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DESCRIPTION

[0001] The present invention relates to assays for detection of biochemical markers valuable for diagnostic purposes in cardiovascular disease and prognosis of disease development, including biochemical markers indicative of the risk of cardiovascular events resulting from atherosclerotic development and plaque instability.

[0002] Worldwide, cardiovascular disease (CVD) is the leading cause of morbidity and mortality. At present, there are no effective and non-invasive diagnostic methods that allow for diagnosis and classification of patients into different risk-groups and for the diagnosis of low risk patients. Diagnostic and prognostic tools are composed mainly of multivariate analysis of simple markers, such as age, smoking and various lipid and lipoprotein concentrations.

[0003] CVD covers several clinical syndromes, primarily, angina pectoris, myocardial infarction (coronary thrombosis) and stroke. All of these syndromes are usually the sequelae of complicated atherosclerosis.

[0004] Atherosclerosis begins with intimal thickening in childhood and progresses to fatty streaks in the intima of arteries - these lesions are characterized as type I and II, respectively. Fatty streaks are the earliest macroscopically visible lesions in the development of atherosclerosis and occur among almost all human beings of all races and societies. In the non pathogenic state, endothelial cells (EC) resist adhesive interactions with leukocytes. However, the actions of proinflammatory cytokines and accumulated oxidized lipoprotein in the arterial wall during atherogenesis, initiate expression of adhesion molecules, such as intercellular adhesion molecules (ICAM)-1 and vascular cell adhesion molecules (VCAM)-1, on the surface of aortic ECs. This allows for capturing and transmigration of leukocytes through the endothelial surface, into the intimal part of the vessel wall. The development of plaques involves an increasing number of smooth muscle cells (SMC) that undergo displacement and apoptosis, which results in increased matrix turnover. The impaired collagen synthesis can result in a weakened fibrous cap and an atherosclerotic plaque that is more prone to rupture; however, most investigators believe that the actions of a proteolytic enzymes such as matrix metallo-proteases (MMPs) and other proteases importantly contribute to the risk of plaque rupture (Clarkson and Kaplan 509-28).

[0005] Plaques are divisible into two different types: 'vulnerable' and 'stabilized' plaques. However, for detailed histological analyses and molecular understanding, a more detailed classification is often used. There are three major stages in development of plaque: initiation, fatty streaks and the complex/advanced plaque (Stary H.C.).

[0006] Atherosclerotic plaques develop within the intima of arteries, and may be classified depending on their composition and structure. This classification divides lesions into eight types (Stary H.C.):

1. I. Macrophages loaded with and enlarged by lipid droplets (macrophage foam cells) are increased in the intima.
2. II. Macrophage foam cells accumulate in the deep part of the proteoglycan layer along with lipid droplets within the intimal SMC. The layers of foam cells are visible as fatty streaks. In type II lesions monocytes penetrate the endothelial lining by monocyte chemo attractant proteins (mainly MCP-1), which are over expressed in human atheroma. The early types of lesion (type I and II) can start in infancy and do not necessarily lead to plaque rupture. Furthermore, the development of atherosclerosis may end after the formation of type III lesion, and the formation of plaque is not predictable (Stary H.C.).

3. III. The type III lesion is determined as the intermediate lesion between the fatty streaks (type II) and the atheroma (type IV). These lesions contain pools of extracellular lipid and thereby expand the spaces between the normally closely adjoining SMCs of the deep musculo-elastic layer of the intima. The pools of material may replace proteoglycans and collagen fibres that normally reside here, but this occurs with little impact at this stage of atherogenesis.
4. IV. The atheroma is the first clinical sign of atherosclerosis. Displacement of SMCs in the intima of arteries by accumulating extracellular pools of lipids and disruption of the intimal architecture is a hallmark of a type IV lesion. The formation of the lipid cores is the end result of this SMC displacement. Formation of a lipid core accounts for the increased wall thickening. The lipid core is a large and well delineated region of the deep intima where the normal structural elements of this part of the arterial wall have been replaced by densely packed foam cell remnants, free lipids droplets, cholesterol crystals and calcium particles. SMCs normally resident in this area are decreased or completely absent at this stage of atherosclerosis progression. Any remnant SMCs become widely dispersed and have developed elongated cell bodies and very often unusually thick basement membranes. At this stage, the development of a layer overlying the lipid core begins. This layer consists of collagen and proteoglycan-rich intercellular matrix, SMCs with and without lipid droplets, macrophages, and foam cells.
5. V. The response to type IV lesion is the formation of a reparative fibrous tissue matrix, forming a fibrous "cap". Typically, these lesions will consist of layers of lipid cores and reparative tissue irregularly stacked on top of each other. Events such as hematoma and thrombus formation may additionally complicate these types of lesions. If not fatal, these lesion complications are integrated into the lesion and overgrown by a thin layer of reparative matrix tissue, consisting of collagens and proteoglycans. The content of extracellular matrix proteins collagen and proteoglycans increases in the atherosclerotic plaque during formation of the cap.
6. VI. The defects of the endothelium such as fissures, erosions, ulcerations, hematoma, thrombus, haemorrhage can if combined lead to more complicated lesion type designated type VI lesion.
7. VII. The lesion is often referred to as calcified lesion, where more than 50% of the lesion consists of mineral. In addition to calcifications, these lesions contain abundance of reparative fibrous connective tissue. When the SMCs trapped in this undergo apoptosis and disintegrate; their mineralized organelles become a part of the calcification.
8. VIII. The fibrotic lesion follows the calcific lesion. The fibrotic lesion may consist entirely of collagen and no lipid. (Stary H.C.)

[0007] Cardiovascular events are often the result of plaque rupture, in which inflammation and the release of proteases weaken the shoulder regions of the fibrous cap and allow the fatty materials in the plaque to come into contact with the blood precipitating a mural thrombus (Clarkson and Kaplan). Thinning of the fibrous cap by increased protease activity in the combination with decreased matrix production, is considered a hallmark of plaque instability increasing the risk of rupture. Vulnerability of plaques and their risk of rupture is an area of clinical interest. Definition of a vulnerable plaque (VP) is not standardized, but there is a general agreement stating existence of three histological hallmarks compared to stable plaque:

1. 1) A larger lipid core (> 40 percent of total lesion).
2. 2) A thinner fibrous cap (65 - 150 micrometers).
3. 3) Large amount of acute inflammatory cells.

Major criteria for defining VP include: active inflammation (presence of monocytes, macrophages and T cells), thin cap with large lipid core, endothelial denudation with superficial platelet aggregation, fissured

plaque, and > 90% stenosis of the artery. Other minor criteria include: superficial calcified nodule, intraplaque haemorrhage, endothelial dysfunction, and outward remodelling (Shin, Edelberg, and Hong).

[0008] Plaque complications, instability and rupture may be inhibited by medical treatment and/or lifestyle modification. In some cases, however, more invasive methods may be needed, i.e. angioplasty or bypass surgery.

[0009] Presently, diagnostic tools are based on either static image analyses still under development or low-technology methods such as systolic and diastolic blood pressure levels related to the risk of CVD. The field has devoted much attention to the development of multivariate analysis that may better identify patients at high risk. One such model is the SCORE-model (Systematic Coronary Risk Evaluation model). In 1994, with a revision in 2003, The European Atherosclerosis Society, The European Society of Cardiology and The European Society of Hypertension issued a set of recommendations regarding prevention of coronary heart diseases. This guideline is based on several assessment techniques, which have been developed to assess the risk of CVD in asymptomatic subjects, i.e. identification of asymptomatic high-risk patients. The SCORE-model integrates gender, age, smoking, systolic blood pressure and either total cholesterol or the cholesterol/HDL ratio as risk factors (Graham et al.).

[0010] In order to make a more detailed diagnosis, the SCORE model is not sufficient and imaging techniques are used. Imaging methods are therefore used mostly on patients in the high-risk group or during research.

IMAGING TECHNIQUES

[0011] Coronary angiography (CAG) is currently the gold standard imaging technique for defining the degree of stenosis. CAG images the lumen of the vessel in two dimensions, but is restricted only to the lumen and not the vessel wall thereby CAG can not distinguish between an artery with a stable plaque and an artery with a vulnerable plaque. CAG is often used to determine whether a patient needs surgery; angioplasty or bypass. In order to determine if a point of luminal narrowing is an advanced plaque, other techniques are needed i.e. intravascular coronary ultrasound (IVUS) or angioscopy. IVUS provides two-dimensional cross-sectional images of the plaque and vessel wall, and is considered as a method good for characterization of vessel wall and morphology and the degree of calcification, but poor for assessing the lipids in the lesion. However, IVUS is invasive and requires expertise and expense: therefore, its use is not wide spread. Angioscopy is another useful method in understanding and identifying atherosclerosis. Angioscopy is a direct visualization of plaque surface and has the capability of detecting colour of plaque and thrombosis. Angioscopy is, however, invasive and technically difficult, and so far it has not been able to detect the degree of plaque extension. Another imaging technique that currently is receiving much attention is Magnetic Resonance imaging (MRI). MRI is non-invasive and able to identify carotid plaque at high risk of stroke. On the other hand, MRI is not the best technique to image coronary arteries, because of small plaque sizes and location of the coronary arteries. Other imaging techniques are under development, i.e. elastography, thermography and optical coherence tomography (Schaar et al.).

[0012] The imaging techniques mentioned are all under development and alone, none can identify a vulnerable plaque, but they are useful tools in understanding both the molecular events and plaque turnover prior to rupture. Presently, the only opportunity to diagnose CVD at an early stage is to utilize a range of risk factors for established coronary heart disease, peripheral artery disease and

cerebrovascular atherosclerotic disease of the patient in question, as well as close relatives of the patient.

PRESENT BIOCHEMICAL MARKERS

[0013] At present, several biochemical markers are known as risk factors for atherosclerosis. Recently much attention has been directed to the measurement of biochemical marker concentrations in serum; both lipids such as total cholesterol, low-density lipoprotein cholesterol (LDL-C) and the high-density lipoprotein cholesterol (HDL-C) and inflammatory markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), Interleukin-18 (IL-18), Tumor Necrosis Factor-alpha (TNF α), CD40, CD40 ligand (CD40L) and others.

[0014] Among lipoprotein markers, there have been at least two noteworthy advances. The size of LDL particles seems to predict the degree of atherosclerosis progression. Increased concentrations of small LDL particles are more related to CVD risk than increased concentrations of large particles (Gardner, Fortmann, and Krauss).

[0015] The level of HDL-C is strongly related to triglyceride, and high triglyceride level is correlated to a higher risk of CHD. A cohort study by Jeppesen et al. (2003) found high TG/low HDL-C as the strongest risk factors of IHD (ischemic heart disease) (Jeppesen et al.).

[0016] Lipid profiles are important for evaluation of risk factors, but do not allow understanding and measurement of the molecular events associated with plaque turnover. A number of biochemical markers have been suggested as risk factors for CVD, although not specific product of the disease. These include CRP and Bone natriuretic peptide (BNP) (see Table 1). Table 1 summarizes some of the known markers of CVD.

Table 1: A selection of present biochemical markers in CVD.

Marker	Type	Description
C-reactive protein (CRP)	Inflammatory	Produced in the liver, increases during inflammatory states.
Pregnancy-associated plasma protein (PAPP-A)	Inflammatory	Zinc-binding protein that acts as an enzyme, specifically a metalloproteinase.
Interleukin-6 (IL-6)	Inflammatory cytokine	Elevated level in heart failure and myocardial infarction.
Interleukin-8 (IL-8)	Inflammatory cytokine	Elevated in myocardial infarctions.
Interleukin-18	Inflammatory cytokine	Elevated in myocardial infarction.
TNF- α (Tumor Necrosis Factor)	Cytokine	Conc. Elevated in the settings of heart failure.
MCP-1	Chemokine	Recruits monocytes from the blood into early atherosclerotic lesion.
Intercellular adhesion molecule-1 (ICAM-1)	Adhesion molecule	Elevated in myocardial infarctions and stroke.
Vascular cellular adhesion	Adhesion molecule	Elevated in myocardial infarctions

Marker	Type	Description
molecule-1 (VCAM-1)		and stroke.
Brain natriuretic peptide (BNP)	Neurohormonal activity	Produced in atria and ventricles of normal healthy heart.
Lipoprotein-associated phospholipase A2 (Lp-PLA ₂)	Phospholipase	LDL-associated Lp-PLA ₂ has proatherogenic effects.
Creatine phosphokinase (CK-MB)	Enzyme	Useful as early detection of myocardial infarction.
Myeloperoxidase (MPO)	Heme enzyme	Activates metallo-proteases and promotes destabilization of plaque.
Myoglobin	Heme protein	Released upon tissue necrosis.
CD40L	Protein	Released in the early stages of atherogenesis through to plaque rupture. Elevated in stroke.
Troponin T (TnT)	Protein	Tool for risk stratification.
Heart-Type Fatty Acid-binding protein (H-FABP)	Protein	H-FABP is released from the heart immediately after infarction.
Microalbuminuria	Protein	Marker of vascular endothelial dysfunction.
Low density lipoprotein cholesterol (LDL-C)	Lipoprotein	Transport cholesterol in the blood.
High Density lipoprotein cholesterol (HDL-C)	Lipoprotein	Holds antioxidant and antiinflammatory properties.
Triglyceride	Lipid	
PIIINP	Procollagen	Marker of type III collagen turnover.

[0017] Thus, a range of different biochemical markers have been suggested as markers of cardiovascular events. Wang et al (2006) have measured 10 different biochemical markers in 3200 patients participating in the Framingham study, described in Table 1. The conclusion was that the measurement of 10 biochemical markers only contributes moderately to diagnosis over and above standard risk factors. Of the 10 biochemical markers, B-type natriuretic peptide level, C-reactive protein level and the urinary albumin-to-creatinine ratio showed the best correlation between marker and death/cardiovascular events (Wang et al.).

C-REACTIVE PROTEIN

[0018] C-reactive protein (CRP) is an acute phase serum protein produced by the liver in response to different clinical conditions such as, inflammation, infection, or trauma (Gabay & Kushner 1999). The production of CRP is induced by cytokines such as IL-6, released from the affected or damaged tissues. The physiological role of CRP is yet unknown and discussions on its pro-or antiinflammatory actions are ongoing.

[0019] There is accumulating evidence that the CRP is a risk factor for CVD in humans. In a study by Ridker et al. 2002, CRP was shown to be a better predictor of future cardiovascular events than LDL

cholesterol, in a large population consisting of 28,000 healthy women followed for eight years for the occurrences of acute myocardial infarction, stroke, coronary revascularization, or death from CVD. Many other studies have also reported that baseline CRP levels constitute an independent risk factor for cardiovascular events (Thompson et al. 1995, Mendall et al. 1996, Kuller et al. 1996, Ridker et al. 1997, Tracy et al. 1997, Ridker et al. 2000).

[0020] It has been speculated that circulating CRP only reflects the general inflammation occurring in the atherosclerotic process and is not an active component in the pathogenesis of the disease. However, several lines of evidence also support the view that CRP has a role in atherogenesis. First, chronic infections giving rise to CRP are also associated with increased risk for CVD (Leinonen & Saikku 2002). Secondly, we and others have identified CRP is in different levels of atherosclerotic lesions (Reynolds & Vance 1987, Hatanaka *et al.* 1995). Finally, CRP has been shown to have proatherogenic properties *in vitro*: CRP may activate endothelial cells to produce adhesion molecules (Pasceri *et al.* 2000). It may also decrease the production of eNOS in endothelial cells (Venugopal *et al.* 2002) and enhance the uptake of LDL by macrophages (Zwaka *et al.* 2001).

BRAIN NATRIURETIC PEPTIDE

[0021] Brain (B-type) natriuretic peptide (BNP) is a peptide hormone secreted by the ventricles of the heart in response to excessive stretching of cardiac myocytes in the ventricles. T-proBNP (the inactive N-terminal fragment) is, along with the active hormone (BNP), released to the blood stream upon cleavage of proBNP. Both BNP and NT-proBNP have been suggested as potential biochemical markers of cardiovascular events (Wang et al.).

CHEMOKINES

[0022] Chemokines are also potential markers of CVD; chemokines are low molecular weight cytokines produced in inflammation. One major chemokine in relation to CVD is monocyte chemo attractant protein 1 (MCP-1). MCP-1 appears to play an early and important role in the recruitment of monocytes to atherosclerotic lesions. In a study using a monkey model of atherosclerosis, plasma concentrations of MCP-1 were highly associated with plaque size and plaque complications (Register et al.).

LIPIDS INCLUDING CHOLESTEROL

[0023] Recently much attention has been directed to the measurement of cholesterol concentrations in serum; both total cholesterol, as well as the concentrations of low-density lipoprotein cholesterol (LDL-C) and the high-density lipoprotein cholesterol (HDL-C). Among lipoprotein markers, there have been at least two noteworthy advances. First, LDL particle size seems to predict the degree of atherosclerosis progression. Increased concentrations of small LDL particles are more related to CVD risk than increased concentrations of large particles (Gardner et al). Secondly, the cholesteryl oleate content of LDL particles may become a particularly important marker of CVD risk. In monkeys, enrichment of lipoprotein particle cores with cholesteryl oleate was strongly and positively associated with more severe coronary artery atherosclerosis (Rudel et al) and was additive to the contributions of LDL and HDL cholesterol concentrations. These findings in experimental animals are further supported by earlier human studies (Lawrie et al) that showed plasma lipoproteins with lower proportions of cholesteryl

linoleate (and conversely higher proportions of cholesteryl oleate) are typical of patients with complications of CHD (coronary heart disease) compared to normal controls.

[0024] The level of HDL-C is strongly related to triglyceride, and high triglyceride level is correlated to a higher risk of CHD. A cohort study by Jeppesen et al found high TG/low HDL-C as the strongest risk factors of IHD (ischemic heart disease).

[0025] These lipid profiles are important for evaluation of risk factors, but do not allow understanding and measurement of the molecular events associated with plaque turnover. A number of biochemical markers have been suggested as risk factors for CVD, although these are not the specific products of the disease. These include CRP and ApoE.

LIPOPROTEINS

[0026] The biomarker most commonly used to predict CVD is cholesterol concentration (both total and the cholesterol/HDL ratio). These are used along with other risk factors, such as blood pressure and level of LDL. Both factors are used in the previously mentioned SCORE-model. The level of LDL is important as LDL transports cholesterol in the blood and accumulation of oxidized LDL can promote atherosclerosis (Graham et al). In addition, a significant association between CHD and triglyceride (TG) levels are found, in which an increased risk of CHD was associated with increasing TG levels, independent of both LDL-C and HDL-C levels, although the level of cholesterol is viewed as one of the major risk factors of CVD (Jeppesen et al).

APO-E

[0027] Apolipoprotein E is found in chylomicrons, VLDL, and HDL. It is mainly synthesised in the liver, but also in many other organs such as brain, spleen, kidney (Siest et al. 1995). ApoE plays an essential role in lipoprotein metabolism by acting as a ligand for two receptors: the LDL receptor and Apo E specific chylomicron remnant receptor. The interaction between ApoE with these receptors gives a basis for the metabolic regulation of cholesterol. Polymorphism at the apoE gene locus results in three alleles found in most populations: $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ that determine six apoE phenotypes. Isoforms differ from each other by one amino acid at positions 112 and 158. Apo E2 has cysteine on both residues and E4 has arginine at both positions. Apo E3 contains cysteine at position 112 and arginine at 158. Allele frequencies differ in different populations. Some studies have assessed the possible relationship between apoE polymorphism and atherosclerosis. A meta-analysis of 14 observation studies demonstrated $\epsilon 4$ allele as associated with coronary disease among both men and women (Wilson et al. 1996). Furthermore, $\epsilon 4$ allele has been associated with carotid artery atherosclerosis (Terry et al. 1996, Cattin et al. 1997, Haraki et al. 2002).

[0028] ApoE is 299 amino acids long and transports lipoprotein, fat soluble vitamins, and cholesterol into the lymph system and further into the blood circulation. ApoE is primarily synthesized in the liver. Currently, there are seven mammalian receptors for ApoE which belong to conserved low density lipoprotein receptor gene family.

ADDITIONAL BIOCHEMICAL MARKERS

[0029] Microalbuminuria (albumin to creatinine level) is also a potential and independent marker. The urinary albumin excretion rate is a marker of changes in the kidney and, when compared with a small creatinine elevation, it may indicate atherosclerosis (Wang et al.).

[0030] Of the procollagen markers, the marker for type III collagen turnover rate (PIIINP) has been investigated as a prognostic marker for hypertension and has been associated with myocardial infarction. Satta et al. examined the correlation between abdominal aortic aneurysm (AAA) and the concentration of the procollagen (PIIINP) in blood. They showed that the turnover of collagen type III is increased in patients with AAA and may be due to enhanced synthesis, enhanced degradation or a combination of both. In the same experiment, the carboxyterminal propeptide of type I procollagen (PICP) was measured, and there was no accelerated synthesis of type I collagen in the aneurysm sac.

PROTEIN PROFILE OF PLAQUE

[0031] Human arteries can be divided into larger or elastic arteries, medium or muscular arteries, and small arteries. The walls of arteries are composed of intima, media and adventitia, separated by the internal elastic lamina and external elastic lamina. The intima consists of connective tissue, smooth muscle cells and a few isolated macrophages. The boundaries of the intima can be defined as a layer between the luminal surface of the endothelium and the internal elastic lamina.

[0032] The arterial intima can further be divided into two layers. The inner layer, called a proteoglycan layer, composed of abundant proteoglycans, smooth muscle cells and macrophages. The lower layer, musculoelastic layer, is composed of abundant smooth muscle cells and elastic fibers. In the normal conditions, the two layers of the intima are barely visible by light microscopy, but are distinct and prominent when intimal thickening occurs.

The media is the muscular part of the arterial wall, composed of smooth muscle cells, elastin, collagen fibrils.

[0033] The adventitia, outer layer, is highly microvascular and contains collagens, elastic fibrils, smooth muscle cells, and lymphatic channels.

