2375                2380                2385

Glu Lys  Leu Tyr Phe Ser Asp  Ala Thr Leu Asp Lys  Ile Glu Arg
    2390                2395                2400

Cys Glu  Tyr Asp Gly Ser His  Arg Tyr Val Ile Leu  Lys Ser Glu
    2405                2410                2415

Pro Val  His Pro Phe Gly Leu  Ala Val Tyr Gly Glu  His Ile Phe
    2420                2425                2430

Trp Thr  Asp Trp Val Arg Arg  Ala Val Gln Arg Ala  Asn Lys His
    2435                2440                2445

Val Gly  Ser Asn Met Lys Leu  Leu Arg Val Asp Ile  Pro Gln Gln
    2450                2455                2460

Pro Met  Gly Ile Ile Ala Val  Ala Asn Asp Thr Asn  Ser Cys Glu
    2465                2470                2475

Leu Ser  Pro Cys Arg Ile Asn  Asn Gly Gly Cys Gln  Asp Leu Cys
    2480                2485                2490

Leu Leu  Thr His Gln Gly His  Val Asn Cys Ser Cys  Arg Gly Gly
    2495                2500                2505

Arg Ile  Leu Gln Asp Asp Leu  Thr Cys Arg Ala Val  Asn Ser Ser
    2510                2515                2520

Cys Arg  Ala Gln Asp Glu Phe  Glu Cys Ala Asn Gly  Glu Cys Ile
    2525                2530                2535

Asn Phe  Ser Leu Thr Cys Asp  Gly Val Pro His Cys  Lys Asp Lys
```

-continued

```
    2540                2545                2550

Ser Asp  Glu Lys Pro Ser Tyr  Cys Asn Ser Arg Arg  Cys Lys Lys
    2555                2560                2565

Thr Phe  Arg Gln Cys Ser Asn  Gly Arg Cys Val Ser  Asn Met Leu
    2570                2575                2580

Trp Cys  Asn Gly Ala Asp Asp  Cys Gly Asp Gly Ser  Asp Glu Ile
    2585                2590                2595

Pro Cys  Asn Lys Thr Ala Cys  Gly Val Gly Glu Phe  Arg Cys Arg
    2600                2605                2610

Asp Gly  Thr Cys Ile Gly Asn  Ser Ser Arg Cys Asn  Gln Phe Val
    2615                2620                2625

Asp Cys  Glu Asp Ala Ser Asp  Glu Met Asn Cys Ser  Ala Thr Asp
    2630                2635                2640

Cys Ser  Ser Tyr Phe Arg Leu  Gly Val Lys Gly Val  Leu Phe Gln
    2645                2650                2655

Pro Cys  Glu Arg Thr Ser Leu  Cys Tyr Ala Pro Ser  Trp Val Cys
    2660                2665                2670

Asp Gly  Ala Asn Asp Cys Gly  Asp Tyr Ser Asp Glu  Arg Asp Cys
    2675                2680                2685

Pro Gly  Val Lys Arg Pro Arg  Cys Pro Leu Asn Tyr  Phe Ala Cys
    2690                2695                2700

Pro Ser  Gly Arg Cys Ile Pro  Met Ser Trp Thr Cys  Asp Lys Glu
    2705                2710                2715

Asp Asp  Cys Glu His Gly Glu  Asp Glu Thr His Cys  Asn Lys Phe
    2720                2725                2730

Cys Ser  Glu Ala Gln Phe Glu  Cys Gln Asn His Arg  Cys Ile Ser
    2735                2740                2745

Lys Gln  Trp Leu Cys Asp Gly  Ser Asp Asp Cys Gly  Asp Gly Ser
    2750                2755                2760

Asp Glu  Ala Ala His Cys Glu  Gly Lys Thr Cys Gly  Pro Ser Ser
    2765                2770                2775

Phe Ser  Cys Pro Gly Thr His  Val Cys Val Pro Glu  Arg Trp Leu
    2780                2785                2790

Cys Asp  Gly Asp Lys Asp Cys  Ala Asp Gly Ala Asp  Glu Ser Ile
    2795                2800                2805

Ala Ala  Gly Cys Leu Tyr Asn  Ser Thr Cys Asp Asp  Arg Glu Phe
    2810                2815                2820

Met Cys  Gln Asn Arg Gln Cys  Ile Pro Lys His Phe  Val Cys Asp
    2825                2830                2835

His Asp  Arg Asp Cys Ala Asp  Gly Ser Asp Glu Ser  Pro Glu Cys
    2840                2845                2850

Glu Tyr  Pro Thr Cys Gly Pro  Ser Glu Phe Arg Cys  Ala Asn Gly
    2855                2860                2865

Arg Cys  Leu Ser Ser Arg Gln  Trp Glu Cys Asp Gly  Glu Asn Asp
    2870                2875                2880

Cys His  Asp Gln Ser Asp Glu  Ala Pro Lys Asn Pro  His Cys Thr
    2885                2890                2895

Ser Pro  Glu His Lys Cys Asn  Ala Ser Ser Gln Phe  Leu Cys Ser
    2900                2905                2910

Ser Gly  Arg Cys Val Ala Glu  Ala Leu Leu Cys Asn  Gly Gln Asp
    2915                2920                2925
```

-continued

```
Asp Cys  Gly Asp Ser Ser Asp  Glu Arg Gly Cys His  Ile Asn Glu
    2930                2935                2940

Cys Leu  Ser Arg Lys Leu Ser  Gly Cys Ser Gln Asp  Cys Glu Asp
    2945                2950                2955

Leu Lys  Ile Gly Phe Lys Cys  Arg Cys Arg Pro Gly  Phe Arg Leu
    2960                2965                2970

Lys Asp  Asp Gly Arg Thr Cys  Ala Asp Val Asp Glu  Cys Ser Thr
    2975                2980                2985

Thr Phe  Pro Cys Ser Gln Arg  Cys Ile Asn Thr His  Gly Ser Tyr
    2990                2995                3000

Lys Cys  Leu Cys Val Glu Gly  Tyr Ala Pro Arg Gly  Gly Asp Pro
    3005                3010                3015

His Ser  Cys Lys Ala Val Thr  Asp Glu Glu Pro Phe  Leu Ile Phe
    3020                3025                3030

Ala Asn  Arg Tyr Tyr Leu Arg  Lys Leu Asn Leu Asp  Gly Ser Asn
    3035                3040                3045

Tyr Thr  Leu Leu Lys Gln Gly  Leu Asn Asn Ala Val  Ala Leu Asp
    3050                3055                3060

Phe Asp  Tyr Arg Glu Gln Met  Ile Tyr Trp Thr Asp  Val Thr Thr
    3065                3070                3075

Gln Gly  Ser Met Ile Arg Arg  Met His Leu Asn Gly  Ser Asn Val
    3080                3085                3090

Gln Val  Leu His Arg Thr Gly  Leu Ser Asn Pro Asp  Gly Leu Ala
    3095                3100                3105

Val Asp  Trp Val Gly Gly Asn  Leu Tyr Trp Cys Asp  Lys Gly Arg
    3110                3115                3120

Asp Thr  Ile Glu Val Ser Lys  Leu Asn Gly Ala Tyr  Arg Thr Val
    3125                3130                3135

Leu Val  Ser Ser Gly Leu Arg  Glu Pro Arg Ala Leu  Val Val Asp
    3140                3145                3150

Val Gln  Asn Gly Tyr Leu Tyr  Trp Thr Asp Trp Gly  Asp His Ser
    3155                3160                3165

Leu Ile  Gly Arg Ile Gly Met  Asp Gly Ser Ser Arg  Ser Val Ile
    3170                3175                3180

Val Asp  Thr Lys Ile Thr Trp  Pro Asn Gly Leu Thr  Leu Asp Tyr
    3185                3190                3195

Val Thr  Glu Arg Ile Tyr Trp  Ala Asp Ala Arg Glu  Asp Tyr Ile
    3200                3205                3210

Glu Phe  Ala Ser Leu Asp Gly  Ser Asn Arg His Val  Val Leu Ser
    3215                3220                3225

Gln Asp  Ile Pro His Ile Phe  Ala Leu Thr Leu Phe  Glu Asp Tyr
    3230                3235                3240

Val Tyr  Trp Thr Asp Trp Glu  Thr Lys Ser Ile Asn  Arg Ala His
    3245                3250                3255

Lys Thr  Thr Gly Thr Asn Lys  Thr Leu Leu Ile Ser  Thr Leu His
    3260                3265                3270

Arg Pro  Met Asp Leu His Val  Phe His Ala Leu Arg  Gln Pro Asp
    3275                3280                3285

Val Pro  Asn His Pro Cys Lys  Val Asn Asn Gly Gly  Cys Ser Asn
    3290                3295                3300

Leu Cys  Leu Leu Ser Pro Gly  Gly Gly His Lys Cys  Ala Cys Pro
    3305                3310                3315
```

-continued