[0034] Human atherosclerotic plaques are characterized by a lipid-rich core covered by a fibrous cap composed of fibrillar collagens, elastin, proteoglycans and SMC. Proteoglycans hyaluronan are major nonfibrillar components of the extracellular matrix that have the potential to affect lesion development by regulating events such as lipid accumulation, thrombosis, and cell proliferation and migration and by affecting the material properties of the tissue (Wight 1995). Infiltrating ApoE and CRP are also present and we have demonstrated localisation of both in atherosclerotic plaques of coronary arteries at different stages of the atherosclerotic disease.

ApoE and CRP DISTRIBUTION IN HUMAN BEINGS

[0035] Table 2 below shows the distribution of ApoE and CRP in the human body.

Table 2:

Protein	Sites of expression
APOE	Blood, Serum, Plasma, Liver, Saliva, Monocyte, Cerebellum, Cerebrospinal Fluid, Frontal Cortex, Hippocampus, Temporal Cortex
CRP	Blood, Kidney, Liver, Peritoneal Fluid, Plasma, Serum

[0036] Table 3 below illustrates known interactions of ApoE and CRP with proteins demonstrated in vivo and/or in vitro.

Table 3

Protein	Interactions with proteins
ApoE	Albumin, Amyloid beta A4 protein, Macroglobulin, Microtubule associated protein tau, LDL receptor, Cathepsin B, Neurofilament 3, Phospholipid transfer protein, Prion protein, VLDL receptors, Scavenger receptors class B,
CRP	Serum amyloid P, Complement factor H, Fibronectin 1, Histone 1, FC gamma RI, FC gamma RIIb, CD32, Platelet glycoprotein VI, Leptin.
	<i>Non protein interaction:</i> Calcium, Cholesterol

COLLAGEN DISTRIBUTION IN HUMAN BEINGS

[0037] Collagen is widely distributed in the human body, i.e. ~ 30% of the protein mass in the human body is composed of collagen. In Table 4, the major collagen types are listed with their major tissue distribution.

Table 4

Collagen type	Tissue distribution
I	Skin, bone, tendon, ligament, cornea
II	Cartilage, vitreous
III	Skin, vessel, intestine, uterus
IV	Basement membranes
V	Bone, skin, cornea, placenta
VI	Bone, cartilage, cornea, skin, vessel
VII	Skin, bladder, oral mucosa, umbilical cord, amnion
VIII	Descemet's membrane, vessel, bone, brain, heart, kidney, skin, cartilage
XIII	Endothelial cells, skin, eye, heart, skeletal muscle
XIV	Vessel, bone, skin, cartilage, eye, nerve, tendon, uterus
XXI	Vessel, heart, stomach, kidney, skeletal muscle, placenta

[0038] Type I collagen is the most abundant collagen and is found in most connective tissue. It is especially important for the structure of bone and skin. The major content of collagen in the human body is distributed in the skin and bone, where the major collagenous components are type I and III collagens. Collagen type III is a major component of large arteries, and is also found in smaller amounts in tissues rich type I collagen. In addition, collagen type IV is found in the basement membrane and around blood

vessels and nerves. The most common localization of type V collagen is within the characteristic collagen fibrils, in association with the collagen type I and III (Garrone et al).

[0039] Some collagens have a restricted tissue distribution: for example, type II, which are found almost exclusively in cartilage (Mayne R.).

[0040] Collagen fibrils often consist of more than one collagen type. For example, the type I collagen fibrils often contain small amounts of types III, V and XII, whereas the type II collagen fibrils of cartilage also contain types IX and XI.

COLLAGENS IN ARTERIES

[0041] In arteries, six types of collagen are found (types I, III, IV, V, VI and VIII), where type I and III are the most abundant, 80 - 90 % of collagen content. Type I and III are also predominant in the vessel wall. They appear to be co-distributed in different amounts within all three layers of the artery wall, synthesis of collagen type I and III tends to be located in the intima (Mayne R) .

COLLAGENS AND OTHER STRUCTURAL PROTEINS IN PLAQUE - TURNOVER

[0042] During development of atherosclerotic plaques collagen is accumulated in the fibrous cap (Stary H.C.). In a study by Katsuda et al (1992) collagen types I, III and IV were found in the thickening intima at all stages of the lesion in aortic human tissues. Collagen type VI was distributed in the basement membrane in the region of intimal cells and in advanced lesions also detected around the elongated SMC. Earlier studies of type I and III have provided evidence of an equal distribution in atherosclerotic arterial wall (Shekhonin et al). According to McCullagh et al (1980) type III is the predominant collagen in normal human aortic media (appr. 70 % of the extractable collagen). A recent study by Eriksen *et al* (2006) found a decrease of total collagen content in human aortic valve depending on the degree of stenosis. The molecular mechanism of stenosis is thought to be similar to atherosclerosis. In healthy aortic valves, the collagen content is mainly type I and III. During stenosis, the total content of collagen decreases, which is presumably caused by an increased turnover of collagen type I. Type I collagen accounted for approximately 60-70% of total collagen; whereas the proportion of type III collagen was 30-40% both in healthy valves and in calcified valves.

[0043] Type V collagen also increases in advanced atherosclerotic lesions and is distributed throughout the extracellular matrix in both aortic media and in the subendothelial region of the plaques (McCullagh et al).

[0044] There seems to be a consensus that the main collagen types to be found in atherosclerotic plaque are type I and III, whether they are equally distributed in healthy and atherosclerotic vessel remains to be further investigated.

[0045] In the study by Katsuda et al (1992) no collagen was detected in the center of the atheroma of more advanced lesions.

ELASTIN

[0046] Elastin is one of the most stable proteins in the body and is found in most connective tissue caused by its elasticity and resilience. Elastin dominates the protein content of the arterial wall, where it is the major extracellular matrix protein.

[0047] Elastin is the main component in elastic fibers and is related to calcification. Vascular calcification occurs at two distinct sites within the vessel wall: the intima and the media. Intimal calcification is related to atherosclerosis, mainly within the necrotic core. Calcified elastic fiber constitutes the plaque shoulder where the plaques are most prone to rupture; suggesting that calcification of elastic fiber may affect plaque stability (Bobryshev Y. V.). In atherosclerosis, the content of elastic fibers decreases along with lipid deposition, this generates an enhanced susceptibility to elastin degrading enzymes. Thereby the content of elastin in contrast to collagen decreases as the lesion develops.

DISTRIBUTION OF ELASTIN IN HUMAN BEINGS

[0048] Table 5 shows the distribution of Elastin in the human body.

Table 5:

Protein	Sites of expression
Elastin	Aorta and other Blood vessels, Lung, Skin Fibroblasts

[0049] Table 6 illustrates known interactions of Elastin with proteins demonstrated in vivo and/or in vitro.

Table 6:

Protein	Interactions with proteins
Elastin	Decorin, Elastase, Fibrillin, Fibulin, Lysozyme, Lysyl Oxidase, Galectin, Biglycan, Nidogen, Ficolin, Proteinase3.

PROTEOGLYCANS AS MATRIX COMPONENTS

[0050] Proteoglycans (PG) are polysaccharide-protein macromolecules localized predominately in the intercellular matrix of vessel wall (Salisbury and Wagner 1981). PGs are macromolecules characterized by the presence of one, or more, long un-branched and highly polyanionic sugar side chains called GAGs, covalently attached to a core protein through a link region. The repeating unit of the GAG consists of an amino sugar, either N-acetyl-glucosamine (GlcNAc) or N-acetyl-galactosamine (GalNAc), and a hexuronic acid, either glucouronic acid (GlcA) or iduronic acid (IdoA). One or both of the sugars in the repeating unit contain one or more sulfate groups (Rodríguez-Lee 2007). In addition to the GAG chains, most core proteins carry N- and/or O-linked oligosaccharides.

CLASSIFICATION AND NOMENCLATURE OF PGs

[0051] PGs are a very heterogeneous group of macromolecules. A single type of core protein can vary in the number and type of attached GAG chains. The length of the chains and the arrangement of the

sulfated residues along the chains vary also.

[0052] Four main classes of GAGs are distinguished according to the structure of the repeating disaccharide unit: chondroitin sulfate (CS) and dermatan sulfate (DS), heparin sulfate (HS) and heparin, hyaluronan, and keratin sulfate (KS).

[0053] Hyaluronan is the simplest of GAGs. In contrast to all of the others, it does not contain any sulfated sugars. All of its disaccharide units are identical, its chain length is enormous and it is not linked to any core protein.

[0054] KS is a sulfated polylactosamine chain. KS-I has originally been described in cornea, and is N-linked to asparagine residues in the core protein, whereas KS-II or cartilage KS, is O-linked to serine or threonine residues (Funderburgh 2000).

PGs can be classified according to several parameters:

- Attached GAG chain (CS/DS- or HS containing PGs)
- Topographic distribution in relation to the cell (extracellular and basement membrane PGs, cell-associated PGs or intracellular PGs)
- Core protein homology (hyalectans, small leucine-rich PGs (SLRPs))

[0055] Chondroitin/dermatan sulfate PGs (Versican, aggrecan, neurocan, and brevican) belong to the family of hyaluronan-binding proteoglycans. This gene family is collectively termed hyalectans. Each family member has a characteristic distribution, with aggrecan prominent in cartilage, neurocan and brevican prominent in the central nervous system, and versican present in a variety of soft tissues, including arterial walls. The gene and protein structure of versican follows a domain template. The amino-terminal globular end (G1) binds to GAG hyaluronan, and the carboxy-terminal globular domain (G3) resembles the selectin family of proteins, consisting of a C-type lectin adjacent to two epidermal growth factor (EGF) domains and a complement regulatory region. The middle region of versican core protein is encoded by two large exons that specify the CS attachment regions of versican. The region encoded by exon 7 is called α GAG, whereas the region encoded by exon 8 is called β GAG. Four mRNA transcripts arise from alternative splicing of versican, giving rise to V0, V1, V2, and V3 which differ in the length of the core protein and the number of attached GAGs (Dours-Zimmermann and Zimmermann). The number of potential GAG attachment sites in human versican is: 17-23 for V0, 12-15 for V1, 5-8 for V2, and none for V3 (Wight 617-23).

[0056] Decorin and biglycan are members of SLRP-family that comprises at least nine members grouped into three classes (I, II, and III) and different subfamilies. They are all characterized by the presence of a central domain containing leucine-rich repeats to achieve strong presence of a central domain containing leucine-rich repeats to achieve strong protein-protein interactions. Decorin and biglycan are members of class I, and show highest amino-acid homology of the family (~57%) and are the only SLRPs with a propeptide. The propeptide is highly conserved across species and may function as a recognition sequence for xylosyltransferase, the first enzyme involved in synthesis of the GAG chain.

[0057] Versican, decorin, and biglycan are the major CS/DS PGs in the matrix of the mammalian arterial wall (Wight et al. 1986). The size of Versican V0 core protein is 370 kDa, which makes it roughly 10 times larger than decorin 36 kDa and biglycan 38 kDa. Side-chains show a wide range of sizes, but

generally average around 40-90 kDa each.

[0058] Heparan sulfate proteoglycans: HSPGs are divided into five distinct classes of cell-associated and pericellular PGs and they account for at least 95% of the HS of mammalian cell surfaces, basement membranes and ECMs. The cell-associated HSPGs include integral membrane syndecans and anchored glypicans. Pericellular HSPGs include mainly perlecan, agrin. These PGs are termed pericellular because of their close association with the plasmamembrane via integrins (Whitelock and Iozzo).

[0059] Perlecan is a modular HSPG that is expressed in nearly all basement membranes as well as mesenchymal organs and connective tissues and is one of the largest single-chain polypeptides found in vertebrate and invertebrate animals. The five modules of perlecan and its HS side-chains take part in a large number of molecular interactions such as with fibroblast growth factor - 2, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and other matrix proteins. The core protein of human perlecan is ~470 kDa and, together with numerous O-linked oligosaccharides and four HS side chains, it can reach a molecular weight of over 800 kDa (Knox and Whitelock).

PROTEOGLYCAN DISTRIBUTION

[0060] Proteoglycans (PGs) are macromolecules distributed almost everywhere in the human body. The structure and size of PGs vary extremely. The basic structure of all PGs includes a core protein and at least one, but often many carbohydrate chains - glycosaminoglycans (GAGs). PGs can be found intracellularly, on the surface of cells, and in the extracellular matrix. The structural diversity of PGs suggests numerous biological functions, see Table 7.

Table 7:

Proteoglycan family	Proteoglycan	Distribution	Function
Keratan sulphate-Small leucine rich PG	Lumican	Cornea	Collagen fibril organization and growth. Corneal transparency. Epithelial cell migration and tissue repair.
Chondroitin sulphate	Versican	Smooth muscle cells of blood vessels. Epithelial cells of skin. Cells of central and peripheral nervous system.	Cell adhesion, migration and proliferation.
Dermatan Sulphate (Small leucine rich PGs)	Decorin	Connective tissue. Artery wall.	Plays a role in matrix assembly.
	Biglycan	Extracellular matrix tissue: bone, cartilage, tendon, arteries.	Role in mineralization of the bone.
Heparan sulphate	Perlecan	Extracellular matrix of blood vessels.	Binds to and cross-links many extracellular matrix components and cell-surface molecules.
Chondroitin sulphate - Large aggregating PG	Aggrecan	Cartilage. Extracellular matrix.	Gives tissues ability to resist compressive loads.

[0061] Table 7 above gives an overview of PG distribution and function.

PROTEOGLYCANS IN ARTERIES

[0062] At least five types of PGs are present in the extracellular matrix of the artery wall; versican - which interacts with hyaluronan to form large aggregates; small-leucine rich decorin and biglycan, which interact with fibrillar matrix components like collagen and elastin; heparan sulphate - perlecan, which is a component of basal lamina and keratin sulphate - lumican (Talusán et al.).

[0063] Versican is one of several ECM molecules that accumulate in lesions of atherosclerosis. Although a number of studies indicate that versican is clearly capable of binding to LDL, versican is generally not detected in the lipid-rich center of the necrotic core (Evanko et al.).

[0064] Lumican has been shown to directly bind to macrophages and to enhance macrophage migration. Lumican may therefore directly influence macrophage behavior in the vascular intima as well as stimulate the formation of the necrotic core, characteristic of advanced atherosclerotic lesions (Funderburgh et al. 1997).

[0065] Biglycan is found in the fibrous cap. Versican and biglycan have affinity for LDL and form insoluble complexes, which accelerates oxidation of LDL. Biglycan may contribute to the pathogenesis of atherosclerosis by trapping lipoproteins in the artery wall. Changes in the proteoglycan metabolism of the intima of arteries constitute the initial lesions of atherosclerosis and the accumulation of proteoglycans play a fundamental role in the progression of atherosclerosis (Kunz J.).

[0066] Perlecan was reported in human intimal hyperplasia as one of the central components of intimal extracellular matrix, by mass spectrometry-based analysis and by immunohistochemistry.

[0067] Table 8 illustrates distribution of some PGs in immunohistochemical stainings of PGs in normal and atherosclerotic arteries (Evanko et al).

Table 8:

	Normal Vessel		Fibrous Core				
PG or GAG	Endothelial cells	SMCs	Endothelial cells	SMC's	Macrophages	Fibrous Cap	Plaque core
Perlecan	+++	++	+++	+++	++	+	+++
Decorin	+	++	+	+	+++	+	+++
Biglycan	-/+	++	++	+++	+	+++	-/+
Versican	-	++	-/+	+++	-	+++	-
Hyaluronan	++	+	++	+++	+++	+++	+++
Staining results: - undetectable; -/+ variably detectable; + detectable; ++ moderate; +++ strong							

PROTEOGLYCAN INVOLVEMENT IN MATRIX REMODELLING

[0068] A study of atherosclerosis progression in nonhuman primates has demonstrated that accumulation of specific PGs varies with lesion severity and with the distribution of cells and growth factors, suggesting that different PGs play distinct roles during progression of atherosclerosis. Different levels of specific PGs may directly affect material properties of the tissue via their contribution to altering structural arrangements of fibrous matrix components such as elastin and collagen.

[0069] Versican and hyaluronan show similar localization in the matrix, suggesting aggregate formation between the two in the atherogenesis. The marked increase in versican and hyaluronan in early lesions could suggest that they play a role in early atherosclerotic lesions, such as proliferation and migration of SMCs and leukocytes. Furthermore, versican and hyaluronan are principal matrix components of human restenotic lesions and have been shown to contribute to neo-intimal thickening after vascular injury *in vitro*. An abundance of versican early in atherogenesis could also predispose the extracellular matrix to increase lipid entrapment due to the binding of lipoproteins to chondroitin sulphate chains of versican. This idea is supported by co-localization of versican with apoprotein (a) and apolipoprotein E in transplant arteriopathy (Evanko et al). Loss of versican from the plaque may result in matrix instability.

[0070] This is further evidenced by upregulation of versican gene observed after vascular injury. Versican was also here identified in all stages of atherogenesis; in the intima of early developing plaques, but also throughout advanced lesions and at the borders of lipid-filled necrotic cores as well as at the plaque-thrombus interface (Wight and Merrilees 2005). These observations implicate versican in lipid accumulation, inflammation, and thrombosis. Furthermore, versican plays an important role in the assembly of ECM and in control of elastic fiber fibrillogenesis, which is of fundamental importance in ECM remodelling during vascular disease (Wight and Merrilees 2005).

[0071] The role of biglycan in arterial cell biology is unclear. Some immunohistochemical studies have shown biglycan association with collagen I and III staining in human restenotic lesions (Evanko et al.) .

[0072] The importance of biglycan as matrix protein was further stated by the generation of BALB/cA mice homozygous for a null mutation of the biglycan gene, where 50% of biglycan-deficient male mice died suddenly within the first 3 months of life as a result of from aortic rupture. This observation suggests biglycan to be essential for the structural and functional integrity of the aortic wall, as well as a potential role of biglycan gene defects in the pathogenesis of aortic dissection and rupture in humans. (Heegaard et al. 2007)

Other studies indicate that biglycan is a major PG associated with elastin in primate arteries; these observations are similar to those of in human coronary arteriopathy (Evanko et al).

[0073] Decorin has been shown to bind to collagen and regulate collagen fibril formation (Brown and Vogel) (Danielson et al.).

PROTEASE PROFILES

[0074] Proteases hydrolyse peptide bonds and are responsible for the degradation of extracellular matrix proteins such as collagen, proteoglycans and elastin in atheroma, see Table 9. In atherosclerotic plaques three main types are found: metallo-proteinases (i.e. MMPs), serine proteases and cysteine proteases (i.e. cathepsins). Cathepsins and MMPs are responsible for degradation of all extracellular matrix proteins. As matrix is essential for plaque stability, its removal from the fibrous cap by proteases

may invoke plaque rupture (Stary H.C.).

[0075] In Table 9 a variety of proteases found in atherosclerotic plaque are listed.

Table 9 Proteases detected in atherosclerotic plaques.

Protease	Degradation substrates
Cathepsin K	Proteoglycans, elastin, collagen
Cathepsin S	Proteoglycans, elastin, collagen
Cathepsin L	Proteoglycans, Collagen type I
Cathepsin B	Proteoglycans
MMP-1	Collagen type I, II and III
MMP-2	Proteoglycans, elastin
MMP-3	Proteoglycans, collagen type III, elastin
MMP-8	Proteoglycans, collagen type I, II and III
MMP-9	Elastin, collagen type I and III
MMP-13	Proteoglycans, collagen type I, II and III
MMP-18	Collagen type I

[0076] The main source of MMP expression in the plaque is suspected to be related to macrophage and SMC activity. Macrophages in plaques contain abundant MMP-1, -8, -9, and -13 and co-localize with sites of collagen and proteoglycan degradation in situ (Kunz J.). Furthermore, own data suggest localization of MMP-8 and Cathepsin K in atherosclerotic plaques.

MATRIX METALLOPROTEINASES (MMP)

[0077] MMP is a large group of endopeptidases, capable of degrading most components of the ECM. Presently, more than 25 MMPs have been identified. Metallo-proteinases are characterized by an active site containing a metal atom, typically zinc, and are secreted as zymogens. Specific tissue inhibitors, TIMPs, regulate the activity of MMPs. A great variety of MMPs are found in the atherosclerotic plaques. They are most often located in macrophages bordering the fibrous cap, within plaque shoulders in SMC and macrophages and are rarely identified within the fibrous cap (Kunz J.).]

[0078] MMPs are classified in different groups according to their substrate specificity: Collagenases, which degrade fibrillar collagen, like collagen type I, II, III and V but also proteoglycans; Gelatinases, which degrade proteoglycans, collagen type IV, V, VII and elastin; Stromelysin that is active against proteoglycans and elastin (Rouis M). These three subgroups are of particular interest with regards to matrix remodelling in atherosclerotic plaques.

GELATINASES

[0079] Insoluble elastin is digested by MMP-2 and -9, both belonging to the gelatinase-family of MMPs. MMP-9 has an important role affecting the size and composition of atherosclerotic plaque. In unstable human atherosclerotic plaques and in vulnerable regions of plaques, greater expression and

concentration of MMP-9 have been observed. Moreover, MMP-9 is found intracellularly (indicating active synthesis) in coronary plaques more often in patients with unstable angina compared with those with stable angina. Blood MMP-9 level increases in association with coronary atherosclerosis and predicts adverse cardiovascular events (Sundstrom and Vasan). A recent study by Kuzuya et al (2006) indicates that MMP-2 is responsible for accumulation of SMC in the fibrous cap and thereby inducing plaque instability.

STROMELYSIN

[0080] MMP-3 belongs to the stromelysin proteases and is capable of degrading both elastin and proteoglycans. A study by Yamada et al (2002) indicates that MMP-3 may prove to be a reliable mean of predicting the genetic risk of myocardial infarction in women.

COLLAGENASES

[0081] MMP-1, -8 and -13 have all been identified in atherosclerotic plaques where they degrade proteoglycans and collagen types I and III.

[0082] MMP-1, -8 and -13 are collagenases, which cleave collagen into two fragments that are further degraded by MMP-2, -3 or -9.

[0083] MMP-8 is expressed by neutrophils, not commonly found in human atheroma but has been identified in atherosclerotic plaques. MMP-8 may be partly responsible for degradation of the fibrous cap as MMP-8 has a preference for collagen type I (Herman et al), having a three fold greater activity in degradation of collagen I than MMP-1 and 13. This is supported by Turu et al (2006), in this study the content of MMP-8 in the plasma are significantly higher for patients with vulnerable plaques, than patients with stable plaques.

[0084] MMP-13 has been reported to cleave SLRPS, with high specificity for biglycan. Degradation of biglycan by MMP-13 at a specific cleavage site (...G₁₇₇/V₁₇₈) has previously been demonstrated by Monfort et al. (2005) and proposed to play a important role in early detection of cartilage degradation in osteoarthritis.)

CATHEPSINS

[0085] Human cysteine cathepsins consist of 11 members, including cathepsins B, K, L, and S, and are predominantly expressed within the endosomal/lysosomal compartments of cells. Cathepsins are capable of catalysing the hydrolytic breakdown of proteoglycans, collagen and elastin.

[0086] In abdominal aortic aneurysm (AAA) high levels of cathepsins S, K, and L were found compared to normal aorta. Normal human vascular SMC contain no detectable cathepsin K by immunostaining, but cells within atherosclerotic plaques are clearly positive. Cathepsin K is localized in rupture-prone areas such as the fibrous cap, plaque shoulders and at the actual site of plaque ruptures (Chapman et al). Cathepsin S is found to co-localize with regions of increased elastin breakdown in atherosclerotic

plaques, and reduced atherosclerosis is observed in cathepsin S- and K-deficient mice (Liu et al).

[0087] Both cathepsin L and K degrade several proteoglycans and collagen type I and II, cathepsin K degrades within covalently cross-linked triple helices, while cathepsin L cleaves only in the nonhelical telopeptide regions. Cathepsin K is localized in the fibrous cap and plaque shoulder. Cathepsin K expression in normal arteries is very low. Early human atherosclerotic lesions showed cathepsin K expression in the intimal and medial SMCs. In advanced atherosclerotic plaques, cathepsin K was localized mainly in macrophages and SMCs of the fibrous cap (Lutgens et al). Cathepsin K protein levels were increased in atherosclerotic lesions when compared with normal arteries, whereas cathepsin K mRNA levels were similar in both atherosclerotic and normal arteries. Furthermore, it was shown that cathepsin K mRNA and protein levels were highest in advanced but stable human atherosclerotic plaques compared with early atherosclerotic lesions and lesions containing thrombus (Chapman et al).

[0088] Cathepsin S is only sparsely expressed in intimal and medial SMCs in early human atherosclerotic lesion and fatty streaks. In advanced human atherosclerotic plaques cathepsin S was localized in macrophages and SMCs of the fibrous cap. EC lining the lumen of the vessel itself and the plaque microvessels also expressed cathepsin S. Furthermore, cathepsin S mRNA and protein levels were increased in human atheroma compared with normal arteries (Lutgens et al). Cathepsin S can degrade proteoglycans, elastin and collagen (Liu et al).

[0089] Presently, the determination of CVD risk is occurring at a late stage in atherosclerosis progression; a point in which there is a significant risk of fibrous plaque rupture. There is a need for diagnostic or prognostic assays that will provide information regarding atherosclerosis or CVD risk at both earlier stage and late stages. The findings of Katsuda et al (1992) suggest that there are enzymatic mechanisms for removal of collagens from advanced lesions, suggesting indeed a major role of neo-epitopes in arteriosclerosis.

[0090] WO95/08115 discloses a method of assaying collagen fragments in body fluids, including bringing a sample of body fluid in contact with at least one immunological binding partner for the collagen fragments, said binding partner being immunoreactive with synthetic peptides, the sequences of which are essentially derived from collagen and containing potential sites for cross-linking.

[0091] US6010862 also describes the use of an immunological binding partner to detect degradation of type III collagen in vivo.

[0092] US2004/048321 describes a number of peptides synthesized to match telopeptide components of type III collagen degradation products in body fluids and their use in collagen resorption assays.

[0093] Becker et al describe a cross-linked fragment that can be isolated from a tryptic digest of insoluble collagen III in calf skin.

[0094] A sandwich-type immunoassay for the detection and /or quantitation of collagen degradation products in biological samples is described in EP0829724.

[0095] Monoclonal antibodies produced against human type III collagen which are capable of binding the epitope Gly-Ala-Hyp-Gly-Leu-Arg-Gly-Gly-Ala-Gly are described by Hori et al.

[0096] The present provides a method of bioassay for the quantification of peptide fragments comprising a neo-epitope formed by cleavage of collagen Type III by MMP-1, MMP-3, MMP-8, MMP-9, MMP-13,

Cathepsin K, Cathepsin S, ADAMTS1, ADAMTS4, or ADAMTS8, said method comprising contacting a sample comprising said peptide fragments with a monoclonal antibody having specific binding affinity for a said neo-epitope and determining the level of binding of said monoclonal antibody to peptide fragments in said sample, wherein said monoclonal antibody is not reactive with intact collagen type III, wherein said monoclonal antibody has specific binding affinity for the N-terminal neo-epitope sequence KNGETG and is non-reactive with an N-prolongated version of such a peptide.

[0097] The result of said assay may produce an index indicative of the degree of risk in a particular patient of rupture of an atherosclerotic plaque or of the vulnerable status of the atherosclerotic plaques of a patient.

[0098] Patients having a value for said index above a threshold level may be recommended for further investigation by plaque imaging methods (including those discussed above) or for the prescribing of medication for treatment of atherosclerosis or for surgical treatment of atherosclerosis, and such follow up investigations or treatment may form part of the method of the invention.

[0099] Preferably, the invention further provides, wherein the sample is a patient derived sample, said method further comprising comparing the determined level of said binding of said peptide fragments with values characteristic of (a) comparable healthy individuals and/or (b) a pathological atherosclerotic condition.

[0100] The invention also provides a monoclonal antibody against an N-terminal neo-epitope formed by proteinase cleavage of collagen type III, the antibody being specifically immunoreactive with the N-terminal neo-epitope sequence KNGETG and being non-reactive with an N-prolongated version of such a peptide.

[0101] The invention further provides a cell line producing the monoclonal antibody of the invention; and an immunoassay kit comprising a monoclonal antibody of the invention, and a competition agent which binds said monoclonal antibody, and optionally one or more of a wash reagent, a buffer, a stopping reagent, an enzyme label, an enzyme label substrate, calibration standards, an anti-mouse antibody and instructions for conducting an assay using said kit.

[0102] As described herein, proteins of the atherosclerotic plaque include lumican, versican, perlecan, decorin, biglycan, collagen type III, CRP, ApoE and elastin. Collagen type I is not considered to be proteins of the atherosclerotic plaque. Proteins present in the atherosclerotic plaque which are exposed there to proteases to a higher degree than elsewhere in the body are of particular interest.

COLLAGEN ASSAYS

[0103] Peptide assays for peptide fragments of Type III collagen (SEQ ID NO 153), preferably of mature Type III collagen, i.e. not of collagen type III propeptide, are described herein. The main proteins in the atherosclerotic plaques are collagen type I and III as well as elastin, whereas proteoglycan contributes only to a minor extent to the matrix of the plaque. Of the three major proteins found in atherosclerotic plaques collagen type I and III are dominant, whereas elastin dominates the protein profile in arteries, but not the main protein component in the plaque. Collagen type I is abundant throughout the human body, whereas type III has a more restricted tissue location, and thereby in our view constitutes a more specific candidate as biochemical marker.

[0104] Several candidate proteases may be responsible for the digestion of collagen in the plaque as the literature reports many different proteases in the atherosclerotic plaque. Most likely, this is the result of the large range of complicated processes eventually leading to plaque rupture. However, in our assessment, early phases may consist of a range of MMPs, whereas later stages may rely more on cathepsin K degradation of the matrix, resulting in different neo-epitope profiles dependent on the levels of disease. We have determined that the enzymes listed in the following table cleave type III collagen at at least the following cleavage sites (marked *):

Protease	Neo-Epitope	SEQ ID NO
MMP-1	A*GIPGAPGLMGARGPPGPA*G	154
MMP-1	K*GDPGPPGIPGRNGDPGI*P	155
MMP-1	G*LAGPPGMPGPRGSPGPQG*V	156
MMP-1	G*ERGLPGPPGIKGPAGIPGF*P	157
MMP-1	G*IAGITGARGLAGPPGMPGPR*G	158
MMP-1	G*IKGHRGFPGNPGAPGSPGPAG*Q	159
MMP-1	A*RGLAGPPGMPGPRGSPGPQGV*K	160
MMP-1	I*TGARGLAGPPGMPGPRGSPGPQG*V	161
MMP-1	I*TGARGLAGPPGMPGPRGSPGPQGV*K	162
MMP-1	G*ITGARGLAGPPGMPGPRGSPGPQG*V	163
MMP-1	G*VKGESGKPGANGLSGERGPPGPQG*L	164
MMP-1	G*SRGAPGPQGPRGDKGETGERGAAG*I	165
MMP-1	P*KGDAGQPGEKGSPPGAQGGPPGAPGLG*I	166
MMP-1	G*ITGARGLAGPPGMPGPRGSPGPQGV*K	167
MMP-1	G*LRGGAGPPGPEGGKGAAGPPGPPGAAGTPG*L	168
MMP-1	G*HAGAQQPPGPPGINGSPGGKGEMGPAGIPGAPG*L	169
MMP-1	A*GKSGDRGESGPAGPAGAPGPAGSRGAPGPQGPRGDKGETG ERGAAG*I	170
MMP-1	G*LQGLPGTGPPGNGKPGEPGPKGDAGAPGAPGGKGDAGA PGERGPPG*L	171
MMP-3	G*ERGLPGPPGIKGPAGIPGF*P	172
MMP-3	A*VGGLAGYPGPAGPPGPPGPPGT*S	173
MMP-3	K*DGTSGHPPGPIGPPGPRGNRGER*G	174
MMP-3	A*VGGLAGYPGPAGPPGPPGPPGTSGHPG*S	175
MMP-3	G*IAGITGARGLAGPPGMPGPRGSPGPQG*V	176
MMP-3	A*PGAPGGKGDAGAPGERGPPGLAGAPGLRG*G	177
MMP-3	A*VGGLAGYPGPAGPPGPPGPPGTSGHPGSPG*S	178
MMP-2	A*IGSPGPAGPRGPVGPSPGPPG*K	179
MMP-3 and -8	G*AIGSPGPAGPRGPVGPSPGPPG*K	180

Protease	Neo-Epitope	SEQ ID NO
MMP-8	P*AGQQGAIGSPGPA*G	181
MMP-8	G*GPPGVAGPPGGSGPAGPP*G	182
MMP-8	L*AGPPGMPGPRGSPGPQG*V	183
MMP-8	G*LSGERGPPGPQGLPGLA*G	184
MMP-8	R*GLAGPPGMPGPRGSPGPQG*V	185
MMP-8	G*LAGPPGMPGPRGSPGPQGV*K	186
MMP-8	R*GLAGPPGMPGPRGSPGPQG*V	187
MMP-8	G*PQGPPGKNGETGPQGPPGP*T	188
MMP-8	G*VKGERGSPGGPGAAGFPGAR*G	189
MMP-8	A*RGLAGPPGMPGPRGSPGPQG*V	190
MMP-8	N*GLSGERGPPGPQGLPGLAGTA*G	191
MMP-8	A*VGGLAGYPGPAGPPGPPGPPGT*S	192
MMP-8	G*SPGGKGEMGPAGIPGAPGLMGA*R	193
MMP-8	T*GARGLAGPPGMPGPRGSPGPQG*V	194
MMP-8	V*KGESGKPGANGLSGERGPPGPQG*L	195
MMP-8	G*VKGERGSPGGPGAAGFPGARGLPGPPGSNCPGPPGPSGS PGKDGPPGFAG*N	196
MMP-8	G*SPGAQGGPPGAPGLGIAGITGARGLAGPPG*M	197
MMP-8	R*GAPGEKGEggppgvagppggsgpagppgpq*g	198
MMP-8	R*GAPGEKGEggppgvagppggsgpagppgpq*g	199
MMP-8	G*IAGITGARGLAGPPGMPGPRGSPGPQG*V	200
MMP-9	G*IKGPAGIPGFPG*M	201
MMP-9	G*QPGVMGFPGPKG*N	202
MMP-9	G*IKGPAGIPGFPGMK*G	203
MMP-9	G*IKGPAGIPGFPGMK*H	204
MMP-9	I*PGAPGLMGARGPPGPAG*A	205
MMP-9	G*ERGLPGPPGIKGPAGIP*G	206
MMP-9	G*IPGAPGLMGARGPPGPAG*A	207
MMP-9	G*FRGPAGPNGIPGEKGPAG*E	208
MMP-9	P*GIPGQPGSPGSPGPPGIC*E	209
MMP-9	G*ERGLPGPPGIKGPAGIPGF*P	210
MMP-9	A*VGGLAGYPGPAGPPGPPGPPG*T	211
MMP-9	G*VKGERGSPGGPGAAGFPGARG*L	212
MMP-9	G*DAGAPGAPGGKGDAGAPGERGPPG*L	213
MMP-9	Q*GPPGPTGPGGDKGDTGPPGPQGL*Q	214
MMP-9	G*INGSPGGKGEMGPAGIPGAPGLM*G	215

Protease	Neo-Epitope	SEQ ID NO
MMP-9	Q*GPPGEPGQAGPSGPPGPPGAIGPS*G	216
MMP-9	P*GPPGINGSPGGKGEMGPAGIPGAP*G	217
MMP-9	R*GLPGPPGSNGNPGPPGPSGSPGKDGP GPAG*N	218
MMP-9	G*KNGETGPQGPPGPTGPGGDKGDTGPPGPQG*L	219
MMP-9	G*LPGIAGPRGSPGERGETGPPGPAGFPGAPG*Q	220
MMP-9	G*INGSPGGKGEMGPAGIPGAPGLMGARGPPGPAG*A	221
MMP-9	P*GINGSPGGKGEMGPAGIPGAPGLMGARGPPGPAG*A	222
MMP-9	P*PGENGKPGEPGPKGDAGAPGAPGGKGDAGAPGERGPPG*L	223
MMP-9	G*LKGENGLPGENGAPGPMGPRGAPGERGRPGLPGAAG*A	224
MMP-9	G*NTGAPGSPGVSGPKGDAGQPGGKSGPAQGPAGPGLG* I	225
MMP-9	G*LMGARGPPGPAGANGAPGLRGGAGEPGKNGAKGEPGPRG* E	226
MMP-9	G*LRGGAGPPGPEGGKGAAGPPGPPGAAGTGLQGMPGERGG LGSPGPKG*D	227
MMP-8 and -9	G*QQGAIGSPGPAGPRGPVGPSPGPPG*K	228
MMP-9	K*GDPGPPGIPGRNGDPGIPGQPG*S	229
MMP-9	G*LRGGAGPPGPEGGKGAAGPPGPPG*A	230
MMP-9	G*KNGETGPQGPPGPTGPGGDKGDTGPPGPQG*L	231
MMP-9	G*YQGPPGEPGQAGPSGPPGPPG*A	232
MMP-9	G*VAGPPGGSGPAGPPGPQG*V	233
MMP-8, -9 and -13	G*DKGEPGGPGADGVPGKDGPRGPTGPIGPPGPAG*Q	234
ADAMTS-5	Q*GHAGAQQPPGPPGIN*G	235
CathepsinK	A*GERGAPGPA*G	236
CathepsinK	A*GIPGFPGMK*G	237
CathepsinK	F*PGMKGHRGFD*G	238
CathepsinK	G*FPGARGLP GPPG*S	239
CathepsinK	A*GFPGARGLP GPPG*S	240
CathepsinK	P*PGPPGPPGTSGHP*G	241
CathepsinK	G*FPGMKGHRGFD*G	242
CathepsinK	Q*PGDKGEGGAPGLPGI*A	243
CathepsinK	R*GDKGETGERGAAGIK*G	244
CathepsinK	D*GRNGEKGETGAPGLK*G	245

Protease	Neo-Epitope	SEQ ID NO
CathepsinK	A*GQPGDKGEGGAPGLPGIA*G	246
CathepsinK	G*GPPGENGKPGEPGPKGD*A	247
CathepsinK	A*GIPGFPGMKGHRGFD*G	248
CathepsinK	R*GGAGEPGKNGAKGEPGPR*G	249
CathepsinK	K*GERGSPGGPGAAGFPGARGLPGPP*G	250
CathepsinK	I*PGVPGAKGEDGKDGSPGEPGANGLP*G	251
CathepsinK	G*AAGFPGARGLPGPPGSNGNPGPPGPS*G	252
CathepsinK	R*PGPPGPSGPRGQPGVMGFPGPKGN*D	253
CathepsinK	Q*GPPGPPGINGSPGGKGEMGPAGIPGAP*G	254
CathepsinK	A*GKDGESGRPPGRGERGLPGPPGIK*G	255
CathepsinK	A*GARGNDGARGSDGQPGPPGPPGTAGFPG*S	256
CathepsinK	S*PGVSGPKGDAGQPGEKGSPPGAQGGPPGAPG*P	257
CathepsinK	R*GSDGQPGPPGPPGTAGFPGSPGAKGEVGPA*G	258
CathepsinK	Q*GPPGPPGINGSPGGKGEMGPAGIPGAPGLM*G	259
CathepsinK	A*GPPGPPGPPGTSGHPGSPGSPGYQGPPGEPG*Q	260
CathepsinK	F*PGAPGQNGEPGGKGERGAPGEKGEAGPPGVA*G	261
CathepsinK	A*GFPGAPGQNGEPGGKGERGAPGEKGEAGPPG*V	262
CathepsinK	A*GARGNDGARGSDGQPGPPGPPGTAGFPGSPGAKGEVGPA*G	263
CathepsinK	R*GAAGEPGRDGVPGGPGMRGMPGSPGGPGSDGKPGPPGSQG ESGRPGPPGPS*G	264
CathepsinS	G*IAGITGARGL*A	265
CathepsinS	AGPPGPPGAAGTPGLQGM	266
CathepsinS	N*GLSGERGPPGPQGLPG*L	267
CathepsinS	M*GARGPPGPAGANGAPGLR*G	268
CathepsinS	N*GLSGERGPPGPQGLPGLA*G	269
CathepsinS	G*IAGITGARGLAGPPGMPGPRG*S	270
CathepsinS	G*IAGITGARGLAGPPGMPGPRGSPGPQG*V	271
CathepsinS	R*GGAGPPGPEGGKGAAGPPGPPGAAGTPGLQ*G	272
CathepsinS	S*GPKGDAGQPGEKGSPPGAQGGPPGAPGLG*I	273
CathepsinS	G*IAGITGARGLAGPPGMPGPRGSPGPQGVK*G	274
CathepsinS	A*VGGLAGYPGPAGPPGPPGPPGTSGHPGSPGSPGYQ*G	275
CathepsinS	E*PGPQGHAGAQQPPGPPGINGSPGGKGEMGPAGIPGAPG*L	276
ADAMTS1	I*PGFPGMKGHR*G	277
ADAMTS1	R*GSPGGPGAAGFPGAR*G	278
ADAMTS1	K*GPAGIPGFPGMKGHR*G	279

Protease	Neo-Epitope	SEQ ID NO
ADAMTS1	R*GLAGPPGMPGPRGSPGPQ*G	280
ADAMTS1	A*GITGARGLAGPPGMPGPR*G	281
ADAMTS1	L*GIAGITGARGLAGPPGMPGPR*G	282
ADAMTS1	T*GARGLAGPPGMPGPRGSPGPQ*G	283
ADAMTS1	Q*GPPGPPGINGSPGGKGEMGPAG*I	284
ADAMTS1	L*PGPPGIKGPAGIPGFPGMKGHR*G	285
ADAMTS1	A*GITGARGLAGPPGMPGPRGSPGPQ*G	286
ADAMTS1	T*GARGLAGPPGMPGPRGSPGPQGVK*G	287
ADAMTS1	R*GLPGPPGIKGPAGIPGFPGMKGHR*G	288
ADAMTS1	G*RPGLPGAAGARGNDGARGSDGQPGPPG*P	289
ADAMTS1	N*GAPGPMGPRGAPGERGRPGLPGAAGAR*G	290
ADAMTS1	A*GSRGAPGPQGPRGDKGETGERGAAGIK*G	291
ADAMTS1	R*GLAGPPGMPGPRGSPGPQGVKGESGKPGAN*G	292
ADAMTS1	R*GLAGPPGMPGPRGSPGPQGVKGESGKPGANGL*S	293
ADAMTS1	P*GPPGSNGNPGPPGSPGKDGPPGPAGNTGAPGS*P	294
ADAMTS1	T*GARGLAGPPGMPGPRGSPGPQGVKGESGKPGAN*G	295
ADAMTS1	R*GAPGEKGEPPGVAGPPGSGPAGPPGPQGVKGER*G	296
ADAMTS1	G*GPPGVAGPPGSGPAGPPGPQGVKGERGSPGGPGAAGF*P	297
ADAMTS1	K*SGDRGESGPAGPAGAPGPAGSRGAPGPQGPRGDKGETGER GAAGIK*G	298
ADAMTS4	I*PGFPGMKGHR*G	299
ADAMTS4	R*GLAGPPGMPGPR*G	300
ADAMTS4	G*PQGLQGLPGTGGPP*G	301
ADAMTS4	K*GPAGIPGFPGMKGHR*G	302
ADAMTS4	R*GLAGPPGMPGPRGSPGPQG*V	303
ADAMTS4	G*GPPGENGKPGEPGPKGDAGAP*G	304
ADAMTS4	A*PGFRGPAGPNGIPGEKGPAGER*G	305
ADAMTS4	E*KGSPGAQGGPPGAPGLGIAGITGAR*G	306
ADAMTS4	L*PGPPGIKGPAGIPGFPGMKGHR*G	307
ADAMTS4	R*GAPGFRGPAGPNGIPGEKGPAGER*G	308
ADAMTS4	R*GLPGPPGIKGPAGIPGFPGMKGHR*G	309
ADAMTS4	R*GPVGPSPGPKDGTSGHPGPIGPPGPR*G	310
ADAMTS4	A*PGPQGPRGDKGETGERGAAGIKGHR*G	311
ADAMTS4	R*GAPGPQGPRGDKGETGERGAAGIKGHR*G	312
ADAMTS4	R*GFPGNPGAPGSPGAGQQGAIGSPGPAGPR*G	313
ADAMTS4	L*PGPPGIKGPAGIPGFPGMKGHRGFDGR*N	314