```
Thr Asn  Phe Tyr Leu Gly Ser  Asp Gly Arg Thr Cys  Val Ser Asn
    3320                3325                3330

Cys Thr  Ala Ser Gln Phe Val  Cys Lys Asn Asp Lys  Cys Ile Pro
    3335                3340                3345

Phe Trp  Trp Lys Cys Asp Thr  Glu Asp Asp Cys Gly  Asp His Ser
    3350                3355                3360

Asp Glu  Pro Pro Asp Cys Pro  Glu Phe Lys Cys Arg  Pro Gly Gln
    3365                3370                3375

Phe Gln  Cys Ser Thr Gly Ile  Cys Thr Asn Pro Ala  Phe Ile Cys
    3380                3385                3390

Asp Gly  Asp Asn Asp Cys Gln  Asp Asn Ser Asp Glu  Ala Asn Cys
    3395                3400                3405

Asp Ile  His Val Cys Leu Pro  Ser Gln Phe Lys Cys  Thr Asn Thr
    3410                3415                3420

Asn Arg  Cys Ile Pro Gly Ile  Phe Arg Cys Asn Gly  Gln Asp Asn
    3425                3430                3435

Cys Gly  Asp Gly Glu Asp Glu  Arg Asp Cys Pro Glu  Val Thr Cys
    3440                3445                3450

Ala Pro  Asn Gln Phe Gln Cys  Ser Ile Thr Lys Arg  Cys Ile Pro
    3455                3460                3465

Arg Val  Trp Val Cys Asp Arg  Asp Asn Asp Cys Val  Asp Gly Ser
    3470                3475                3480

Asp Glu  Pro Ala Asn Cys Thr  Gln Met Thr Cys Gly  Val Asp Glu
    3485                3490                3495

Phe Arg  Cys Lys Asp Ser Gly  Arg Cys Ile Pro Ala  Arg Trp Lys
    3500                3505                3510

Cys Asp  Gly Glu Asp Asp Cys  Gly Asp Gly Ser Asp  Glu Pro Lys
    3515                3520                3525

Glu Glu  Cys Asp Glu Arg Thr  Cys Glu Pro Tyr Gln  Phe Arg Cys
    3530                3535                3540

Lys Asn  Asn Arg Cys Val Pro  Gly Arg Trp Gln Cys  Asp Tyr Asp
    3545                3550                3555

Asn Asp  Cys Gly Asp Asn Ser  Asp Glu Glu Ser Cys  Thr Pro Arg
    3560                3565                3570

Pro Cys  Ser Glu Ser Glu Phe  Ser Cys Ala Asn Gly  Arg Cys Ile
    3575                3580                3585

Ala Gly  Arg Trp Lys Cys Asp  Gly Asp His Asp Cys  Ala Asp Gly
    3590                3595                3600

Ser Asp  Glu Lys Asp Cys Thr  Pro Arg Cys Asp Met  Asp Gln Phe
    3605                3610                3615

Gln Cys  Lys Ser Gly His Cys  Ile Pro Leu Arg Trp  Arg Cys Asp
    3620                3625                3630

Ala Asp  Ala Asp Cys Met Asp  Gly Ser Asp Glu Glu  Ala Cys Gly
    3635                3640                3645

Thr Gly  Val Arg Thr Cys Pro  Leu Asp Glu Phe Gln  Cys Asn Asn
    3650                3655                3660

Thr Leu  Cys Lys Pro Leu Ala  Trp Lys Cys Asp Gly  Glu Asp Asp
    3665                3670                3675

Cys Gly  Asp Asn Ser Asp Glu  Asn Pro Glu Glu Cys  Ala Arg Phe
    3680                3685                3690

Val Cys  Pro Pro Asn Arg Pro  Phe Arg Cys Lys Asn  Asp Arg Val
```

-continued

```
    3695                3700                3705

Cys Leu  Trp Ile Gly Arg Gln  Cys Asp Gly Thr Asp  Asn Cys Gly
    3710                3715                3720

Asp Gly  Thr Asp Glu Glu Asp  Cys Glu Pro Pro Thr  Ala His Thr
    3725                3730                3735

Thr His  Cys Lys Asp Lys Lys  Glu Phe Leu Cys Arg  Asn Gln Arg
    3740                3745                3750

Cys Leu  Ser Ser Ser Leu Arg  Cys Asn Met Phe Asp  Asp Cys Gly
    3755                3760                3765

Asp Gly  Ser Asp Glu Glu Asp  Cys Ser Ile Asp Pro  Lys Leu Thr
    3770                3775                3780

Ser Cys  Ala Thr Asn Ala Ser  Ile Cys Gly Asp Glu  Ala Arg Cys
    3785                3790                3795

Val Arg  Thr Glu Lys Ala Ala  Tyr Cys Ala Cys Arg  Ser Gly Phe
    3800                3805                3810

His Thr  Val Pro Gly Gln Pro  Gly Cys Gln Asp Ile  Asn Glu Cys
    3815                3820                3825

Leu Arg  Phe Gly Thr Cys Ser  Gln Leu Cys Asn Asn  Thr Lys Gly
    3830                3835                3840

Gly His  Leu Cys Ser Cys Ala  Arg Asn Phe Met Lys  Thr His Asn
    3845                3850                3855

Thr Cys  Lys Ala Glu Gly Ser  Glu Tyr Gln Val Leu  Tyr Ile Ala
    3860                3865                3870

Asp Asp  Asn Glu Ile Arg Ser  Leu Phe Pro Gly His  Pro His Ser
    3875                3880                3885

Ala Tyr  Glu Gln Ala Phe Gln  Gly Asp Glu Ser Val  Arg Ile Asp
    3890                3895                3900

Ala Met  Asp Val His Val Lys  Ala Gly Arg Val Tyr  Trp Thr Asn
    3905                3910                3915

Trp His  Thr Gly Thr Ile Ser  Tyr Arg Ser Leu Pro  Pro Ala Ala
    3920                3925                3930

Pro Pro  Thr Thr Ser Asn Arg  His Arg Arg Gln Ile  Asp Arg Gly
    3935                3940                3945

Val Thr  His Leu Asn Ile Ser  Gly Leu Lys Met Pro  Arg Gly Ile
    3950                3955                3960

Ala Ile  Asp Trp Val Ala Gly  Asn Val Tyr Trp Thr  Asp Ser Gly
    3965                3970                3975

Arg Asp  Val Ile Glu Val Ala  Gln Met Lys Gly Glu  Asn Arg Lys
    3980                3985                3990

Thr Leu  Ile Ser Gly Met Ile  Asp Glu Pro His Ala  Ile Val Val
    3995                4000                4005

Asp Pro  Leu Arg Gly Thr Met  Tyr Trp Ser Asp Trp  Gly Asn His
    4010                4015                4020

Pro Lys  Ile Glu Thr Ala Ala  Met Asp Gly Thr Leu  Arg Glu Thr
    4025                4030                4035

Leu Val  Gln Asp Asn Ile Gln  Trp Pro Thr Gly Leu  Ala Val Asp
    4040                4045                4050

Tyr His  Asn Glu Arg Leu Tyr  Trp Ala Asp Ala Lys  Leu Ser Val
    4055                4060                4065

Ile Gly  Ser Ile Arg Leu Asn  Gly Thr Asp Pro Ile  Val Ala Ala
    4070                4075                4080
```

-continued

```
Asp Ser  Lys Arg Gly Leu Ser  His Pro Phe Ser Ile  Asp Val Phe
    4085                4090                4095

Glu Asp  Tyr Ile Tyr Gly Val  Thr Tyr Ile Asn Asn  Arg Val Phe
    4100                4105                4110

Lys Ile  His Lys Phe Gly His  Ser Pro Leu Val Asn  Leu Thr Gly
    4115                4120                4125

Gly Leu  Ser His Ala Ser Asp  Val Val Leu Tyr His  Gln His Lys
    4130                4135                4140

Gln Pro  Glu Val Thr Asn Pro  Cys Asp Arg Lys Lys  Cys Glu Trp
    4145                4150                4155

Leu Cys  Leu Leu Ser Pro Ser  Gly Pro Val Cys Thr  Cys Pro Asn
    4160                4165                4170

Gly Lys  Arg Leu Asp Asn Gly  Thr Cys Val Pro Val  Pro Ser Pro
    4175                4180                4185

Thr Pro  Pro Pro Asp Ala Pro  Arg Pro Gly Thr Cys  Asn Leu Gln
    4190                4195                4200

Cys Phe  Asn Gly Gly Ser Cys  Phe Leu Asn Ala Arg  Arg Gln Pro
    4205                4210                4215

Lys Cys  Arg Cys Gln Pro Arg  Tyr Thr Gly Asp Lys  Cys Glu Leu
    4220                4225                4230

Asp Gln  Cys Trp Glu His Cys  Arg Asn Gly Gly Thr  Cys Ala Ala
    4235                4240                4245