Protease	Neo-Epitope	SEQ ID NO
ADAMTS4	D*AGQPGEKGSPPGAQGGPPGAPGPLGIAGITGAR*G	315
ADAMTS4	R*GPTGPIGPPGPAGQPGDKGEGGAPGLPGIAGPR*G	316
ADAMTS4	K*GDAGQPGEKGSPPGAQGGPPGAPGPLGIAGITGAR*G	317
ADAMTS4	R*NGEKGETGAPGLKGENGLPGENGAPGPMGPR*G	318
ADAMTS4	A*PGFRGPAGPNGIPGEKGPAGERGAPGPAGPRGA*A	319
ADAMTS4	R*GAPGFRGPAGPNGIPGEKGPAGERGAPGPAGPR*G	320
ADAMTS4	R*GSPGERGETGPPGPAGFPAGQNGEPGGKGER*G	321
ADAMTS4	G*HAGAQQGPPGPPGINGSPPGKGEMGPAGIPGAPGLMG*A	322
ADAMTS4	R*GLAGPPGMPGPRGSPGPQGVKGESGKPGANGLSGER*G	323
ADAMTS8	L*GIAGITGARGL*A	324
ADAMTS8	I*PGFPGMKGHR*G	325
ADAMTS8	R*GLAGPPGMPGPR*G	326
ADAMTS8	Q*GPPGAPGPLGIAGITGAR*G	327
ADAMTS8	A*GITGARGLAGPPGMPGPR*G	328
ADAMTS8	A*GIPGAPGLMGARGPPGPAGAN*G	329
ADAMTS8	R*GLAGPPGMPGPRGSPGPQGVKG*E	330
ADAMTS8	K*GSPGAQQGPPGAPGPLGIAGITGAR*G	331
ADAMTS8	L*PGPPGIKGPAGIPGFPGMKGHR*G	332
ADAMTS8	K*DGTSGHPGPIGPPGPRGNRGER*G	333
ADAMTS8	A*GITGARGLAGPPGMPGPRGSPGPQ*G	334
ADAMTS8	R*GLAGPPGMPGPRGSPGPQGVKGESG*K	335
ADAMTS8	R*GLAGPPGMPGPRGSPGPQGVKGESGKPGAN*G	336
ADAMTS8	R*GLAGPPGMPGPRGSPGPQGVKGESGKPGANGL*S	337
ADAMTS8	P*GPPGSNGNPGPPGPSGSPGKDGPAGNTGAPGS*P	338
ADAMTS8	R*GAPGEKGEPPGPPGVAGPPGGSGPAGPPGPQGVKGER*G	339
ADAMTS8	K*SGDRGESGPAGPAGAPGPAGSRGAPGPQGPGRGDKGETGER GA*A	340
ADAMTS8	R*GAPGEKGEPPGPPGVAGPPGGSGPAGPPGPQGVKGERGSPG GPGAAGFPGAR*G	341
MMP9	__*AIGPSG_____*	342
unknown	-AGGFAP*	781

[0105] Accordingly, in a method described herein, said peptide fragments preferably comprise a neo-epitope formed by cleavage of Type III collagen by a protease at a site marked by the sign * in any one of the above partial sequences of Type III collagen.

[0106] Also, in a method described herein, said peptide fragments preferably comprise a neo-epitope formed by cleavage of collagen type III by a (or more) protease(s) at a site in any one of the above partial sequences of collagen type III between the *s, or the immunological binding partner is specifically reactive with a sequence extending between the *s in any entry in the above table.

[0107] Preferably, said immunological binding partner is not reactive with intact type III collagen. Preferably, said immunological binding partner is not reactive with a said sequence listed above if prolonged past the respective cleavage site.

[0108] The immunological binding partner may be one specifically reactive with a C-terminal or N-terminal neoepitope formed by cleavage of type III collagen.

[0109] Suitable immunological binding partners described herein may therefore be specifically reactive with any of the following sequences at the N terminal of a peptide: (Sequence ID Nos follow each sequence)

GIPGAP 343	GDPGPP 408	LAGPPG 470	ERGLPG 534	IAGITG 598
IKGHRG 344	RGLAGP 409	TGARGL 471		ITGARG 599
VKGESG 345	SRGAPG 410	KGDAGQ 472	ITGARG 535	LRGGAG 600
HAGAQQ 346	GKSGDR 411	LQGLPG 473	ERGLPG 536	KDGTSG 763
DGTSGH 347	VGGLAG 412	IAGITG 474	PGAPGG 537	VGGLAG 601
IGSPGP 348	AIGSPG 413	AGQQGA 475	GPPGVA 538	AGPPGM 602
LSGERG 349	GLAGPP 414	LAGPPG 476	GLAGPP 539	PQGPPG 603
VKGERG 350	RGLAGP 415	GLSGER 477	VGGLAG 540	SPGGKG 604
GARGLA 351	KGESGK 416	VKGERG 478	SPGAQG 541	GAPGEK 605
GAPGEK 352	IAGITG 417	IKGPAG 479	QPGVMG 542	IKGPAG 606
IKGPAG 353	PGAPGL 418	ERGLPG 480	IPGAPG 543	FRGPAG 607
GIPGQP 354	ERGLPG 419	VGGLAG 481	VKGERG 544	DAGAPG 608
GPPGPT 355	INGSPG 420	GPPGEP 482	GPPGIN 545	GLPGPP 609
KNGETG 356	LPGIAG 421	INGSPG 483	GINGSP 546	PGENGK 610
LKGENG 357	NTGAPG 422	LMGARG 484	LRGGAG 547	QQGAIG 611
GDPGPP 358	LRGGAG 423	KNGETG 485	YQGPPG 548	VAGPPG 612
DKGEPP 359	GHAGAQ 424	GERGAP 486	GIPGFP 549	PGMKGH 613
FPGARG 360	GFPGAR 425	PGPPGP 487	FPGMKG 550	PGDKGE 614
GDKGET 361	GRNGEK 426	GQPGDK 488	GPPGEN 551	
GGAGEP 362	GERGSP 427	PGVPGA 489	AAGFPG 552	
GPPGPP 363	GKDGES 428	GARGND 490	PGVSGP 553	GSDGQP 615
		PGAPGQ 491	GFPGAP 554	GARGND 616
GAAGEP 365	IAGITG 429	GPPGPP 492	GLSGER 555	GARGPP 617
GLSGER 366		IAGITG 493	GGAGPP 556	GPKGDA 618
IAGITG 367	GPKGDA 430		VGGLAG 557	PGPQGH 619
PGFPGM 368	GSPGGP 431	GPAGIP 494	GLAGPP 558	
GIAGIT 369		GPPGPP 495	PGPPGI 559	GITGAR 620

GARGLA 370	GLPGPP 432	RPGLPG 496	GAPGPM 560	GSRGAP 621
GLAGPP 371		GPPGSN 497	GARGLA 561	GAPGEK 622
GPPGVA 372	SGDRGE 433	PGFPGM 498	GLAGPP 562	PQGLQG 623
GPAGIP 373	GLAGPP 434	GPPGEN 499	PGFRGP 563	KGSPGA 624
PGPPGI 374	GAPGFR 435	GLPGPP 500	GPVGPS 564	PGPQGP 625
GAPGPQ 375	GFPGNP 436	PGPPGI 501	AGQPGE 565	GPTGPI 626
GDAGQP 376	NGEKGE 437	PGFRGP 502	GAPGFR 566	GSPGER 627
HAGAQQ 377	GLAGPP 438	GIAGIT 503	PGFPGM 567	
GPPGAP 378	GITGAR 439	GIPGAP 504	GLAGPP 568	GSPGAQ 628
	DGTSGH 440	GITGAR 505		GLAGPP 629
GLAGPP 379	GPPGSN 441	GAPGEK 506	SGDRGE 569	GAPGEK 630
AIGPSG 380				

or with any of the following sequences at the C-terminal of a peptide:

GPPGPA 381	NGDPGI 442	SPGPQG 507	AGIPGF 570	GMPGPR 631
SPGPAG 382	PGPQGV 443	PPGPQG 508	ERGAAG 571	PGPLGI 632
AAGTPG 383	IPGAPG 444	ERGPPG 509	PGPPGT 572	GNRGER 633
TSGHPG 384	SPGPQG 445	APGLRG 510	HPGSPG 573	PSGPPG 634
PSGPPG 385	GSPGPA 446	GPAGPP 511	SPGPQG 574	GLPGLA 635
	QGPPGP 447	SPGPQG 512	GLAGTA 575	PGPPGT 636
PGLMGA 386		LAGPPG 513	GPPGPQ 576	GPPGPQ 637
SPGPQG 387	IPGFPG 448	FPGPKG 514	GFPGMK 577	FPGMKG 638
	GPAGIP 449	PPGPAG 515	EKGPAG 578	GPPGIC 640
PPGPPG 388	FPGARG 450		PGPQGL 579	GAPGLM 641
GAIGPS 389	GIPGAP 451		FPGAPG 580	
PPGPAG 390	ERGPPG 452	LPGAAG 516	APGPLG 581	EPGPRG 642
SPGPKG 391	PSGPPG 453	IPGQPG 517		
PPGPAG 392	GPPGIN 454	GAPGPA 518	GFPGMK 582	GHRGFD 643
LPGPPG 393	GTSGHP 455	GHRGFD 519	PGLPGI 583	GAAGIK 644
GAPGLK 394	GLPGIA 456	PGPKGD 520	GHRGFD 584	GEPGPR 645
GLPGPP 395	GANGLP 457	GPPGPS 521	PGPKG N 585	GIPGAP 646
GPPGIK 396	TAGFPG 458	PPGAPG 522	GEVGPA 586	GAPGLM 647
GPPGVA 397	EGGPPG 459	GEVGPA 523	GPPGPS 587	TGARGL 648
TPGLQG 398	PQGLPG 460	GAPGLR 524	GLPGLA 588	MPGPRG 649
GTPGLQ 399	APGPLG 461	GPQGVK 525	GSPGYQ 589	GMKGHR 650
GFPGAR 400	GSPGPQ 462	GMPGPR 526	EMGPAG 590	GPQGVK 651
QPGPPG 401	GAAGAR 463	GAAGIK 527	GKPGAN 591	PGANGL 652
TGAPGS 402	GVKGER 464	PGAAGF 528	GMPGPR 592	GTGGPP 653
SPGPQG 403	GDAGAP 465	GPAGER 529	GITGAR 593	GPPGPR 654
GPAGPR 404	RGFDGR 466	GIAGPR 530	AGPRGA 594	GKGGER 655

APGLMG 405	GLSGER 467	TGARGL 531	GPAGAN 595	PQGVKG 656
GNRGER 406	GSPGPQ 468	VKGESG 532	GKPGAN 596	PGANGL 657
TGAPGS 407	GVKGER 469	TGERGA 533	GFPGAR 597	

[0110] In the method of the invention the monoclonal antibody has specific binding affinity for the N-terminal neo-epitope sequence KNGETG and is non-reactive with an N-prolongated version of such a peptide.

[0111] Further cleavage sites defining neoepitopes that may be assayed in a similar manner can be identified by exposing collagen type III or another atherosclerotic plaque protein to any of the enzymes described herein and isolating and sequencing peptides thereby produced.

[0112] The result of an assay according to the invention may be combined with one or more other measured biomarkers to form a composite index of diagnostic or prognostic value.

[0113] The term 'immunological binding partner' as used herein includes polyclonal and monoclonal antibodies and also specific binding fragments of antibodies such as Fab or F(ab')₂. Thus, said immunological binding partner may be a monoclonal antibody or a fragment of a monoclonal antibody having specific binding affinity.

[0114] The term 'protein' used herein includes lipoproteins and proteoglycans and other protein-(non-protein) naturally occurring conjugates.

[0115] Generally, all previously known immunoassay formats can be used in accordance with this invention including heterogeneous and homogeneous formats, sandwich assays, competition assays, enzyme linked assays, radio-immune assays and the like. Thus, optionally, said method is conducted as a competition immunoassay in which said immunological binding partner and a competition agent are incubated in the presence of said sample and the competition agent competes with the peptide fragments in the sample to bind to the immunological binding partner.

[0116] Said competition agent may be a synthetic peptide or a purified native peptide formed by cleavage of the protein to which the neo-epitope belongs to reveal said neo-epitope. Thus, the peptide may be derived from collagen type III.

[0117] One suitable method could be a competition immunoassay using monoclonal antibodies or antibody binding fragments binding to neo-epitopes of fragments of any of these proteins or neo-epitopes on peptide fragments from other proteins derived from atherosclerotic plaques. Appropriately selected synthetic peptides coated onto the solid surface of a microtitre plate could compete with the sample for binding to the monoclonal antibodies or binding fragments. Alternatively, purified, native fragments from one or more of these proteins carrying the neo-epitope recognised by the monoclonal antibody or binding fragment could be used on the solid surface. Yet another alternative is to immobilise the monoclonal antibody or binding fragment on the solid surface and then co-incubate the sample with a synthetic peptide appropriately linked to a signal molecule, e.g. horseradish peroxidase or biotin. The sample may be a sample of urine, serum, blood, plasma or other, e.g. atherosclerotic plaque biopsy.

[0118] In certain preferred methods, the sample is a patient derived sample, and the method further comprises comparing the determined level of said binding of said peptide fragments with values

characteristic of (a) comparable healthy individuals and/or (b) a pathological atherosclerotic condition and optionally associating a higher level of the measured peptide (normally indicated by a higher level of binding) with a more severe degree of a said condition.

[0119] An aspect of the present invention relates to the development of monoclonal antibodies recognising neo-epitopes as described above. This can be achieved by immunising mice with synthetic peptides originating from the amino acid sequence of the protein molecule concerned (including the sequences listed above or sequences terminating therein), fusing the spleen-cells from selected mice to myeloma cells, and testing the monoclonal antibodies for binding to neo-epitopes on relevant synthetic peptides. Specificity for neo-epitopes can be ensured by requiring reactivity with a synthetic peptide and a lack of reactivity with either a C-prolongated form of the immunising peptide (for a C-terminal neo-epitope) or an N-terminal prolonged form of the immunising peptide (for an N-terminal neo-epitope). Antibodies for neo-epitopes may also be evaluated to establish a lack of binding capacity to native protein. Alternatively, specificity for a neo-epitope can be ensured by requiring the reactivity of the antibody to be negatively dependent on the presence of biotin or other functional groups covalently linked to one of the terminal amino acids.

[0120] The disclosure describes an immunological binding partner which is specifically immunoreactive with a neo-epitope formed by cleavage of a said protein by a protease at an end-site in any one of the partial sequences set out above, and may be for instance a monoclonal antibody or a binding fragment thereof.

[0121] The disclosure describes a cell line producing a monoclonal antibody against a C-terminal or N-terminal neo-epitope formed by cleavage of an atherosclerotic plaque protein at the end-sites of sequences in any one of the partial sequences set out above.

[0122] The disclosure further describes a peptide comprising a C-terminal or N-terminal neo-epitope formed by cleavage of a said protein in any one of the partial sequences of these proteins set out above. Such a peptide may be conjugated as a hapten to a carrier for producing an immune response to said peptide, or immobilised to a solid surface or conjugated to a detectable marker for use in an immunoassay.

[0123] The disclosure further describes an isolated nucleic acid molecule coding for a peptide comprising a C-terminal or N-terminal neo-epitope formed by cleavage of a said protein in any one of the partial sequences set out above.

[0124] The invention further comprises a vector comprising a nucleic acid sequence comprising an expression signal and a coding sequence which codes for the expression of a peptide comprising a C-terminal or N-terminal neo-epitope formed by cleavage of a said protein in any one of the partial sequences set out above and further includes a host cell transformed with such a vector and expressing a said peptide.

[0125] Yet another aspect of the disclosure relates to kits, which can be used conveniently for carrying out the methods described above. Such kits may include (1) a microtitre plate coated with synthetic peptide; (2) a monoclonal antibody or antibody binding fragment of the invention reactive with said synthetic peptide; and (3) a labelled anti-mouse IgG immunoglobulin. Alternatively, such kits may include (1) a microtitre plate coated with purified native protein fragments; (2) a monoclonal antibody recognising a neo-epitope on fragments of any one of said proteins, and reactive with said purified

fragments; and (3) a labelled anti-mouse IgG immunoglobulin. Alternatively, such kits may include (1) a microtitre plate coated with streptavidin; (2) a synthetic peptide linked to biotin; (3) a monoclonal antibody recognising a neo-epitope on said protein fragments and reactive with said synthetic peptide; and (4) a labelled anti-mouse IgG immunoglobulin. Yet another alternative could be kits including (1) a microtitre plate coated with streptavidin; (2) a synthetic peptide linked to biotin; (3) a monoclonal antibody recognising a neo-epitope on said protein fragments (and reactive with said synthetic peptide) and conjugated to horseradish peroxidase.

[0126] Thus, the invention includes an immunoassay kit comprising a monoclonal antibody being specifically immunoreactive with the N-terminal neo-epitope sequence KNGETG and being non-reactive with an N-prolongated version of such a peptide, and a competition agent which binds said monoclonal antibody, and optionally one or more of a wash reagent, a buffer, a stopping reagent, an enzyme label, an enzyme label substrate, calibration standards, an anti-mouse antibody and instructions for conducting a said immunoassay.

[0127] The assays described herein are useful in the diagnosis of atherosclerotic disease in patients. In addition, the tests are useful for the assessment of disease progression, and the monitoring of response to therapy. The immunological binding partners of the invention may also be used in immunostaining to show the presence or location of cleavage products of any atherosclerotic plaque protein described herein.

[0128] The invention will be further explained and illustrated with reference to the accompanying drawings, in which:

Figure 1 shows Biglycan staining (magnifications 2, 4, 4 and 10 x respectively) using a monoclonal mouse antibody on an aortic sample with type III lesion.

Figure 2 shows Cathepsin K staining (magnifications 2, 4, 10 and 10 x respectively) using a monoclonal mouse antibody on an aortic sample with type III lesion.

Figure 3 shows Biglycan staining (magnifications 2, 4, 10 and 10 x respectively) using a monoclonal mouse antibody on an aortic sample with type V lesion.

Figure 4 shows Cathepsin K staining (magnifications 2, 4, 10 and 10 x respectively) using a monoclonal mouse antibody on an aortic sample containing type V lesion.

Figure 5 shows cleavage products of biglycan generated by proteases: MMP2, MMP3, MMP8, cathepsin K, cathepsin S, cathepsin B, and cathepsin L. M=Rainbow marker. -enz = no enzyme digestion, run on a gel in Example 2.

Figures 6 to 8 show competition study results obtained in Example 4.

Figure 9 shows competition study results obtained in Example 6.

Figures 10 and 11 show competition study results obtained in Example 7.

Reference Example 1.

[0129] For analysis of localization of proteoglycans and proteases we performed immunohistochemical stainings of human arterial samples derived from left coronary descending arteries (LAD).

[0130] In the following, co-localization of Cathepsin K protease and biglycan is demonstrated.

[0131] Immunohistochemical staining as seen in Figures 1 and 2 revealed a co-localization of biglycan and cathepsin K. This may suggest that biglycan is a preferred substrate of cathepsin K.

[0132] The same immunohistochemical staining was performed on the aortic samples, where the atherosclerotic plaque was formed and as a result of this normal aortic architecture was replaced by macrophage foam cell infiltrates and calcifications. The results of these immunostainings are collected in Figures 3 and 4.

[0133] Immunohistochemical staining of biglycan and cathepsin K were shown to co-localize in a progressed atherosclerotic lesion. These results together generate hypothesis of specific cathepsin K cleavage sites in biglycan, resulting in increased neo-epitope generation in atherosclerotic lesions. To test this hypothesis, we cleaved biglycan with different proteases.

Reference Example 2.

[0134] Degradation of biglycan for assessment of degradation fragments. Biglycan from bovine articular cartilage (B8041 - Sigma-Aldrich) was cleaved by following proteases: MMP2, MMP3, MMP8, Cathepsin K, Cathepsin S, Cathepsin B, and Cathepsin L. Fragments of proteoglycans generated by enzymatic cleavage of above mentioned proteases were separated on 10% NuPage® Bis-Tris gels and afterwards silver-stained by "Silver Express" - silver staining kit (Invitrogen cat.nr. LC6100, lot.nr.341099). Results of separation of proteolytically derived and biglycan and silver-stainings are represented by Figure 5.

Example 3

[0135] Mice were immunised with collagen type III derived peptides conjugated with ovalbumin. Sera were screened for reactivity with screening peptide sequences conjugated to biotin. Monoclonal antibody secreting clones were produced and screened using the screening sequences. Clones were checked for lack of reactivity with elongated versions of the target peptide which are continued with the adjacent sequences from collagen type III (deselection peptide) and for lack of reactivity with a nonsense peptide. None of the clones positive for the target sequences reacted with either the elongated or the nonsense sequences.