Ser Pro  Ser Gly Met Pro Thr  Cys Arg Cys Pro Thr  Gly Phe Thr
    4250                4255                4260

Gly Pro  Lys Cys Thr Gln Gln  Val Cys Ala Gly Tyr  Cys Ala Asn
    4265                4270                4275

Asn Ser  Thr Cys Thr Val Asn  Gln Gly Asn Gln Pro  Gln Cys Arg
    4280                4285                4290

Cys Leu  Pro Gly Phe Leu Gly  Asp Arg Cys Gln Tyr  Arg Gln Cys
    4295                4300                4305

Ser Gly  Tyr Cys Glu Asn Phe  Gly Thr Cys Gln Met  Ala Ala Asp
    4310                4315                4320

Gly Ser  Arg Gln Cys Arg Cys  Thr Ala Tyr Phe Glu  Gly Ser Arg
    4325                4330                4335

Cys Glu  Val Asn Lys Cys Ser  Arg Cys Leu Glu Gly  Ala Cys Val
    4340                4345                4350

Val Asn  Lys Gln Ser Gly Asp  Val Thr Cys Asn Cys  Thr Asp Gly
    4355                4360                4365

Arg Val  Ala Pro Ser Cys Leu  Thr Cys Val Gly His  Cys Ser Asn
    4370                4375                4380

Gly Gly  Ser Cys Thr Met Asn  Ser Lys Met Met Pro  Glu Cys Gln
    4385                4390                4395

Cys Pro  Pro His Met Thr Gly  Pro Arg Cys Glu Glu  His Val Phe
    4400                4405                4410

Ser Gln  Gln Gln Pro Gly His  Ile Ala Ser Ile Leu  Ile Pro Leu
    4415                4420                4425

Leu Leu  Leu Leu Leu Leu Val  Leu Val Ala Gly Val  Val Phe Trp
    4430                4435                4440

Tyr Lys  Arg Arg Val Gln Gly  Ala Lys Gly Phe Gln  His Gln Arg
    4445                4450                4455

Met Thr  Asn Gly Ala Met Asn  Val Glu Ile Gly Asn  Pro Thr Tyr
    4460                4465                4470
```

-continued

```
Lys Met  Tyr Glu Gly Gly Glu  Pro Asp Asp Val Gly  Gly Leu Leu
    4475                4480                4485

Asp Ala  Asp Phe Ala Leu Asp  Pro Asp Lys Pro Thr  Asn Phe Thr
    4490                4495                4500

Asn Pro  Val Tyr Ala Thr Leu  Tyr Met Gly Gly His  Gly Ser Arg
    4505                4510                4515

His Ser  Leu Ala Ser Thr Asp  Glu Lys Arg Glu Leu  Leu Gly Arg
    4520                4525                4530

Gly Pro  Glu Asp Glu Ile Gly  Asp Pro Leu Ala
    4535                4540


<210> SEQ ID NO 42
<211> LENGTH: 375
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

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

Val Ser Ala Thr Thr Pro Glu Pro Cys Glu Leu Asp Asp Glu Asp Phe
            20                  25                  30

Arg Cys Val Cys Asn Phe Ser Glu Pro Gln Pro Asp Trp Ser Glu Ala
        35                  40                  45

Phe Gln Cys Val Ser Ala Val Glu Val Glu Ile His Ala Gly Gly Leu
    50                  55                  60

Asn Leu Glu Pro Phe Leu Lys Arg Val Asp Ala Asp Ala Asp Pro Arg
65                  70                  75                  80

Gln Tyr Ala Asp Thr Val Lys Ala Leu Arg Val Arg Arg Leu Thr Val
                85                  90                  95

Gly Ala Ala Gln Val Pro Ala Gln Leu Leu Val Gly Ala Leu Arg Val
            100                 105                 110

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

Thr Gly Thr Met Pro Pro Leu Pro Leu Glu Ala Thr Gly Leu Ala Leu
    130                 135                 140

Ser Ser Leu Arg Leu Arg Asn Val Ser Trp Ala Thr Gly Arg Ser Trp
145                 150                 155                 160

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

Ile Ala Gln Ala His Ser Pro Ala Phe Ser Cys Glu Gln Val Arg Ala
            180                 185                 190

Phe Pro Ala Leu Thr Ser Leu Asp Leu Ser Asp Asn Pro Gly Leu Gly
        195                 200                 205

Glu Arg Gly Leu Met Ala Ala Leu Cys Pro His Lys Phe Pro Ala Ile
    210                 215                 220

Gln Asn Leu Ala Leu Arg Asn Thr Gly Met Glu Thr Pro Thr Gly Val
225                 230                 235                 240

Cys Ala Ala Leu Ala Ala Ala Gly Val Gln Pro His Ser Leu Asp Leu
                245                 250                 255

Ser His Asn Ser Leu Arg Ala Thr Val Asn Pro Ser Ala Pro Arg Cys
            260                 265                 270

Met Trp Ser Ser Ala Leu Asn Ser Leu Asn Leu Ser Phe Ala Gly Leu
        275                 280                 285
```

-continued

```
Glu Gln Val Pro Lys Gly Leu Pro Ala Lys Leu Arg Val Leu Asp Leu
    290                 295                 300

Ser Cys Asn Arg Leu Asn Arg Ala Pro Gln Pro Asp Glu Leu Pro Glu
305                 310                 315                 320

Val Asp Asn Leu Thr Leu Asp Gly Asn Pro Phe Leu Val Pro Gly Thr
                325                 330                 335

Ala Leu Pro His Glu Gly Ser Met Asn Ser Gly Val Val Pro Ala Cys
            340                 345                 350

Ala Arg Ser Thr Leu Ser Val Gly Val Ser Gly Thr Leu Val Leu Leu
        355                 360                 365

Gln Gly Ala Arg Gly Phe Ala
    370                 375


<210> SEQ ID NO 43
<211> LENGTH: 198
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Met Ala Ser Gly Asn Ala Arg Ile Gly Lys Pro Ala Pro Asp Phe Lys
1               5                   10                  15

Ala Thr Ala Val Val Asp Gly Ala Phe Lys Glu Val Lys Leu Ser Asp
            20                  25                  30

Tyr Lys Gly Lys Tyr Val Val Leu Phe Phe Tyr Pro Leu Asp Phe Thr
        35                  40                  45

Phe Val Cys Pro Thr Glu Ile Ile Ala Phe Ser Asn Arg Ala Glu Asp
    50                  55                  60

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

Phe Thr His Leu Ala Trp Ile Asn Thr Pro Arg Lys Glu Gly Gly Leu
                85                  90                  95

Gly Pro Leu Asn Ile Pro Leu Leu Ala Asp Val Thr Arg Arg Leu Ser
            100                 105                 110

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

Leu Phe Ile Ile Asp Gly Lys Gly Val Leu Arg Gln Ile Thr Val Asn
    130                 135                 140

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

Ala Phe Gln Tyr Thr Asp Glu His Gly Glu Val Cys Pro Ala Gly Trp
                165                 170                 175

Lys Pro Gly Ser Asp Thr Ile Lys Pro Asn Val Asp Asp Ser Lys Glu
            180                 185                 190

Tyr Phe Ser Lys His Asn
        195


<210> SEQ ID NO 44
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Ser Phe Ser Ser Met Glu Ala Ser Ser Ala Leu Cys Trp Gly Val Met
1               5                   10                  15
```

-continued

```
Ala Ser Ser Leu Leu Ala Ser Leu Ala Ile Glu Arg Val Met Arg Pro
            20                  25                  30

Leu Arg Leu Pro Trp Leu Leu Ala Val Leu Arg Pro Leu Glu Ala Thr
        35                  40                  45

Ala Ser Phe Ser Ser Leu Ser Ser Pro Glu Val Ser Ser Val Phe Ser
    50                  55                  60

Leu Arg Arg Ser Ser Leu Ser Phe Ser Thr Ser Gly Phe Ser Ser Ser
65                  70                  75                  80

Phe Ser Ala Ser Phe Ser Phe Ser Phe Ser Ser Phe Ser Ser Trp Leu
                85                  90                  95

Leu Arg Gly Met Gly Cys Cys Cys Cys Cys Cys Cys Cys Cys Cys Cys
            100                 105                 110