[0136] The target sequences, immunogens, screening sequences and deselection sequences were as follows:

No:	Target sequence	Immunogen	Screening Sequence	De-selection sequence	Mouse No.
NB51	KNGETG 356	KNGETGPQGPGGC-OVA	KNGETGPQGP-PG-K-Biotin	KDGETGAAGPPGK-Biotin	278; 279; 289; 345; 346; 347
				KDGEAGAQQPPGK-Biotin	
				PGKNGETPGPQ-GP-K-Biotin	
NB26	IAGITG 429	IAGITGARGLGCC-KLH	IAGITGARGL-AG-K-Biotin	LGIAGITGARGL-AG-K-Biotin	146; 147; 148; 149; 156; 157;
			IAGLTGARGL-AG-K-Biotin)		
NB52	IAGITG	IAGITGARGLGCC-OVA	IAGITGARGL-AG-K-Biotin	LGIAGITGARGL-AG-K-Biotin	348; 349; 357; 358; 359;
			IAGLTGARGL-AG-K-Biotin)		
NB27	KDGTS 763	KDGTSGHPPGPGCC-OVA	KDGTSGHPPG-IG-K-Biotin	PGKDGTSGHPPG-K-Biotin	158; 159; 167; 168; 169; 178;
			KDGSSGHPPG-IG-K-Biotin		
NB67	APGPLG 581	OVA-CGG-GPPGAPGPLG	Biotin-AQ-GPPGAPGPLG	Biotin-DD-GPSGAEGPPG	167; 168; 169; 178; 179; 189;
			Biotin-AQ-GPPGSPGPLG	Biotin-GP-PGAPGPLGIA	
NB68	NTGAPG 422	NTGAPGSPGV-CGG-OVA	NTGAPGSPGVSG-K-Biotin	AGNTGAPGSP-GV-Biotin	234; 235; 236; 237; 238; 239;
			NSGSPGNPGVAG-K-Biotin		
NB69	AIGPSG 380	AIGPSGPAGK-GCC-OVA (808680)	AIGPSGPAGKDG-K-Biotin	PGAIGPSGPAG-KD-Biotin	245; 246; 247; 248; 249; 256;
			AIGPAGPAGKDG-K-Biotin		
NB57	AGGFAP 781	KLH-CGG-EKAGGFAP	Biotin-CG-EKAGGFAP	Biotin-GG-EKAGGFAPYY	1; 2; 3; 4; 5; 6;
			Biotin-CG-EKSGGFSP		

Example 4

Reactivity of collagen type III neo-epitope monoclonal antibodies with human urine

[0137] The reactivity of selected monoclonal antibody clones from example 3 with human urine was determined in a competition assay format using the immunising peptides as competition agent. In a typical procedure, 96 well streptavidin coated plates were coated for 30 min with 10 ng/mL Biotin-peptide in PBS-BTE at 20° C with shaking and washed 5x in washing buffer. 20 µl of diluted sample was added (either urine or peptide solution). 100 µL of unpurified antibody solution (supernatant from cell culture) diluted as detailed below was added. The plates were incubated for 1 hr at 20°C with shaking at 300 rpm and were then washed 5x in washing buffer. 100 µL secondary antibody-POD (1:5000) was added and incubated for 1hr at 20°C with shaking at 300 rpm before washing 5x in washing buffer. 100 µL TMB was added and incubated for 15 min in darkness shaking at 300 rpm before adding 100 µL stopping solution. The plates were read at 450 nm on an ELISA reader with 650 nm as reference. Competition therefore occurred between the peptide on the plate and peptide in solution for the antibody and the amount of plate bound antibody was determined by the peroxidase colour forming reaction.

[0138] Results are seen in Figure 6 for four different clones. It can be seen that the antibodies each detect relevant sequences in urine.

[0139] Further competition studies were performed on one selected clone to test competition for antibody binding between the immunising peptide and native collagen type III cleaved in vitro by MMP9. Results are shown in Figure 7 for the cleaved collagen, the peptide KNGETG and an elongated version of that sequence. It can be seen that the antibody binds the immunising peptide sequence and the enzyme cleaved collagen, but not the extended sequence.

[0140] Further competition studies on the same clone are seen in Figure 8 where the competition agents were the peptide KNGETG, human serum, rat serum, FCS (fetal calf serum), and atherosclerotic plaque extracts respectively. It is seen that the antibody is reactive with the peptide, the plaque extract and human serum, but not the rat serum or FCS.

Reference Example 5**Raising of anti-sera to decorin, biglycan and versican sequences**

[0141] Anti-sera were raised and monoclonal antibodies were obtained as in Example 3, but using the following immunogens, screening sequences and deselection sequences:

No:	Epitope	Target sequence	Immunogen	Screening Sequence	De-selection sequence	Mouse No.
NB62	Decorin-176N	IVIELG 91	IVIELGTNPL-GGC-KLH	IVIELGTNPL-KS-K-Biotin	QMIVIELGTNPLK-K-Biotin	7;8;9;10;12;13
				LVIELGGNPL-KN-K-Biotin	NVLVIELGGNPL-K-Biotin	
				IVVELGGNPL-TN-K-Biotin		

No:	Epitope	Target sequence	Immunogen	Screening Sequence	De-selection sequence	Mouse No.
NB63	Biglycan-108C	NNDISE 116	OVA-CGG-LDLQNNDISE	Biotin-TL-LDLQNNDISE	Biotin-LDLQNNDISELR	14;15;16;17;18;19
NB64	Versican-87N	QNGNIK 143	QNGNIKIGQD-GGC-KLH	QNGNIKIGQD-YK-Biotin	VAQNGNIKIGQD-K-Biotin	23;24;25;26;27;28;
				QDGNIKIGQD-YK-Biotin	VAQDGNIKIGQD-K-Biotin	

Reference Example 6

Reactivity of decorin neo-epitope monoclonal antibody with human urine

[0142] A competition ELISA was carried out generally as in Example 5 using one anti-decorin unpurified monoclonal antibody (NB62)

Results are shown in Figure 9. Reactivity is seen against the peptide sequence against which the antibody was raised and selected and against urine, but not against the irrelevant peptide sequence NB18.

Reference Example 7

Reactivity of versican neo-epitope monoclonal antibody with human urine

[0143] A competition ELISA was carried out generally as in Example 5 using two anti-versican unpurified monoclonal antibody clones raised against sequence (NB64).

[0144] Results are shown in Figures 10 and 11 for the respective clones. In each case reactivity is seen against the peptide sequence against which the antibody was raised and selected and against urine, but not against the irrelevant peptide sequence NB18.

[0145] In this specification, unless expressly otherwise indicated, the word 'or' is used in the sense of an operator that returns a true value when either or both of the stated conditions is met, as opposed to the operator 'exclusive or' which requires that only one of the conditions is met. The word 'comprising' is used in the sense of 'including' rather than in to mean 'consisting of'.

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Thr	Glu	Ser	Ser	Val	Glu	Met	Thr	Lys	Ser	Phe	Asp	Phe	Pro	Thr	Leu																																								
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Ile	Thr	Lys	Leu	Ser	Ala	Glu	Pro	Thr	Glu	Val	Arg	Asp	Met	Glu	Glu																																								
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Asp	Phe	Thr	Ala	Thr	Pro	Gly	Thr	Thr	Lys	Tyr	Asp	Glu	Asn	Ile	Thr																																								
		770				775					780																																												
Thr	Val	Leu	Leu	Ala	His	Gly	Thr	Leu	Ser	Val	Glu	Ala	Ala	Thr	Val																																								
		785			790					795				800																																									
Ser	Lys	Trp	Ser	Trp	Asp	Glu	Asp	Asn	Thr	Thr	Ser	Lys	Pro	Leu	Glu																																								
			805					810					815																																										
Ser	Thr	Glu	Pro	Ser	Ala	Ser	Ser	Lys	Leu	Pro	Pro	Ala	Leu	Leu	Thr																																								
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Thr	Val	Gly	Met	Asn	Gly	Lys	Asp	Lys	Asp	Ile	Pro	Ser	Phe	Thr	Glu																																								
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Asp	Gly	Ala	Asp	Glu	Phe	Thr	Leu	Ile	Pro	Asp	Ser	Thr	Gln	Lys	Gln																																								
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Leu	Glu	Glu	Val	Thr	Asp	Glu	Asp	Ile	Ala	Ala	His	Gly	Lys	Phe	Thr																																								
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Ile	Arg	Phe	Gln	Pro	Thr	Thr	Ser	Thr	Gly	Ile	Ala	Glu	Lys	Ser	Thr																																								
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		945			950				955				960																																										
Gln	Glu	Pro	Thr	Thr	Tyr	Val	Asp	Ser	Ser	His	Thr	Ile	Pro	Leu	Ser																																								

Glu	Asp	Glu	Val	Leu	Gly	Glu	Pro	Ser	Gln	Asp	Ile	Leu	Val	Ile	Asp
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Gln	Thr	Arg	Leu	Glu	Ala	Thr	Ile	Ser	Pro	Glu	Thr	Met	Arg	Thr	
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Glu	Gln	Thr	Ala	Glu	Lys	Pro	Val	Pro	Ala	Leu	Ser	Ser	Thr	Ala	
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Trp	Thr	Pro	Lys	Glu	Ala	Val	Thr	Pro	Leu	Asp	Glu	Gln	Glu	Gly	
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Asp	His	Ser	Val	Ser	Tyr	Pro	Pro	Gly	Ala	Val	Thr	Glu	His	Lys	
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Val	Ile	Ile	Gly	Glu	Ser	Thr	Ser	His	Val	Pro	Pro	Thr	Thr	Leu	
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Pro	Thr	Val	Glu	Asp	Lys	Glu	Ala	Phe	Gly	Pro	Gln	Ala	Leu	Ser	
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Lys His	Leu Val	Thr Thr	Val	Pro Lys	Asp Pro	Glu	Ala Ala	Glu	
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Ala Arg	Arg Gly	Gln Phe	Glu	Ser Val	Ala Pro	Ser	Gln Asn	Phe	
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Ser Asp	Ser Ser	Glu Ser	Asp	Thr His	Pro Phe	Val	Ile Ala	Lys	
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Thr Glu	Leu Ser	Thr Ala	Val	Gln Pro	Asn Glu	Ser	Thr Glu	Thr	
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Thr Glu	Ser Leu	Glu Val	Thr	Trp Lys	Pro Glu	Thr	Tyr Pro	Glu	
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Thr Ser	Glu His	Phe Ser	Gly	Gly Glu	Pro Asp	Val	Phe Pro	Thr	
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Val Pro	Phe His	Glu Glu	Phe	Glu Ser	Gly Thr	Ala	Lys Lys	Gly	
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Ala Glu	Ser Val	Thr Glu	Arg	Asp Thr	Glu Val	Gly	His Gln	Ala	
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His Glu	His Thr	Glu Pro	Val	Ser Leu	Phe Pro	Glu	Glu Ser	Ser	
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Gly Glu	Ile Ala	Ile Asp	Gln	Glu Ser	Gln Lys	Ile	Ala Phe	Ala	
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Arg Ala	Thr Glu	Val Thr	Phe	Gly Glu	Glu Val	Glu	Lys Ser	Thr	
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Ser Val	Thr Tyr	Thr Pro	Thr	Ile Val	Pro Ser	Ser	Ala Ser	Ala	
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Tyr Val	Ser Glu	Glu Glu	Ala	Val Thr	Leu Ile	Gly	Asn Pro	Trp	
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Pro Asp	Asp Leu	Leu Ser	Thr	Lys Glu	Ser Trp	Val	Glu Ala	Thr	
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Pro Arg	Gln Val	Val Glu	Leu	Ser Gly	Ser Ser	Ser	Ile Pro	Ile	
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Thr Glu	Gly Ser	Gly Glu	Ala	Glu Glu	Asp Glu	Asp	Thr Met	Phe	
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Thr Met	Val Thr	Asp Leu	Ser	Gln Arg	Asn Thr	Thr	Asp Thr	Leu	
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Ile Thr	Leu Asp	Thr Ser	Arg	Ile Ile	Thr Glu	Ser	Phe Phe	Glu	
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Val Pro	Ala Thr	Thr Ile	Tyr	Pro Val	Ser Glu	Gln	Pro Ser	Ala	
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Lys Val	Val Pro	Thr Lys	Phe	Val Ser	Glu Thr	Asp	Thr Ser	Glu	
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Trp Ile	Ser Ser	Thr Thr	Val	Glu Glu	Lys Lys	Arg	Lys Glu	Glu	
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Glu Gly	Thr Thr	Gly Thr	Ala	Ser Thr	Phe Glu	Val	Tyr Ser	Ser	
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Thr Gln	Arg Ser	Asp Gln	Leu	Ile Leu	Pro Phe	Glu	Leu Glu	Ser	
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Pro Asn	Val Ala	Thr Ser	Ser	Asp Ser	Gly Thr	Arg	Lys Ser	Phe	
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Ser Thr	Pro Val	Phe Thr	Glu	Thr Asn	Thr Leu	Glu	Asn Leu	Gly	
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Glu Gly Leu Thr Thr Leu Pro	Arg Ser Pro Ala Ser	Val Phe Met
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Glu Gln Gly Ser Gly Glu Ala	Ala Ala Asp Pro Glu	Thr Thr Thr
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Val Ser Ser Phe Ser Leu Asn	Val Glu Tyr Ala Ile	Gln Ala Glu
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Lys Glu Val Ala Gly Thr Leu	Ser Pro His Val Glu	Thr Thr Phe
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Ser Thr Glu Pro Thr Gly Leu	Val Leu Ser Thr Val	Met Asp Arg
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Val Val Ala Glu Asn Ile Thr	Gln Thr Ser Arg Glu	Ile Val Ile
1895	1900	1905
Ser Glu Arg Leu Gly Glu Pro	Asn Tyr Gly Ala Glu	Ile Arg Gly
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Phe Ser Thr Gly Phe Pro Leu	Glu Glu Asp Phe Ser	Gly Asp Phe
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Arg Glu Tyr Ser Thr Val Ser	His Pro Ile Ala Lys	Glu Glu Thr
1940	1945	1950
Val Met Met Glu Gly Ser Gly	Asp Ala Ala Phe Arg	Asp Thr Gln
1955	1960	1965
Thr Ser Pro Ser Thr Val Pro	Thr Ser Val His Ile	Ser His Ile
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Ser Asp Ser Glu Gly Pro Ser	Ser Thr Met Val Ser	Thr Ser Ala
1985	1990	1995
Phe Pro Trp Glu Glu Phe Thr	Ser Ser Ala Glu Gly	Ser Gly Glu
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Gln Leu Val Thr Val Ser Ser	Ser Val Val Pro Val	Leu Pro Ser
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Ala Val Gln Lys Phe Ser Gly	Thr Ala Ser Ser Ile	Ile Asp Glu
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Gly Leu Gly Glu Val Gly Thr	Val Asn Glu Ile Asp	Arg Arg Ser
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Glu Lys Glu Glu Val Lys Val	Ser Gly Thr Val Ser	Thr Asn Phe
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Pro Gln Thr Ile Glu Pro Ala	Lys Leu Trp Ser Arg	Gln Glu Val
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Asn Pro Val Arg Gln Glu Ile	Glu Ser Glu Thr Thr	Ser Glu Glu
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Gln Ile Gln Glu Glu Lys Ser	Phe Glu Ser Pro Gln	Asn Ser Pro
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Ala Thr Glu Gln Thr Ile Phe	Asp Ser Gln Thr Phe	Thr Glu Thr
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Glu Leu Lys Thr Thr Asp Tyr	Ser Val Leu Thr Thr	Lys Lys Thr
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Tyr Ser Asp Asp Lys Glu Met	Lys Glu Glu Asp Thr	Ser Leu Val
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Asn Met Ser Thr Pro Asp Pro	Asp Ala Asn Gly Leu	Glu Ser Tyr
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Thr Thr Leu Pro Glu Ala Thr	Glu Lys Ser His Phe	Phe Leu Ala

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Asp Ser Pro Ile Lys Lys Glu Glu Ser Thr Lys His Phe Pro Lys		
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Gly Met Arg Pro Thr Ile Gln Glu Ser Asp Thr Glu Leu Leu Phe		
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Ser Gly Leu Gly Ser Gly Glu Glu Val Leu Pro Thr Leu Pro Thr		
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Tyr Pro His Thr Ser Gln Val Glu Ser Thr Ser Ser Asp Lys Ile		
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Pro Thr Val Ala Pro Leu Pro Phe Ser Thr Asp Ile Gly His Pro		
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Pro Gln Thr Ile Thr Glu Gln Asp Ser Asn Lys Asn Ser Ser Thr		
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Ala Glu Ile Asn Glu Thr Thr Thr Ser Ser Thr Asp Phe Leu Ala		
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Pro Lys Pro Ser Asp Leu Tyr Tyr Glu Pro Ser Gly Glu Gly Ser		
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Gly Glu Val Asp Ile Val Asp Ser Phe His Thr Ser Ala Thr Thr		
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Phe Arg Glu Phe Glu Asp Ser Thr Leu Lys Pro Asn Arg Lys Lys		
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Leu Ile Leu Thr Ile Thr Glu Ser Thr Ile Leu Glu Ile Leu Pro		
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Glu Leu Thr Ser Asp Lys Asn Thr Ile Ile Asp Ile Asp His Thr		
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Lys Pro Val Tyr Glu Asp Ile Leu Gly Met Gln Thr Asp Ile Asp		
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<211> 338

<212> PRT

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<400> 2

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 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
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Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
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Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
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Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
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245      250      255
Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
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290      295      300
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<400> 3

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Met Gly Trp Arg Ala Pro Gly Ala Leu Leu Leu Ala Leu Leu Leu His
1      5      10      15
Gly Arg Leu Leu Ala Val Thr His Gly Leu Arg Ala Tyr Asp Gly Leu
20     25     30
Ser Leu Pro Glu Asp Ile Glu Thr Val Thr Ala Ser Gln Met Arg Trp
35     40     45
Thr His Ser Tyr Leu Ser Asp Asp Glu Asp Met Leu Ala Asp Ser Ile
50     55     60
Ser Gly Asp Asp Leu Gly Ser Gly Asp Leu Gly Ser Gly Asp Phe Gln
65     70     75     80
Met Val Tyr Phe Arg Ala Leu Val Asn Phe Thr Arg Ser Ile Glu Tyr
85     90     95
Ser Pro Gln Leu Glu Asp Ala Gly Ser Arg Glu Phe Arg Glu Val Ser
100    105    110
Glu Ala Val Val Asp Thr Leu Glu Ser Glu Tyr Leu Lys Ile Pro Gly
115    120    125
Asp Gln Val Val Ser Val Val Phe Ile Lys Glu Leu Asp Gly Trp Val
130    135    140
Phe Val Glu Leu Asp Val Gly Ser Glu Gly Asn Ala Asp Gly Ala Gln
145    150    155    160
Ile Gln Glu Met Leu Leu Arg Val Ile Ser Ser Gly Ser Val Ala Ser
165    170    175
Tyr Val Thr Ser Pro Gln Gly Phe Gln Phe Arg Arg Leu Gly Thr Val
180    185    190
Pro Gln Phe Pro Arg Ala Cys Thr Glu Ala Glu Phe Ala Cys His Ser
195    200    205
Tyr Asn Glu Cys Val Ala Leu Glu Tyr Arg Cys Asp Arg Arg Pro Asp
210    215    220
Cys Arg Asp Met Ser Asp Glu Leu Asn Cys Glu Glu Pro Val Leu Gly
225    230    235    240
Ile Ser Pro Thr Phe Ser Leu Leu Val Glu Thr Thr Ser Leu Pro Pro
245    250    255
Arg Pro Glu Thr Thr Ile Met Arg Gln Pro Pro Val Thr His Ala Pro
260    265    270
Gln Pro Leu Leu Pro Gly Ser Val Arg Pro Leu Pro Cys Gly Pro Gln
275    280    285
Glu Ala Ala Cys Arg Asn Gly His Cys Ile Pro Arg Asp Tyr Leu Cys
290    295    300
Asp Gly Gln Glu Asp Cys Glu Asp Gly Ser Asp Glu Leu Asp Cys Gly
305    310    315    320
Pro Pro Pro Pro Cys Glu Pro Asn Glu Phe Pro Cys Gly Asn Gly His
325    330    335
Cys Ala Leu Lys Leu Trp Arg Cys Asp Gly Asp Phe Asp Cys Glu Asp
340    345    350
Arg Thr Asp Glu Ala Asn Cys Pro Thr Lys Arg Pro Glu Glu Val Cys
355    360    365
Gly Pro Thr Gln Phe Arg Cys Val Ser Thr Asn Met Cys Ile Pro Ala
370    375    380
Ser Phe His Cys Asp Glu Glu Ser Asp Cys Pro Asp Arg Ser Asp Glu

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385          390          395          400
Phe Gly Cys Met Pro Pro Gln Val Val Thr Pro Pro Arg Glu Ser Ile
405
Gln Ala Ser Arg Gly Gln Thr Val Thr Phe Thr Cys Val Ala Ile Gly
420          425          430
Val Pro Thr Pro Ile Ile Asn Trp Arg Leu Asn Trp Gly His Ile Pro
435          440          445
Ser His Pro Arg Val Thr Val Thr Ser Glu Gly Gly Arg Gly Thr Leu
450          455          460
Ile Ile Arg Asp Val Lys Glu Ser Asp Gln Gly Ala Tyr Thr Cys Glu
465          470          475          480
Ala Met Asn Ala Arg Gly Met Val Phe Gly Ile Pro Asp Gly Val Leu