Cys Cys Cys Cys Cys Trp Leu Leu Pro Arg Arg Arg
        115                 120
```

1. A method for determining if a subject has myocardial ischemia, comprising

a) providing a blood sample obtained from a subject suspected of having myocardial ischemia;

b) determining in the sample the amount of one or more of the following proteins:

i) Lumican and/or

ii) Extracellular matrix protein 1 and/or

iii) Carboxypeptidase N; and

c) comparing the amount(s) of the protein(s) to a baseline value that is indicative of the amount of the protein in a subject that does not have myocardial ischemia,

wherein a statistically significantly increased amount of the protein(s) compared to the baseline value is indicative of myocardial ischemia.

2. A method for determining if a subject has myocardial ischemia, comprising

a) providing a blood sample obtained from a subject suspected of having myocardial ischemia;

b) determining in the sample the amount of four or more of the following proteins:

i) Lumican, and/or

ii) Extracellular matrix protein 1, and/or

iii) Carboxypeptidase N, and/or

iv) Angiogenin, and/or

v) Semenogelin, and/or

vi) Long palate, lung and nasal epithelium carcinoma-associated protein 1, and/or

vii) Perioxiredoxin isoform 2, and/or

viii) Syntaxin 3, and/or

ix) S100 isoform A7, and/or

x) S100 isoform A8, and/or

xi) S100 isoform A9, and/or

xii) Sortilin-related receptor, and/or

xiii) Catalase, and/or

xiv) Low density lipoprotein receptor related protein 1, and/or

xv) Low density lipoprotein receptor related protein 2.

c) comparing the amount(s) of the protein(s) to a baseline value that is indicative of the amount of the protein in a subject that does not have myocardial ischemia,

wherein a statistically significantly increased amount of the protein(s) compared to the baseline value is indicative of myocardial ischemia.

3. The method of claim **1**, further comprising determining in the sample the amount, compared to a baseline value, of one or more of the following proteins:

iv) Angiogenin, and/or

v) Semenogelin, and/or

vi) Long palate, lung and nasal epithelium carcinoma-associated protein 1,

wherein a statistically significantly increased amount of the protein(s) compared to the baseline value is indicative of myocardial ischemia that was caused by metabolic demand.

4. The method of claim **1**, further comprising determining in the sample the amount, compared to a baseline value, of one or more of the following proteins:

vii) Perioxiredoxin isoform 2, and/or

viii) Syntaxin 3, and/or

ix) S100 isoform A7, and/or

x) S100 isoform A8, and/or

xi) S100 isoform A9, and/or

xii) Sortilin-related receptor, and/or

xiii) Catalase, and/or

xiv) Low density lipoprotein receptor related protein 1, and/or

xv) Low density lipoprotein receptor related protein 2,

wherein a statistically significantly increased amount of the protein(s) compared to the baseline value is indicative of myocardial ischemia that was caused by coronary blood vessel blockage.

5. The method of claim **1** or **2**, further comprising determining in the sample the amount(s) of one or more of the following additional proteins:

xvi) Hepatocyte growth factor activator, and/or

xvii) Alpha-2-HS-glycoprotein, and/or

xviii), Insulin like growth factor protein 6, and/or

xix) Galectin-7, and/or

xx) Hornerin, and/or

xxi) Proteoglycan-4, and/or

xxii) Profilaggrin (also referred to as Filaggrin), and/or

xxiii) Vitamin D binding protein, and/or

xxiv) C4b-binding protein alpha chain, and/or

xxv) Thyroxine binding globulin, and/or

xxvi) Alpha-2-glycoprotein 1, zinc, and/or
xxvii) Serine 3 protease, and/or
xxviii) Caspase 14, and/or
xxix) Desmogelin, and/or
xxx) Kininogen-1, and/or
xxxi) Hepatocyte growth factor like protein.

6. The method of claim **1** or **2**, further comprising measuring the amount of one or more of the cardiac specific isoforms of troponin I (TnI) or troponin T (TnT), CK-MB, or myoglobin, wherein a statistically significant increase of the one or more markers is further indicative that the subject has myocardial ischemia.

7. The method of any of claims **1-6**, wherein the sample is from blood.

8. The method of any of claims **1-6**, wherein the sample is from cardiac tissue, urine or sweat.