485          490          495
Glu Leu Val Pro Gln Arg Gly Pro Cys Pro Asp Gly His Phe Tyr Leu
500          505          510
Glu His Ser Ala Ala Cys Leu Pro Cys Phe Cys Phe Gly Ile Thr Ser
515          520          525
Val Cys Gln Ser Thr Arg Arg Phe Arg Asp Gln Ile Arg Leu Arg Phe
530          535          540
Asp Gln Pro Asp Asp Phe Lys Gly Val Asn Val Thr Met Pro Ala Gln
545          550          555          560
Pro Gly Thr Pro Pro Leu Ser Ser Thr Gln Leu Gln Ile Asp Pro Ser
565          570          575
Leu His Glu Phe Gln Leu Val Asp Leu Ser Arg Arg Phe Leu Val His
580          585          590
Asp Ser Phe Trp Ala Leu Pro Glu Gln Phe Leu Gly Asn Lys Val Asp
595          600          605
Ser Tyr Gly Gly Ser Leu Arg Tyr Asn Val Arg Tyr Glu Leu Ala Arg
610          615          620
Gly Met Leu Glu Pro Val Gln Arg Pro Asp Val Val Leu Val Gly Ala
625          630          635          640
Gly Tyr Arg Leu Leu Ser Arg Gly His Thr Pro Thr Gln Pro Gly Ala
645          650          655
Leu Asn Gln Arg Gln Val Gln Phe Ser Glu Glu His Trp Val His Glu
660          665          670
Ser Gly Arg Pro Val Gln Arg Ala Glu Leu Leu Gln Val Leu Gln Ser
675          680          685
Leu Glu Ala Val Leu Ile Gln Thr Val Tyr Asn Thr Lys Met Ala Ser
690          695          700
Val Gly Leu Ser Asp Ile Ala Met Asp Thr Thr Val Thr His Ala Thr
705          710          715          720
Ser His Gly Arg Ala His Ser Val Glu Glu Cys Arg Cys Pro Ile Gly
725          730          735
Tyr Ser Gly Leu Ser Cys Glu Ser Cys Asp Ala His Phe Thr Arg Val
740          745          750
Pro Gly Gly Pro Tyr Leu Gly Thr Cys Ser Gly Cys Ser Cys Asn Gly
755          760          765
His Ala Ser Ser Cys Asp Pro Val Tyr Gly His Cys Leu Asn Cys Gln
770          775          780
His Asn Thr Glu Gly Pro Gln Cys Asn Lys Cys Lys Ala Gly Phe Phe
785          790          795          800
Gly Asp Ala Met Lys Ala Thr Ala Thr Ser Cys Arg Pro Cys Pro Cys
805          810          815

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Pro Tyr Ile Asp Ala Ser Arg Arg Phe Ser Asp Thr Cys Phe Leu Asp
 820 825 830
 Thr Asp Gly Gln Ala Thr Cys Asp Ala Cys Ala Pro Gly Tyr Thr Gly
 835 840 845
 Arg Arg Cys Glu Ser Cys Ala Pro Gly Tyr Glu Gly Asn Pro Ile Gln
 850 855 860
 Pro Gly Gly Lys Cys Arg Pro Val Asn Gln Glu Ile Val Arg Cys Asp
 865 870 875 880
 Glu Arg Gly Ser Met Gly Thr Ser Gly Glu Ala Cys Arg Cys Lys Asn
 885 890 895
 Asn Val Val Gly Arg Leu Cys Asn Glu Cys Ala Asp Gly Ser Phe His
 900 905 910
 Leu Ser Thr Arg Asn Pro Asp Gly Cys Leu Lys Cys Phe Cys Met Gly
 915 920 925
 Val Ser Arg His Cys Thr Ser Ser Ser Trp Ser Arg Ala Gln Leu His
 930 935 940
 Gly Ala Ser Glu Glu Pro Gly His Phe Ser Leu Thr Asn Ala Ala Ser
 945 950 955 960
 Thr His Thr Thr Asn Glu Gly Ile Phe Ser Pro Thr Pro Gly Glu Leu
 965 970 975
 Gly Phe Ser Ser Phe His Arg Leu Leu Ser Gly Pro Tyr Phe Trp Ser
 980 985 990
 Leu Pro Ser Arg Phe Leu Gly Asp Lys Val Thr Ser Tyr Gly Gly Glu
 995 1000 1005
 Leu Arg Phe Thr Val Thr Gln Arg Ser Gln Pro Gly Ser Thr Pro
 1010 1015 1020
 Leu His Gly Gln Pro Leu Val Val Leu Gln Gly Asn Asn Ile Ile
 1025 1030 1035
 Leu Glu His His Val Ala Gln Glu Pro Ser Pro Gly Gln Pro Ser
 1040 1045 1050
 Thr Phe Ile Val Pro Phe Arg Glu Gln Ala Trp Gln Arg Pro Asp
 1055 1060 1065
 Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu Ala Gly
 1070 1075 1080
 Ile Asp Thr Leu Leu Ile Arg Ala Ser Tyr Ala Gln Gln Pro Ala
 1085 1090 1095
 Glu Ser Arg Val Ser Gly Ile Ser Met Asp Val Ala Val Pro Glu
 1100 1105 1110
 Glu Thr Gly Gln Asp Pro Ala Leu Glu Val Glu Gln Cys Ser Cys
 1115 1120 1125
 Pro Pro Gly Tyr Arg Gly Pro Ser Cys Gln Asp Cys Asp Thr Gly
 1130 1135 1140
 Tyr Thr Arg Thr Pro Ser Gly Leu Tyr Leu Gly Thr Cys Glu Arg
 1145 1150 1155
 Cys Ser Cys His Gly His Ser Glu Ala Cys Glu Pro Glu Thr Gly
 1160 1165 1170
 Ala Cys Gln Gly Cys Gln His His Thr Glu Gly Pro Arg Cys Glu
 1175 1180 1185
 Gln Cys Gln Pro Gly Tyr Tyr Gly Asp Ala Gln Arg Gly Thr Pro
 1190 1195 1200
 Gln Asp Cys Gln Leu Cys Pro Cys Tyr Gly Asp Pro Ala Ala Gly
 1205 1210 1215
 Gln Ala Ala His Thr Cys Phe Leu Asp Thr Asp Gly His Pro Thr
 1220 1225 1230

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Cys Asp Ala Cys Ser Pro Gly His Ser Gly Arg His Cys Glu Arg
1235      1240      1245

Cys Ala Pro Gly Tyr Tyr Gly Asn Pro Ser Gln Gly Gln Pro Cys
1250      1255      1260

Gln Arg Asp Ser Gln Val Pro Gly Pro Ile Gly Cys Asn Cys Asp
1265      1270      1275

Pro Gln Gly Ser Val Ser Ser Gln Cys Asp Ala Ala Gly Gln Cys
1280      1285      1290

Gln Cys Lys Ala Gln Val Glu Gly Leu Thr Cys Ser His Cys Arg
1295      1300      1305

Pro His His Phe His Leu Ser Ala Ser Asn Pro Asp Gly Cys Leu
1310      1315      1320

Pro Cys Phe Cys Met Gly Ile Thr Gln Gln Cys Ala Ser Ser Ala
1325      1330      1335

Tyr Thr Arg His Leu Ile Ser Thr His Phe Ala Pro Gly Asp Phe
1340      1345      1350

Gln Gly Phe Ala Leu Val Asn Pro Gln Arg Asn Ser Arg Leu Thr
1355      1360      1365

Gly Glu Phe Thr Val Glu Pro Val Pro Glu Gly Ala Gln Leu Ser
1370      1375      1380

Phe Gly Asn Phe Ala Gln Leu Gly His Glu Ser Phe Tyr Trp Gln
1385      1390      1395

Leu Pro Glu Thr Tyr Gln Gly Asp Lys Val Ala Ala Tyr Gly Gly
1400      1405      1410

Lys Leu Arg Tyr Thr Leu Ser Tyr Thr Ala Gly Pro Gln Gly Ser
1415      1420      1425

Pro Leu Ser Asp Pro Asp Val Gln Ile Thr Gly Asn Asn Ile Met
1430      1435      1440

Leu Val Ala Ser Gln Pro Ala Leu Gln Gly Pro Glu Arg Arg Ser
1445      1450      1455

Tyr Glu Ile Met Phe Arg Glu Glu Phe Trp Arg Arg Pro Asp Gly
1460      1465      1470

Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu Ala Asp Leu
1475      1480      1485

Asp Glu Leu Leu Ile Arg Ala Thr Phe Ser Ser Val Pro Leu Val
1490      1495      1500

Ala Ser Ile Ser Ala Val Ser Leu Glu Val Ala Gln Pro Gly Pro
1505      1510      1515

Ser Asn Arg Pro Arg Ala Leu Glu Val Glu Glu Cys Arg Cys Pro
1520      1525      1530

Pro Gly Tyr Ile Gly Leu Ser Cys Gln Asp Cys Ala Pro Gly Tyr
1535      1540      1545

Thr Arg Thr Gly Ser Gly Leu Tyr Leu Gly His Cys Glu Leu Cys
1550      1555      1560

Glu Cys Asn Gly His Ser Asp Leu Cys His Pro Glu Thr Gly Ala
1565      1570      1575

Cys Ser Gln Cys Gln His Asn Ala Ala Gly Glu Phe Cys Glu Leu
1580      1585      1590

Cys Ala Pro Gly Tyr Tyr Gly Asp Ala Thr Ala Gly Thr Pro Glu
1595      1600      1605

Asp Cys Gln Pro Cys Ala Cys Pro Leu Thr Asn Pro Glu Asn Met
1610      1615      1620

Phe Ser Arg Thr Cys Glu Ser Leu Gly Ala Gly Gly Tyr Arg Cys
1625      1630      1635

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1625	1630	1635
Thr Ala Cys Glu Pro Gly	Tyr Thr Gly Gln Tyr Cys	Glu Gln Cys
1640	1645	1650
Gly Pro Gly Tyr Val Gly	Asn Pro Ser Val Gln Gly	Gly Gln Cys
1655	1660	1665
Leu Pro Glu Thr Asn Gln Ala	Pro Leu Val Val Glu	Val His Pro
1670	1675	1680
Ala Arg Ser Ile Val Pro	Gln Gly Gly Ser His Ser	Leu Arg Cys
1685	1690	1695
Gln Val Ser Gly Ser Pro	Pro His Tyr Phe Tyr Trp	Ser Arg Glu
1700	1705	1710
Asp Gly Arg Pro Val Pro	Ser Gly Thr Gln Gln Arg	His Gln Gly
1715	1720	1725
Ser Glu Leu His Phe Pro	Ser Val Gln Pro Ser Asp	Ala Gly Val
1730	1735	1740
Tyr Ile Cys Thr Cys Arg	Asn Leu His Gln Ser Asn	Thr Ser Arg
1745	1750	1755
Ala Glu Leu Leu Val Thr	Glu Ala Pro Ser Lys Pro	Ile Thr Val
1760	1765	1770
Thr Val Glu Glu Gln Arg	Ser Gln Ser Val Arg Pro	Gly Ala Asp
1775	1780	1785
Val Thr Phe Ile Cys Thr	Ala Lys Ser Lys Ser Pro	Ala Tyr Thr
1790	1795	1800
Leu Val Trp Thr Arg Leu	His Asn Gly Lys Leu Pro	Thr Arg Ala
1805	1810	1815
Met Asp Phe Asn Gly Ile	Leu Thr Ile Arg Asn Val	Gln Leu Ser
1820	1825	1830
Asp Ala Gly Thr Tyr Val	Cys Thr Gly Ser Asn Met	Phe Ala Met
1835	1840	1845
Asp Gln Gly Thr Ala Thr	Leu His Val Gln Ala Ser	Gly Thr Leu
1850	1855	1860
Ser Ala Pro Val Val Ser	Ile His Pro Pro Gln Leu	Thr Val Gln
1865	1870	1875
Pro Gly Gln Leu Ala Glu	Phe Arg Cys Ser Ala Thr	Gly Ser Pro
1880	1885	1890
Thr Pro Thr Leu Glu Trp	Thr Gly Gly Pro Gly Gly	Gln Leu Pro
1895	1900	1905
Ala Lys Ala Gln Ile His	Gly Gly Ile Leu Arg Leu	Pro Ala Val
1910	1915	1920
Glu Pro Thr Asp Gln Ala	Gln Tyr Leu Cys Arg Ala	His Ser Ser
1925	1930	1935
Ala Gly Gln Gln Val Ala	Arg Ala Val Leu His Val	His Gly Gly
1940	1945	1950
Gly Gly Pro Arg Val Gln	Val Ser Pro Glu Arg Thr	Gln Val His
1955	1960	1965
Ala Gly Arg Thr Val Arg	Leu Tyr Cys Arg Ala Ala	Gly Val Pro
1970	1975	1980
Ser Ala Thr Ile Thr Trp	Arg Lys Glu Gly Gly Ser	Leu Pro Pro
1985	1990	1995
Gln Ala Arg Ser Glu Arg	Thr Asp Ile Ala Thr Leu	Leu Ile Pro
2000	2005	2010
Ala Ile Thr Thr Ala Asp	Ala Gly Phe Tyr Leu Cys	Val Ala Thr
2015	2020	2025

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Ser Pro  Ala Gly Thr Ala Gln  Ala Arg Ile Gln Val  Val Val Leu
2030                      2035                      2040

Ser Ala  Ser Asp Ala Ser Pro  Pro Pro Val Lys Ile  Glu Ser Ser
2045                      2050                      2055

Ser Pro  Ser Val Thr Glu Gly  Gln Thr Leu Asp Leu  Asn Cys Val
2060                      2065                      2070

Val Ala  Gly Ser Ala His Ala  Gln Val Thr Trp Tyr  Arg Arg Gly
2075                      2080                      2085

Gly Ser  Leu Pro Pro His Thr  Gln Val His Gly Ser  Arg Leu Arg
2090                      2095                      2100

Leu Pro  Gln Val Ser Pro Ala  Asp Ser Gly Glu Tyr  Val Cys Arg
2105                      2110                      2115

Val Glu  Asn Gly Ser Gly Pro  Lys Glu Ala Ser Ile  Thr Val Ser
2120                      2125                      2130

Val Leu  His Gly Thr His Ser  Gly Pro Ser Tyr Thr  Pro Val Pro
2135                      2140                      2145

Gly Ser  Thr Arg Pro Ile Arg  Ile Glu Pro Ser Ser  Ser His Val
2150                      2155                      2160

Ala Glu  Gly Gln Thr Leu Asp  Leu Asn Cys Val Val  Pro Gly Gln
2165                      2170                      2175

Ala His  Ala Gln Val Thr Trp  His Lys Arg Gly Gly  Ser Leu Pro
2180                      2185                      2190

Ala Arg  His Gln Thr His Gly  Ser Leu Leu Arg Leu  His Gln Val
2195                      2200                      2205

Thr Pro  Ala Asp Ser Gly Glu  Tyr Val Cys His Val  Val Gly Thr
2210                      2215                      2220

Ser Gly  Pro Leu Glu Ala Ser  Val Leu Val Thr Ile  Glu Ala Ser
2225                      2230                      2235

Val Ile  Pro Gly Pro Ile Pro  Pro Val Arg Ile Glu  Ser Ser Ser
2240                      2245                      2250

Ser Thr  Val Ala Glu Gly Gln  Thr Leu Asp Leu Ser  Cys Val Val
2255                      2260                      2265

Ala Gly  Gln Ala His Ala Gln  Val Thr Trp Tyr Lys  Arg Gly Gly
2270                      2275                      2280

Ser Leu  Pro Ala Arg His Gln  Val Arg Gly Ser Arg  Leu Tyr Ile
2285                      2290                      2295

Phe Gln  Ala Ser Pro Ala Asp  Ala Gly Gln Tyr Val  Cys Arg Ala
2300                      2305                      2310

Ser Asn  Gly Met Glu Ala Ser  Ile Thr Val Thr Val  Thr Gly Thr
2315                      2320                      2325

Gln Gly  Ala Asn Leu Ala Tyr  Pro Ala Gly Ser Thr  Gln Pro Ile
2330                      2335                      2340

Arg Ile  Glu Pro Ser Ser Ser  Gln Val Ala Glu Gly  Gln Thr Leu
2345                      2350                      2355

Asp Leu  Asn Cys Val Val Pro  Gly Gln Ser His Ala  Gln Val Thr
2360                      2365                      2370

Trp His  Lys Arg Gly Gly Ser  Leu Pro Val Arg His  Gln Thr His
2375                      2380                      2385

Gly Ser  Leu Leu Arg Leu Tyr  Gln Ala Ser Pro Ala  Asp Ser Gly
2390                      2395                      2400

Glu Tyr  Val Cys Arg Val Leu  Gly Ser Ser Val Pro  Leu Glu Ala
2405                      2410                      2415

Ser Val  Leu Val Thr Ile Glu  Pro Ala Gly Ser Val  Pro Ala Leu
2420                      2425                      2430

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Gly Val	Thr Pro Thr Val	Arg	Ile Glu Ser Ser	Ser	Ser Gln Val
2435		2440		2445	
Ala Glu	Gly Gln Thr Leu	Asp	Leu Asn Cys Leu	Val	Ala Gly Gln
2450		2455		2460	
Ala His	Ala Gln Val Thr	Trp	His Lys Arg Gly	Gly	Ser Leu Pro
2465		2470		2475	
Ala Arg	His Gln Val His	Gly	Ser Arg Leu Arg	Leu	Leu Gln Val
2480		2485		2490	
Thr Pro	Ala Asp Ser Gly	Glu	Tyr Val Cys Arg	Val	Val Gly Ser
2495		2500		2505	
Ser Gly	Thr Gln Glu Ala	Ser	Val Leu Val Thr	Ile	Gln Gln Arg
2510		2515		2520	
Leu Ser	Gly Ser His Ser	Gln	Gly Val Ala Tyr	Pro	Val Arg Ile
2525		2530		2535	
Glu Ser	Ser Ser Ala Ser	Leu	Ala Asn Gly His	Thr	Leu Asp Leu
2540		2545		2550	
Asn Cys	Leu Val Ala Ser	Gln	Ala Pro His Thr	Ile	Thr Trp Tyr
2555		2560		2565	
Lys Arg	Gly Gly Ser Leu	Pro	Ser Arg His Gln	Ile	Val Gly Ser
2570		2575		2580	
Arg Leu	Arg Ile Pro Gln	Val	Thr Pro Ala Asp	Ser	Gly Glu Tyr
2585		2590		2595	
Val Cys	His Val Ser Asn	Gly	Ala Gly Ser Arg	Glu	Thr Ser Leu
2600		2605		2610	
Ile Val	Thr Ile Gln Gly	Ser	Gly Ser Ser His	Val	Pro Ser Val
2615		2620		2625	
Ser Pro	Pro Ile Arg Ile	Glu	Ser Ser Ser Pro	Thr	Val Val Glu
2630		2635		2640	
Gly Gln	Thr Leu Asp Leu	Asn	Cys Val Val Ala	Arg	Gln Pro Gln
2645		2650		2655	
Ala Ile	Ile Thr Trp Tyr	Lys	Arg Gly Gly Ser	Leu	Pro Ser Arg
2660		2665		2670	
His Gln	Thr His Gly Ser	His	Leu Arg Leu His	Gln	Met Ser Val
2675		2680		2685	
Ala Asp	Ser Gly Glu Tyr	Val	Cys Arg Ala Asn	Asn	Asn Ile Asp
2690		2695		2700	
Ala Leu	Glu Ala Ser Ile	Val	Ile Ser Val Ser	Pro	Ser Ala Gly
2705		2710		2715	
Ser Pro	Ser Ala Pro Gly	Ser	Ser Met Pro Ile	Arg	Ile Glu Ser
2720		2725		2730	
Ser Ser	Ser His Val Ala	Glu	Gly Glu Thr Leu	Asp	Leu Asn Cys
2735		2740		2745	
Val Val	Pro Gly Gln Ala	His	Ala Gln Val Thr	Trp	His Lys Arg
2750		2755		2760	
Gly Gly	Ser Leu Pro Ser	His	His Gln Thr Arg	Gly	Ser Arg Leu
2765		2770		2775	
Arg Leu	His His Val Ser	Pro	Ala Asp Ser Gly	Glu	Tyr Val Cys
2780		2785		2790	
Arg Val	Met Gly Ser Ser	Gly	Pro Leu Glu Ala	Ser	Val Leu Val
2795		2800		2805	
Thr Ile	Glu Ala Ser Gly	Ser	Ser Ala Val His	Val	Pro Ala Pro
2810		2815		2820	
Gly Gly	Ala Pro Pro Ile	Arg	Ile Glu Pro Ser	Ser	Ser Arg Val
2825		2830		2835	

Ala Glu Gly Gln Thr Leu Asp Leu Lys Cys Val Val Pro Gly Gln
 2840 2845 2850
 Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Asn Leu Pro
 2855 2860 2865
 Ala Arg His Gln Val His Gly Pro Leu Leu Arg Leu Asn Gln Val
 2870 2875 2880
 Ser Pro Ala Asp Ser Gly Glu Tyr Ser Cys Gln Val Thr Gly Ser
 2885 2890 2895
 Ser Gly Thr Leu Glu Ala Ser Val Leu Val Thr Ile Glu Pro Ser
 2900 2905 2910
 Ser Pro Gly Pro Ile Pro Ala Pro Gly Leu Ala Gln Pro Ile Tyr
 2915 2920 2925
 Ile Glu Ala Ser Ser Ser His Val Thr Glu Gly Gln Thr Leu Asp
 2930 2935 2940
 Leu Asn Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp
 2945 2950 2955
 Tyr Lys Arg Gly Gly Ser Leu Pro Ala Arg His Gln Thr His Gly
 2960 2965 2970
 Ser Gln Leu Arg Leu His Leu Val Ser Pro Ala Asp Ser Gly Glu
 2975 2980 2985
 Tyr Val Cys Arg Ala Ala Ser Gly Pro Gly Pro Glu Gln Glu Ala
 2990 2995 3000
 Ser Phe Thr Val Thr Val Pro Pro Ser Glu Gly Ser Ser Tyr Arg
 3005 3010 3015
 Leu Arg Ser Pro Val Ile Ser Ile Asp Pro Pro Ser Ser Thr Val
 3020 3025 3030
 Gln Gln Gly Gln Asp Ala Ser Phe Lys Cys Leu Ile His Asp Gly
 3035 3040 3045
 Ala Ala Pro Ile Ser Leu Glu Trp Lys Thr Arg Asn Gln Glu Leu
 3050 3055 3060
 Glu Asp Asn Val His Ile Ser Pro Asn Gly Ser Ile Ile Thr Ile
 3065 3070 3075
 Val Gly Thr Arg Pro Ser Asn His Gly Thr Tyr Arg Cys Val Ala
 3080 3085 3090
 Ser Asn Ala Tyr Gly Val Ala Gln Ser Val Val Asn Leu Ser Val
 3095 3100 3105
 His Gly Pro Pro Thr Val Ser Val Leu Pro Glu Gly Pro Val Trp
 3110 3115 3120
 Val Lys Val Gly Lys Ala Val Thr Leu Glu Cys Val Ser Ala Gly
 3125 3130 3135
 Glu Pro Arg Ser Ser Ala Arg Trp Thr Arg Ile Ser Ser Thr Pro
 3140 3145 3150
 Ala Lys Leu Glu Gln Arg Thr Tyr Gly Leu Met Asp Ser His Ala
 3155 3160 3165
 Val Leu Gln Ile Ser Ser Ala Lys Pro Ser Asp Ala Gly Thr Tyr
 3170 3175 3180
 Val Cys Leu Ala Gln Asn Ala Leu Gly Thr Ala Gln Lys Gln Val
 3185 3190 3195
 Glu Val Ile Val Asp Thr Gly Ala Met Ala Pro Gly Ala Pro Gln
 3200 3205 3210
 Val Gln Ala Glu Glu Ala Glu Leu Thr Val Glu Ala Gly His Thr
 3215 3220 3225
 Ala Thr Leu Arg Cys Ser Ala Thr Gly Ser Pro Ala Pro Thr Ile
 3230 3235 3240

His Trp 3245	Ser Lys	Leu Arg	Ser 3250	Pro Leu	Pro Trp	Gln 3255	His Arg	Leu
Glu Gly	Asp Thr	Leu Ile	Ile	Pro Arg	Val Ala	Gln	Gln Asp	Ser
3260			3265			3270		
Gly Gln 3275	Tyr Ile	Cys Asn	Ala 3280	Thr Ser	Pro Ala	Gly 3285	His Ala	Glu
Ala Thr 3290	Ile Ile	Leu His	Val 3295	Glu Ser	Pro Pro	Tyr 3300	Ala Thr	Thr
Val Pro 3305	Glu His	Ala Ser	Val 3310	Gln Ala	Gly Glu	Thr 3315	Val Gln	Leu
Gln Cys 3320	Leu Ala	His Gly	Thr 3325	Pro Pro	Leu Thr	Phe 3330	Gln Trp	Ser
Arg Val 3335	Gly Ser	Ser Leu	Pro 3340	Gly Arg	Ala Thr	Ala 3345	Arg Asn	Glu
Leu Leu 3350	His Phe	Glu Arg	Ala 3355	Ala Pro	Glu Asp	Ser 3360	Gly Arg	Tyr
Arg Cys 3365	Arg Val	Thr Asn	Lys 3370	Val Gly	Ser Ala	Glu 3375	Ala Phe	Ala
Gln Leu 3380	Leu Val	Gln Gly	Pro 3385	Pro Gly	Ser Leu	Pro 3390	Ala Thr	Ser
Ile Pro 3395	Ala Gly	Ser Thr	Pro 3400	Thr Val	Gln Val	Thr 3405	Pro Gln	Leu
Glu Thr 3410	Lys Ser	Ile Gly	Ala 3415	Ser Val	Glu Phe	His 3420	Cys Ala	Val
Pro Ser 3425	Asp Arg	Gly Thr	Gln 3430	Leu Arg	Trp Phe	Lys 3435	Glu Gly	Gly
Gln Leu 3440	Pro Pro	Gly His	Ser 3445	Val Gln	Asp Gly	Val 3450	Leu Arg	Ile
Gln Asn 3455	Leu Asp	Gln Ser	Cys 3460	Gln Gly	Thr Tyr	Ile 3465	Cys Gln	Ala
His Gly 3470	Pro Trp	Gly Lys	Ala 3475	Gln Ala	Ser Ala	Gln 3480	Leu Val	Ile
Gln Ala 3485	Leu Pro	Ser Val	Leu 3490	Ile Asn	Ile Arg	Thr 3495	Ser Val	Gln
Thr Val 3500	Val Val	Gly His	Ala 3505	Val Glu	Phe Glu	Cys 3510	Leu Ala	Leu
Gly Asp 3515	Pro Lys	Pro Gln	Val 3520	Thr Trp	Ser Lys	Val 3525	Gly Gly	His
Leu Arg 3530	Pro Gly	Ile Val	Gln 3535	Ser Gly	Gly Val	Val 3540	Arg Ile	Ala
His Val 3545	Glu Leu	Ala Asp	Ala 3550	Gly Gln	Tyr Arg	Cys 3555	Thr Ala	Thr
Asn Ala 3560	Ala Gly	Thr Thr	Gln 3565	Ser His	Val Leu	Leu 3570	Leu Val	Gln
Ala Leu 3575	Pro Gln	Ile Ser	Met 3580	Pro Gln	Glu Val	Arg 3585	Val Pro	Ala
Gly Ser 3590	Ala Ala	Val Phe	Pro 3595	Cys Ile	Ala Ser	Gly 3600	Tyr Pro	Thr
Pro Asp 3605	Ile Ser	Trp Ser	Lys 3610	Leu Asp	Gly Ser	Leu 3615	Pro Pro	Asp
Ser Arg 3620	Leu Glu	Asn Asn	Met 3625	Leu Met	Leu Pro	Ser 3630	Val Arg	Pro
Gln Asp	Ala Gly	Thr Tyr	Val	Cys Thr	Ala Thr	Asn	Arg Gln	Glu

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3635          3640          3645
Lys Val  Lys Ala Phe Ala His  Leu Gln Val Pro Glu  Arg Val Val
3650          3655          3660

Pro Tyr  Phe Thr Gln Thr Pro  Tyr Ser Phe Leu Pro  Leu Pro Thr
3665          3670          3675

Ile Lys  Asp Ala Tyr Arg Lys  Phe Glu Ile Lys Ile  Thr Phe Arg
3680          3685          3690

Pro Asp  Ser Ala Asp Gly Met  Leu Leu Tyr Asn Gly  Gln Lys Arg
3695          3700          3705

Val Pro  Gly Ser Pro Thr Asn  Leu Ala Asn Arg Gln  Pro Asp Phe
3710          3715          3720

Ile Ser  Phe Gly Leu Val Gly  Gly Arg Pro Glu Phe  Arg Phe Asp
3725          3730          3735

Ala Gly  Ser Gly Met Ala Thr  Ile Arg His Pro Thr  Pro Leu Ala
3740          3745          3750

Leu Gly  His Phe His Thr Val  Thr Leu Leu Arg Ser  Leu Thr Gln
3755          3760          3765

Gly Ser  Leu Ile Val Gly Asp  Leu Ala Pro Val Asn  Gly Thr Ser
3770          3775          3780

Gln Gly  Lys Phe Gln Gly Leu  Asp Leu Asn Glu Glu  Leu Tyr Leu
3785          3790          3795

Gly Gly  Tyr Pro Asp Tyr Gly  Ala Ile Pro Lys Ala  Gly Leu Ser
3800          3805          3810

Ser Gly  Phe Ile Gly Cys Val  Arg Glu Leu Arg Ile  Gln Gly Glu
3815          3820          3825

Glu Ile  Val Phe His Asp Leu  Asn Leu Thr Ala His  Gly Ile Ser
3830          3835          3840

His Cys  Pro Thr Cys Arg Asp  Arg Pro Cys Gln Asn  Gly Gly Gln
3845          3850          3855

Cys His  Asp Ser Glu Ser Ser  Ser Tyr Val Cys Val  Cys Pro Ala
3860          3865          3870

Gly Phe  Thr Gly Ser Arg Cys  Glu His Ser Gln Ala  Leu His Cys
3875          3880          3885

His Pro  Glu Ala Cys Gly Pro  Asp Ala Thr Cys Val  Asn Arg Pro
3890          3895          3900

Asp Gly  Arg Gly Tyr Thr Cys  Arg Cys His Leu Gly  Arg Ser Gly
3905          3910          3915

Leu Arg  Cys Glu Glu Gly Val  Thr Val Thr Thr Pro  Ser Leu Ser
3920          3925          3930

Gly Ala  Gly Ser Tyr Leu Ala  Leu Pro Ala Leu Thr  Asn Thr His
3935          3940          3945

His Glu  Leu Arg Leu Asp Val  Glu Phe Lys Pro Leu  Ala Pro Asp
3950          3955          3960

Gly Val  Leu Leu Phe Ser Gly  Gly Lys Ser Gly Pro  Val Glu Asp
3965          3970          3975

Phe Val  Ser Leu Ala Met Val  Gly Gly His Leu Glu  Phe Arg Tyr
3980          3985          3990

Glu Leu  Gly Ser Gly Leu Ala  Val Leu Arg Ser Ala  Glu Pro Leu
3995          4000          4005

Ala Leu  Gly Arg Trp His Arg  Val Ser Ala Glu Arg  Leu Asn Lys
4010          4015          4020

Asp Gly  Ser Leu Arg Val Asn  Gly Gly Arg Pro Val  Leu Arg Ser
4025          4030          4035

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Ser Pro Gly Lys Ser Gln Gly Leu Asn Leu His Thr Leu Leu Tyr
 4040 4045 4050
 Leu Gly Gly Val Glu Pro Ser Val Pro Leu Ser Pro Ala Thr Asn
 4055 4060 4065
 Met Ser Ala His Phe Arg Gly Cys Val Gly Glu Val Ser Val Asn
 4070 4075 4080
 Gly Lys Arg Leu Asp Leu Thr Tyr Ser Phe Leu Gly Ser Gln Gly
 4085 4090 4095
 Ile Gly Gln Cys Tyr Asp Ser Ser Pro Cys Glu Arg Gln Pro Cys
 4100 4105 4110
 Gln His Gly Ala Thr Cys Met Pro Ala Gly Glu Tyr Glu Phe Gln
 4115 4120 4125
 Cys Leu Cys Arg Asp Gly Phe Lys Gly Asp Leu Cys Glu His Glu
 4130 4135 4140
 Glu Asn Pro Cys Gln Leu Arg Glu Pro Cys Leu His Gly Gly Thr
 4145 4150 4155
 Cys Gln Gly Thr Arg Cys Leu Cys Leu Pro Gly Phe Ser Gly Pro
 4160 4165 4170
 Arg Cys Gln Gln Gly Ser Gly His Gly Ile Ala Glu Ser Asp Trp
 4175 4180 4185
 His Leu Glu Gly Ser Gly Gly Asn Asp Ala Pro Gly Gln Tyr Gly
 4190 4195 4200
 Ala Tyr Phe His Asp Asp Gly Phe Leu Ala Phe Pro Gly His Val
 4205 4210 4215
 Phe Ser Arg Ser Leu Pro Glu Val Pro Glu Thr Ile Glu Leu Glu
 4220 4225 4230
 Val Arg Thr Ser Thr Ala Ser Gly Leu Leu Leu Trp Gln Gly Val
 4235 4240 4245
 Glu Val Gly Glu Ala Gly Gln Gly Lys Asp Phe Ile Ser Leu Gly
 4250 4255 4260
 Leu Gln Asp Gly His Leu Val Phe Arg Tyr Gln Leu Gly Ser Gly
 4265 4270 4275
 Glu Ala Arg Leu Val Ser Glu Asp Pro Ile Asn Asp Gly Glu Trp
 4280 4285 4290
 His Arg Val Thr Ala Leu Arg Glu Gly Arg Arg Gly Ser Ile Gln
 4295 4300 4305
 Val Asp Gly Glu Glu Leu Val Ser Gly Arg Ser Pro Gly Pro Asn
 4310 4315 4320
 Val Ala Val Asn Ala Lys Gly Ser Val Tyr Ile Gly Gly Ala Pro
 4325 4330 4335
 Asp Val Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser Gly Ile Thr
 4340 4345 4350
 Gly Cys Val Lys Asn Leu Val Leu His Ser Ala Arg Pro Gly Ala
 4355 4360 4365
 Pro Pro Pro Gln Pro Leu Asp Leu Gln His Arg Ala Gln Ala Gly
 4370 4375 4380
 Ala Asn Thr Arg Pro Cys Pro Ser
 4385 4390

<210> 4

<211> 368

<212> PRT

<213> Homo sapiens

<400> 4

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Met Trp Pro Leu Trp Arg Leu Val Ser Leu Leu Ala Leu Ser Gln Ala
1      5      10      15

Leu Pro Phe Glu Gln Arg Gly Phe Trp Asp Phe Thr Leu Asp Asp Gly
20      25      30

Pro Phe Met Met Asn Asp Glu Glu Ala Ser Gly Ala Asp Thr Ser Gly
35      40      45

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

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

Leu Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp
85      90      95

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

Leu Gln His Leu Tyr Ala Leu Val Leu Val Asn Asn Lys Ile Ser Lys
115     120     125

Ile His Glu Lys Ala Phe Ser Pro Leu Arg Lys Leu Gln Lys Leu Tyr
130     135     140

Ile Ser Lys Asn His Leu Val Glu Ile Pro Pro Asn Leu Pro Ser Ser
145     150     155     160

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

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

Asn Pro Leu Glu Asn Ser Gly Phe Glu Pro Gly Ala Phe Asp Gly Leu
195     200     205

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

Lys Asp Leu Pro Glu Thr Leu Asn Glu Leu His Leu Asp His Asn Lys
225     230     235     240

Ile Gln Ala Ile Glu Leu Glu Asp Leu Leu Arg Tyr Ser Lys Leu Tyr
245     250     255

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

Leu Ser Phe Leu Pro Thr Leu Arg Glu Leu His Leu Asp Asn Asn Lys
275     280     285

Leu Ala Arg Val Pro Ser Gly Leu Pro Asp Leu Lys Leu Leu Gln Val
290     295     300

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

Cys Pro Met Gly Phe Gly Val Lys Arg Ala Tyr Tyr Asn Gly Ile Ser
325     330     335

Leu Phe Asn Asn Pro Val Pro Tyr Trp Glu Val Gln Pro Ala Thr Phe
340     345     350

Arg Cys Val Thr Asp Arg Leu Ala Ile Gln Phe Gly Asn Tyr Lys Lys
355     360     365

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<210> 5

<211> 359

<212> PRT

<213> Homo sapiens

<400> 5

Met Lys Ala Thr Ile Ile Leu Leu Leu Leu Ala Gln Val Ser Trp Ala
 1 5 10 15
 Gly Pro Phe Gln Gln Arg Gly Leu Phe Asp Phe Met Leu Glu Asp Glu
 20 25 30
 Ala Ser Gly Ile Gly Pro Glu Val Pro Asp Asp Arg Asp Phe Glu Pro
 35 40 45
 Ser Leu Gly Pro Val Cys Pro Phe Arg Cys Gln Cys His Leu Arg Val
 50 55 60
 Val Gln Cys Ser Asp Leu Gly Leu Asp Lys Val Pro Lys Asp Leu Pro
 65 70 75 80
 Pro Asp Thr Thr Leu Leu Asp Leu Gln Asn Asn Lys Ile Thr Glu Ile
 85 90 95
 Lys Asp Gly Asp Phe Lys Asn Leu Lys Asn Leu His Ala Leu Ile Leu
 100 105 110
 Val Asn Asn Lys Ile Ser Lys Val Ser Pro Gly Ala Phe Thr Pro Leu
 115 120 125
 Val Lys Leu Glu Arg Leu Tyr Leu Ser Lys Asn Gln Leu Lys Glu Leu
 130 135 140
 Pro Glu Lys Met Pro Lys Thr Leu Gln Glu Leu Arg Ala His Glu Asn
 145 150 155 160
 Glu Ile Thr Lys Val Arg Lys Val Thr Phe Asn Gly Leu Asn Gln Met
 165 170 175
 Ile Val Ile Glu Leu Gly Thr Asn Pro Leu Lys Ser Ser Gly Ile Glu
 180 185 190
 Asn Gly Ala Phe Gln Gly Met Lys Lys Leu Ser Tyr Ile Arg Ile Ala
 195 200 205
 Asp Thr Asn Ile Thr Ser Ile Pro Gln Gly Leu Pro Pro Ser Leu Thr
 210 215 220
 Glu Leu His Leu Asp Gly Asn Lys Ile Ser Arg Val Asp Ala Ala Ser
 225 230 235 240
 Leu Lys Gly Leu Asn Asn Leu Ala Lys Leu Gly Leu Ser Phe Asn Ser
 245 250 255
 Ile Ser Ala Val Asp Asn Gly Ser Leu Ala Asn Thr Pro His Leu Arg
 260 265 270
 Glu Leu His Leu Asp Asn Asn Lys Leu Thr Arg Val Pro Gly Gly Leu
 275 280 285
 Ala Glu His Lys Tyr Ile Gln Val Val Tyr Leu His Asn Asn Asn Ile
 290 295 300
 Ser Val Val Gly Ser Ser Asp Phe Cys Pro Pro Gly His Asn Thr Lys
 305 310 315 320
 Lys Ala Ser Tyr Ser Gly Val Ser Leu Phe Ser Asn Pro Val Gln Tyr
 325 330 335
 Trp Glu Ile Gln Pro Ser Thr Phe Arg Cys Val Tyr Val Arg Ser Ala
 340 345 350
 Ile Gln Leu Gly Asn Tyr Lys
 355

<210> 6

<211> 24

<212> PRT

<213> Homo sapiens

<400> 6

Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp Leu
 1 5 10 15

Gln Asn Asn Asp Ile Ser Glu Leu
 20

<210> 7

<211> 25

<212> PRT

<213> Homo sapiens

<400> 7

Leu Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp
 1 5 10 15

Leu Gln Asn Asn Asp Ile Ser Glu Leu
 20 25

<210> 8

<211> 25

<212> PRT

<213> Homo sapiens

<400> 8

Glu Asn Ser Gly Phe Glu Pro Gly Ala Phe Asp Gly Leu Lys Leu Asn
 1 5 10 15

Tyr Leu Arg Ile Ser Glu Ala Lys Leu
 20 25

<210> 9

<211> 26

<212> PRT

<213> Homo sapiens

<400> 9

Gly Leu Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu
 1 5 10 15

Asp Leu Gln Asn Asn Asp Ile Ser Glu Leu
 20 25

<210> 10

<211> 20

<212> PRT

<213> Homo sapiens

<400> 10

Tyr Leu Arg Ile Ser Glu Ala Lys Leu Thr Gly Ile Pro Lys Asp Leu
 1 5 10 15

Pro Glu Thr Leu
 20

<210> 11

<211> 26

<212> PRT

<213> Homo sapiens

<400> 11

Gly Leu Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu
 1 5 10 15

Asp Leu Gln Asn Asn Asp Ile Ser Glu Leu
 20 25

<210> 12

<211> 26

<212> PRT

<213> Homo sapiens

<400> 12

Leu Thr Gly Ile Pro Lys Asp Leu Pro Glu Thr Leu Asn Glu Leu His
 1 5 10 15

Leu Asp His Asn Lys Ile Gln Ala Ile Glu
 20 25

<210> 13

<211> 22

<212> PRT

<213> Homo sapiens

<400> 13

Lys Arg Ile Ser Glu Ala Lys Leu Thr Gly Ile Pro Lys Asp Leu Pro
 1 5 10 15

Glu Thr Leu Asn Glu Leu
 20

<210> 14

<211> 14

<212> PRT

<213> Homo sapiens

<400> 14

Gln Ala Ile Glu Leu Glu Asp Leu Leu Arg Tyr Ser Lys Leu
 1 5 10

<210> 15

<211> 12

<212> PRT

<213> Homo sapiens

<400> 15

Gln Ala Ile Glu Leu Glu Asp Leu Leu Arg Tyr Ser
 1 5 10

<210> 16

<211> 19

<212> PRT

<213> Homo sapiens

<400> 16

Ser Glu Ala Lys Leu Thr Gly Ile Pro Lys Asp Leu Pro Glu Thr Leu
 1 5 10 15

Asn Glu Leu

<210> 17

<211> 25

<212> PRT

<213> Homo sapiens

<400> 17

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

Leu	Gln	Asn	Asn	Asp	Ile	Ser	Glu	Leu
		20					25	

<210> 18

<211> 18

<212> PRT

<213> Homo sapiens

<400> 18

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

Asp Phe

<210> 19

<211> 12

<212> PRT

<213> Homo sapiens

<400> 19

Ala	Ile	Glu	Leu	Glu	Asp	Leu	Leu	Arg	Tyr	Ser	Lys
1				5					10		

<210> 20

<211> 15

<212> PRT

<213> Homo sapiens

<400> 20

Glu	Asn	Ser	Gly	Phe	Glu	Pro	Gly	Ala	Phe	Asp	Gly	Leu	Lys	Leu
1				5					10				15	

<210> 21

<211> 13

<212> PRT

<213> Homo sapiens

<400> 21

Met	Ile	Val	Ile	Glu	Leu	Gly	Thr	Asn	Pro	Leu	Lys	Ser
1				5					10			

<210> 22

<211> 13

<212> PRT

<213> Homo sapiens

<400> 22

Met	Ile	Val	Ile	Glu	Leu	Gly	Thr	Asn	Pro	Leu	Lys	Ser
1				5					10			

<210> 23

<211> 17

<212> PRT

<213> Homo sapiens

<400> 23

Glu	Leu	His	Leu	Asp	Gly	Asn	Lys	Ile	Ser	Arg	Val	Asp	Ala	Ala	Ser
1			5						10					15	

Leu

<210> 24

<211> 18

<212> PRT

<213> Homo sapiens

<400> 24

Leu	Val	Asn	Asn	Lys	Ile	Ser	Lys	Val	Ser	Pro	Gly	Ala	Phe	Thr	Pro
1			5						10					15	

Leu Val

<210> 25

<211> 26

<212> PRT

<213> Homo sapiens

<400> 25

Ala	Leu	Ile	Leu	Val	Asn	Asn	Lys	Ile	Ser	Lys	Val	Ser	Pro	Gly	Ala
1			5						10					15	