9. The method of any of claims **1-8**, wherein the determining of the amount of a protein is accomplished by a method comprising binding the protein to an antibody that is specific for the protein, under conditions effective for specific binding of the protein to the antibody.

10. The method of claim **9**, wherein the method is an ELISA.

11. The method of claim **9**, wherein the antibody is contacted with a histological preparation of a biopsy sample from cardiac tissue, and is visualized by immunohistochemical staining.

12. The method of any of claims **1-8**, wherein the determining of the amount of a protein is accomplished by mass spectrometry.

13. The method of any of claims **1-12**, further comprising,
if the subject is determined to be likely to have myocardial ischemia, making a decision to treat the subject aggressively for the ischemia, and
if the subject is determined not to be likely to have myocardial ischemia, making a decision not to treat the subject aggressively for the ischemia.

14. The method of any of claims **1-12**, which is a method for following the progression of ischemia in the subject.

15. The method of any of claims **1-12**, wherein the detection is carried out both before or at approximately the same time as, and after, the administration of a treatment, and which is a method for determining the effectiveness of the treatment.

16. The method of any of claims **1-15**, wherein the subject is human.

17. A method for treating a subject suspected of having myocardial ischemia, comprising determining by a method of any of any of the preceding claims whether the subject is likely to have myocardial ischemia and,
if the subject is determined to be likely to have myocardial ischemia, treating the subject aggressively for the ischemia, and
if the subject is determined not to be likely to have myocardial ischemia, treating the subject aggressively for the ischemia.

18. A kit for detecting the presence of myocardial ischemia in a subject, comprising reagents for detecting the amount of at least three of the following proteins:
i) Lumican, and/or
ii) Extracellular matrix protein 1, and/or
iii) Carboxypeptidase N, and/or
iv) Angiogenin, and/or
v) Semenogelin, and/or
vi) Long palate, lung and nasal epithelium carcinoma-associated protein 1, and/or
vii) Perioxiredoxin isoform 2, and/or
viii) Syntaxin 3, and/or
ix) S100 isoform A7, and/or
x) S100 isoform A8, and/or
xi) S100 isoform A9, and/or
xii) Sortilin-related receptor, and/or
xiii) Catalase, and/or
xiv) Low density lipoprotein receptor related protein 1, and/or
xv) Low density lipoprotein receptor related protein 2.

19. The kit of claim **18**, further comprising reagents for detecting the amount of at least one of the following proteins:
xvi) Hepatocyte growth factor activator, and/or
xvii) Alpha-2-HS-glycoprotein, and/or
xviii) Insulin like growth factor protein 6, and/or
xix) Galectin-7, and/or
xx) Hornerin, and/or
xxi) Proteoglycan-4, and/or
xxii) Profilaggrin (also referred to as Filaggrin), and/or
xxiii) Vitamin D binding protein, and/or
xxiv) C4b-binding protein alpha chain, and/or
xxv) Thyroxine binding globulin, and/or
xxvi) Alpha-2-glycoprotein 1, zinc, and/or
xxvii) Serine 3 protease, and/or
xxviii) Caspase 14, and/or
xxix) Desmogelin, and/or
xxx) Kininogen-1, and/or
xxxi) Hepatocyte growth factor like protein.

* * * * *

专利名称(译)	用于心肌缺血的生物标志物		
公开(公告)号	US20140186852A1	公开(公告)日	2014-07-03
申请号	US13/953226	申请日	2013-07-29
[标]申请(专利权)人(译)	约翰霍普金斯大学		
申请(专利权)人(译)	约翰·霍普金斯大学		
当前申请(专利权)人(译)	约翰·霍普金斯大学		
[标]发明人	VAN EYK JENNIFER SHENG SIMON FU QIN		
发明人	VAN EYK, JENNIFER SHENG, SIMON FU, QIN		
IPC分类号	G01N33/53 G01N33/68 G01N33/573		
CPC分类号	G01N33/5308 G01N33/6893 G01N33/573 G01N2400/40 G01N2800/324		
优先权	PCT/US2009/045168 2009-05-26 WO 61/128688 2008-05-23 US		
其他公开文献	US9039994		
外部链接	Espacenet USPTO		

摘要(译)

本发明涉及例如确定受试者是否患有心肌缺血的方法，包括（a）提供从怀疑患有心肌缺血的受试者获得的血液样品;（b）在样品中测定一种或多种下列蛋白质的量：（i）Lumican和/或（ii）细胞外基质蛋白1和/或（iii）羧肽酶N;（c）将蛋白质的量与基线值进行比较，该基线值表示受试者中没有心肌缺血的蛋白质的量，其中蛋白质的量在统计学上显着增加（s））相比基线值表明心肌缺血。还描述了指示心肌缺血的其他蛋白质，以及基于本发明的诊断方法治疗受试者的方法，以及用于实施本发明方法的试剂盒。

MKRVLVLLLAVAFGHALERGRDYEKNKVCKEFSHLGKEDFTSLSLVLY

SRKFPSGTFEQVSQLVKEVVSLTEACCAEGADPDCYDTRTSALSAKSCE

SNSFFPVHPGTAECCTKEGLERKLCMAALKHQPQEFPTYVEPTNDEICE

AFRKDPKEYANQFMWEYSTNYGQAPLSLLVSYTKSYLSMVGSCCTSASP