Phe	Thr	Pro	Leu	Val	Lys	Leu	Glu	Arg	Leu
		20					25		

<210> 26

<211> 17

<212> PRT

<213> Homo sapiens

<400> 26

Phe	Ser	Asn	Pro	Val	Gln	Tyr	Trp	Glu	Ile	Gln	Pro	Ser	Thr	Phe	Arg
1			5						10					15	

Cys

<210> 27

<211> 15

<212> PRT

<213> Homo sapiens

<400> 27

Lys	Ser	Ser	Gly	Ile	Glu	Asn	Gly	Ala	Phe	Gln	Gly	Met	Lys	Lys
1			5						10					15

<210> 28

<211> 18

<212> PRT

<213> Homo sapiens

<400> 28

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

Ser Tyr

<210> 29

<211> 13

<212> PRT

<213> Homo sapiens

<400> 29

Asn Lys Ile Thr Glu Ile Lys Asp Gly Asp Phe Lys Asn
1 5 10

<210> 30

<211> 17

<212> PRT

<213> Homo sapiens

<400> 30

Gln Gly Leu Pro Pro Ser Leu Thr Glu Leu His Leu Asp Gly Asn Lys
1 5 10 15

Ile

<210> 31

<211> 12

<212> PRT

<213> Homo sapiens

<400> 31

Lys Leu Leu Ala Ser Asp Ala Gly Leu Tyr Arg Cys
1 5 10

<210> 32

<211> 13

<212> PRT

<213> Homo sapiens

<400> 32

Leu Ala Thr Val Gly Glu Leu Gln Ala Ala Trp Arg Asn
1 5 10

<210> 33

<211> 15

<212> PRT

<213> Homo sapiens

<400> 33

Lys Glu Thr Thr Val Leu Val Ala Gln Asn Gly Asn Ile Lys Ile
1 5 10 15

<210> 34

<211> 12

<212> PRT

<213> Homo sapiens

<400> 34

Ser Leu Glu Asp Leu Gln Leu Thr His Asn Lys Ile
1 5 10

<210> 35

<211> 13

<212> PRT

<213> Homo sapiens

<400> 35

Arg Leu Lys Glu Asp Ala Val Ser Ala Ala Phe Lys Gly
1 5 10

<210> 36

<211> 16

<212> PRT

<213> Homo sapiens

<400> 36

Arg Ser Ile Glu Tyr Ser Pro Gln Leu Glu Asp Ala Gly Ser Arg Glu
1 5 10 15

<210> 37

<211> 12

<212> PRT

<213> Homo sapiens

<400> 37

Arg Leu Glu Gly Asp Thr Leu Ile Ile Pro Arg Val
1 5 10

<210> 38

<211> 15

<212> PRT

<213> Homo sapiens

<400> 38

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

<210> 39

<211> 16

<212> PRT

<213> Homo sapiens

<400> 39

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

<210> 40

<211> 12

<212> PRT

<213> Homo sapiens

<400> 40

Arg Ser Ile Glu Tyr Ser Pro Gln Leu Glu Asp Ala
1 5 10

<210> 41

<211> 22

<212> PRT

<213> Homo sapiens

<400> 41

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

Asn Asn Asp Ile Ser Glu
20

<210> 42

<211> 23

<212> PRT

<213> Homo sapiens

<400> 42

Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp Leu
1 5 10 15

Gln Asn Asn Asp Ile Ser Glu
20

<210> 43

<211> 23

<212> PRT

<213> Homo sapiens

<400> 43

Asn Ser Gly Phe Glu Pro Gly Ala Phe Asp Gly Leu Lys Leu Asn Tyr
1 5 10 15

Leu Arg Ile Ser Glu Ala Lys
20

<210> 44

<211> 24

<212> PRT

<213> Homo sapiens

<400> 44

Leu Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp
1 5 10 15

Leu Gln Asn Asn Asp Ile Ser Glu
20

<210> 45

<211> 18

<212> PRT

<213> Homo sapiens

<400> 45

Leu Arg Ile Ser Glu Ala Lys Leu Thr Gly Ile Pro Lys Asp Leu Pro
1 5 10 15

Glu Thr

<210> 46

<211> 24

<212> PRT

<213> Homo sapiens

<400> 46

Leu Lys Ser Val Pro Lys Glu Ile Ser Pro Asp Thr Thr Leu Leu Asp
 1 5 10 15

Leu Gln Asn Asn Asp Ile Ser Glu
 20

<210> 47

<211> 26

<212> PRT

<213> Homo sapiens

<400> 47

Leu Thr Gly Ile Pro Lys Asp Leu Pro Glu Thr Leu Asn Glu Leu His
 1 5 10 15

Leu Asp His Asn Lys Ile Gln Ala Ile Glu
 20 25

<210> 48

<211> 11

<212> PRT

<213> Homo sapiens

<400> 48

Ile Val Ile Glu Leu Gly Thr Asn Pro Leu Lys
 1 5 10

<210> 49

<211> 10

<212> PRT

<213> Homo sapiens

<400> 49

Leu Leu Ala Ser Asp Ala Gly Leu Tyr Arg
 1 5 10

<210> 50

<211> 12

<212> PRT

<213> Homo sapiens

<400> 50

Leu Ala Thr Val Gly Glu Leu Gln Ala Ala Trp Arg
 1 5 10

<210> 51

<211> 13

<212> PRT

<213> Homo sapiens

<400> 51

Glu Thr Thr Val Leu Val Ala Gln Asn Gly Asn Ile Lys
 1 5 10

<210> 52

<211> 11

<212> PRT

<213> Homo sapiens

<400> 52

Ser Leu Glu Asp Leu Gln Leu Thr His Asn Lys
 1 5 10

<210> 53

<211> 11

<212> PRT

<213> Homo sapiens

<400> 53

Leu Lys Glu Asp Ala Val Ser Ala Ala Phe Lys
 1 5 10

<210> 54

<211> 14

<212> PRT

<213> Homo sapiens

<400> 54

Ser Ile Glu Tyr Ser Pro Gln Leu Glu Asp Ala Gly Ser Arg
 1 5 10

<210> 55

<211> 10

<212> PRT

<213> Homo sapiens

<400> 55

Leu Glu Gly Asp Thr Leu Ile Ile Pro Arg
 1 5 10

<210> 56

<211> 20

<212> PRT

<213> Homo sapiens

<400> 56

Arg Ile Ser Glu Ala Lys Leu Thr Gly Ile Pro Lys Asp Leu Pro Glu
 1 5 10 15

Thr Leu Asn Glu
 20

<210> 57

<211> 12

<212> PRT

<213> Homo sapiens

<400> 57

Ala Ile Glu Leu Glu Asp Leu Leu Arg Tyr Ser Lys
 1 5 10

<210> 58

<211> 10

<212> PRT

<213> Homo sapiens

<400> 58

Ala Ile Glu Leu Glu Asp Leu Leu Arg Tyr Ser Lys
 1 5 10

Ala Ile Glu Leu Glu Asp Leu Leu Arg Tyr
1 5 10

<210> 59

<211> 17

<212> PRT

<213> Homo sapiens

<400> 59

Glu Ala Lys Leu Thr Gly Ile Pro Lys Asp Leu Pro Glu Thr Leu Asn
1 5 10 15

Glu

<210> 60

<211> 24

<212> PRT

<213> Homo sapiens

<400> 60

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

Leu Gln Asn Asn Asp Ile Ser Glu
20

<210> 61

<211> 16

<212> PRT

<213> Homo sapiens

<400> 61

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

<210> 62

<211> 10

<212> PRT

<213> Homo sapiens

<400> 62

Ile Glu Leu Glu Asp Leu Leu Arg Tyr Ser
1 5 10

<210> 63

<211> 13

<212> PRT

<213> Homo sapiens

<400> 63

Asn Ser Gly Phe Glu Pro Gly Ala Phe Asp Gly Leu Lys
1 5 10

<210> 64

<211> 14

<212> PRT

<213> Homo sapiens

<400> 64

Asp Glu Ala Ser Gly Ile Gly Pro Glu Val Pro Asp Asp Arg

1 5 10

<210> 65

<211> 15

<212> PRT

<213> Homo sapiens

<400> 65

Leu His Leu Asp Gly Asn Lys Ile Ser Arg Val Asp Ala Ala Ser
1 5 10 15

<210> 66

<211> 16

<212> PRT

<213> Homo sapiens

<400> 66

Val Asn Asn Lys Ile Ser Lys Val Ser Pro Gly Ala Phe Thr Pro Leu
1 5 10 15

<210> 67

<211> 24

<212> PRT

<213> Homo sapiens

<400> 67

Leu Ile Leu Val Asn Asn Lys Ile Ser Lys Val Ser Pro Gly Ala Phe
1 5 10 15

Thr Pro Leu Val Lys Leu Glu Arg
20

<210> 68

<211> 15

<212> PRT

<213> Homo sapiens

<400> 68

Ser Asn Pro Val Gln Tyr Trp Glu Ile Gln Pro Ser Thr Phe Arg
1 5 10 15

<210> 69

<211> 13

<212> PRT

<213> Homo sapiens

<400> 69

Ser Ser Gly Ile Glu Asn Gly Ala Phe Gln Gly Met Lys
1 5 10

<210> 70

<211> 16

<212> PRT

<213> Homo sapiens

<400> 70

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

<210> 71

<211> 11

<212> PRT

<213> Homo sapiens

<400> 71

Lys	Ile	Thr	Glu	Ile	Lys	Asp	Gly	Asp	Phe	Lys
1				5					10	

<210> 72

<211> 15

<212> PRT

<213> Homo sapiens

<400> 72

Gly	Leu	Pro	Pro	Ser	Leu	Thr	Glu	Leu	His	Leu	Asp	Gly	Asn	Lys
1				5					10				15	

<210> 73

<211> 14

<212> PRT

<213> Homo sapiens

<400> 73

Val	Ser	Glu	Ala	Val	Val	Glu	Lys	Leu	Glu	Pro	Glu	Tyr	Arg
1				5					10				

<210> 74

<211> 15

<212> PRT

<213> Homo sapiens

<400> 74

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

<210> 75

<211> 17

<212> PRT

<213> Homo sapiens

<400> 75

Ser	Ile	Glu	Tyr	Ser	Pro	Gln	Leu	Glu	Asp	Ala	Ser	Ala	Lys	Glu	Phe
1				5					10				15		

Arg

<210> 76

<211> 6

<212> PRT

<213> Homo sapiens

<400> 76

Ser	Val	Pro	Lys	Glu	Ile
1				5	

<210> 77

<211> 6

<212> PRT

<213> Homo sapiens

<400> 77

Asn Ser Gly Phe Glu Pro
1 5

<210> 78

<211> 6

<212> PRT

<213> Homo sapiens

<400> 78

Leu Lys Ser Val Pro Lys
1 5

<210> 79

<211> 6

<212> PRT

<213> Homo sapiens

<400> 79

Leu Arg Ile Ser Glu Ala
1 5

<210> 80

<211> 6

<212> PRT

<213> Homo sapiens

<400> 80

Gly Leu Lys Leu Asn Tyr
1 5

<210> 81

<211> 6

<212> PRT

<213> Homo sapiens

<400> 81

Leu Lys Ser Val Pro Lys
1 5

<210> 82

<211> 6

<212> PRT

<213> Homo sapiens

<400> 82

Gln Cys Ser Asp Leu Gly
1 5

<210> 83

<211> 6

<212> PRT

<213> Homo sapiens

<400> 83

Leu Thr Gly Ile Pro Lys
1 5

<210> 84

<211> 6

<212> PRT

<213> Homo sapiens

<400> 84

Arg Ile Ser Glu Ala Lys
1 5

<210> 85

<211> 6

<212> PRT

<213> Homo sapiens

<400> 85

Ala Ile Glu Leu Glu Asp
1 5

<210> 86

<211> 6

<212> PRT

<213> Homo sapiens

<400> 86

Glu Ala Lys Leu Thr Gly
1 5

<210> 87

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Leu Lys Ala Val Pro Lys
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Leu Leu Asp Leu Gln Asn
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<400> 89

Ile Glu Leu Glu Asp Leu
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Asn Ser Gly Phe Glu Pro
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Ile Val Ile Glu Leu Gly
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Asn Gly Leu Asn Gln Met
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Asp Glu Ala Ser Gly Ile
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Leu His Leu Asp Gly Asn
1 5

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Val Asn Asn Lys Ile Ser
1 5

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Leu Ile Leu Val Asn Asn
1 5

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Ser Asn Pro Val Gln Tyr
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Ser Ser Gly Ile Glu Asn
1 5

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Lys Ile Thr Glu Ile Lys
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Gly Leu Pro Pro Ser Leu
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Leu Leu Ala Ser Asp Ala
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Leu Ala Thr Val Gly Glu

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Glu Thr Thr Val Leu Val
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Ser Leu Thr Val Val Lys
1 5

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Glu Asn Gln Asp Ala Arg
1 5

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Asn Gly Phe Asp Gln Cys
1 5

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Ser Leu Glu Asp Leu Gln
1 5

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Leu Lys Glu Asp Ala Val
1 5

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His Leu Gln His Asn Arg
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Leu Gln His Asn Arg Leu
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Ser Ile Glu Tyr Ser Pro
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Leu Val Asn Phe Thr Arg
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Val Ser Glu Ala Val Val
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Glu Val Ser Glu Ala Val
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Ser Ile Glu Tyr Ser Pro

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Asn Asn Asp Ile Ser Glu

1 5

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<400> 117

Arg Ile Ser Glu Ala Lys

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Leu Arg Lys Asp Asp Phe

1 5

<210> 119

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<213> Homo sapiens

<400> 119

Lys Asp Leu Pro Glu Thr

1 5

<210> 120

<211> 6

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<213> Homo sapiens

<400> 120

Leu Asn Glu Leu His Leu

1 5

<210> 121

<211> 6

<212> PRT

<213> Homo sapiens

<400> 121

Tyr Trp Glu Val Gln Pro

1 5

<210> 122

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<213> Homo sapiens

<400> 122

Lys Ile Gln Ala Ile Glu
1 5

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<213> Homo sapiens

<400> 123

Pro Glu Thr Leu Asn Glu
1 5

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<213> Homo sapiens

<400> 124

Leu Leu Arg Tyr Ser Lys
1 5

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Glu Asp Leu Leu Arg Tyr
1 5

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Asn Asn Asp Ile Ser Glu
1 5

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<400> 127

Glu Leu Arg Lys Asp Asp
1 5

<210> 128

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<213> Homo sapiens

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Asp Leu Leu Arg Tyr Ser
1 5

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Ala Phe Asp Gly Leu Lys
1 5

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<400> 130

Gly Thr Asn Pro Leu Lys
1 5

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<213> Homo sapiens

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Ser Ser Gly Ile Glu Asn
1 5

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<400> 132

Glu Val Pro Asp Asp Arg
1 5

<210> 133

<211> 6

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<400> 133

Arg Val Asp Ala Ala Ser
1 5

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<211> 6

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<213> Homo sapiens

<400> 134

Gly Ala Phe Thr Pro Leu

1 - 5

<210> 135

<211> 6

<212> PRT

<213> Homo sapiens

<400> 135

Leu Val Lys Leu Glu Arg
1 5

<210> 136

<211> 6

<212> PRT

<213> Homo sapiens

<400> 136

Gln Pro Ser Thr Phe Arg
1 5

<210> 137

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<213> Homo sapiens

<400> 137

Ala Phe Gln Gly Met Lys
1 5

<210> 138

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<213> Homo sapiens

<400> 138

Gly Met Lys Lys Leu Ser
1 5

<210> 139

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<212> PRT

<213> Homo sapiens

<400> 139

Lys Asp Gly Asp Phe Lys
1 5

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<213> Homo sapiens

<400> 140

His Leu Asp Gly Asn Lys
1 5

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<213> Homo sapiens

<400> 141

Cys Asp Val Met Tyr Gly
1 5

<210> 142

<211> 6

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<213> Homo sapiens

<400> 142

Asn Gly Phe Asp Gln Cys
1 5

<210> 143

<211> 6

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<213> Homo sapiens

<400> 143

Gln Asn Gly Ile Asn Lys
1 5

<210> 144

<211> 6

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<213> Homo sapiens

<400> 144

Ile Gly Gln Asp Tyr Lys
1 5

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<400> 145

Gln Leu Thr His Asn Lys
1 5

<210> 146

<211> 6

<212> PRT

<213> Homo sapiens

<400> 146

Val Ser Ala Ala Phe Lys
1 5

<210> 147

<211> 6

<212> PRT

<213> Homo sapiens

<400> 147

Gly Leu Lys Ser Leu Glu
1 5

<210> 148

<211> 6

<212> PRT

<213> Homo sapiens

<400> 148

Glu Asp Ala Gly Ser Arg
1 5

<210> 149

<211> 6

<212> PRT

<213> Homo sapiens

<400> 149

Glu Phe Arg Glu Val Ser
1 5

<210> 150

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<212> PRT

<213> Homo sapiens

<400> 150

Val Ala Gln Gln Asp Ser
1 5

<210> 151

<211> 6

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<213> Homo sapiens

<400> 151

Leu Glu Pro Glu Tyr Arg
1 5

<210> 152

<211> 6

<212> PRT

<213> Homo sapiens

<400> 152

Ser Ala Lys Glu Phe Arg
1 5

<210> 153

<211> 1466

<212> PRT

<213> Homo sapiens

<400> 153

Met Met Ser Phe Val Gln Lys Gly Ser Trp Leu Leu Leu Ala Leu Leu

His Pro Thr Ile Ile Leu Ala Gln Gln Glu Ala Val Glu Gly Gly Cys
 20 25 30
 Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu
 35 40 45
 Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
 50 55 60
 Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
 65 70 75 80
 Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
 85 90 95
 Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
 100 105 110
 Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln
 115 120 125
 Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys
 130 135 140
 Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val
 145 150 155 160
 Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala
 165 170 175
 Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly
 180 185 190
 Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
 195 200 205
 Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
 210 215 220
 Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
 225 230 235 240
 Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile
 245 250 255
 Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
 260 265 270
 Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
 275 280 285
 Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
 290 295 300
 Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
 305 310 315 320
 Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
 325 330 335
 Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
 340 345 350
 Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg
 355 360 365
 Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly
 370 375 380
 Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
 385 390 395 400
 Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
 405 410 415
 Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly
 420 425 430
 Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu
 435 440 445

Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp
 450 455 460
 Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
 465 470 475 480
 Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro
 485 490 495
 Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro
 500 505 510
 Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly
 515 520 525
 Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly
 530 535 540
 Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser
 545 550 555 560
 Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly
 565 570 575
 Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
 580 585 590
 Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro
 595 600 605
 Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
 610 615 620
 Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
 625 630 635 640
 Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro
 645 650 655
 Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly
 660 665 670
 Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu
 675 680 685
 Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
 690 695 700
 Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly
 705 710 715 720
 Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser
 725 730 735
 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp
 740 745 750
 Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
 755 760 765
 Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala
 770 775 780
 Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
 785 790 795 800
 Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
 805 810 815
 Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu
 820 825 830
 Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser
 835 840 845
 Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
 850 855 860
 Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu
 865 870 875 880

Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
 885 890 895
 Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly
 900 905 910
 Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln
 915 920 925
 Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro
 930 935 940
 Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly
 945 950 955 960
 Pro Pro Gly Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
 965 970 975
 Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg
 980 985 990
 Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly
 995 1000 1005
 Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly
 1010 1015 1020
 Arg Asp Gly Ser Pro Gly Gly Lys Gly Asp Arg Gly Glu Asn Gly
 1025 1030 1035
 Ser Pro Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly
 1040 1045 1050
 Pro Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Ser Gly
 1055 1060 1065
 Pro Ala Gly Pro Ala Gly Ala Pro Gly Pro Ala Gly Ser Arg Gly
 1070 1075 1080
 Ala Pro Gly Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly
 1085 1090 1095
 Glu Arg Gly Ala Ala Gly Ile Lys Gly His Arg Gly Phe Pro Gly
 1100 1105 1110
 Asn Pro Gly Ala Pro Gly Ser Pro Gly Pro Ala Gly Gln Gln Gly
 1115 1120 1125
 Ala Ile Gly Ser Pro Gly Pro Ala Gly Pro Arg Gly Pro Val Gly
 1130 1135 1140
 Pro Ser Gly Pro Pro Gly Lys Asp Gly Thr Ser Gly His Pro Gly
 1145 1150 1155
 Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn Arg Gly Glu Arg Gly
 1160 1165 1170
 Ser Glu Gly Ser Pro Gly His Pro Gly Gln Pro Gly Pro Pro Gly
 1175 1180 1185
 Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val Gly Ala Ala
 1190 1195 1200
 Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe Ala Pro
 1205 1210 1215
 Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp Glu
 1220 1225 1230
 Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
 1235 1240 1245
 Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg
 1250 1255 1260
 Asp Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp
 1265 1270 1275
 Val Asp Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe
 1280 1285 1290

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Cys Asn Met Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu
1295                      1300                      1305

Asn Val Pro Arg Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys
1310                      1315                      1320

Lys His Val Trp Phe Gly Glu Ser Met Asp Gly Gly Phe Gln Phe
1325                      1330                      1335

Ser Tyr Gly Asn Pro Glu Leu Pro Glu Asp Val Leu Asp Val Gln
1340                      1345                      1350

Leu Ala Phe Leu Arg Leu Leu Ser Ser Arg Ala Ser Gln Asn Ile
1355                      1360                      1365

Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp Gln Ala Ser
1370                      1375                      1380

Gly Asn Val Lys Lys Ala Leu Lys Leu Met Gly Ser Asn Glu Gly
1385                      1390                      1395

Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe Thr Tyr Thr Val Leu
1400                      1405                      1410

Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp Ser Lys Thr Val
1415                      1420                      1425

Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro Ile Val Asp
1430                      1435                      1440

Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe Gly Val
1445                      1450                      1455

Asp Val Gly Pro Val Cys Phe Leu
1460                      1465

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<210> 154

<211> 20

<212> PRT

<213> Homo sapiens

<400> 154

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Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
1           5           10           15

Gly Pro Ala Gly
20

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<210> 155

<211> 19

<212> PRT

<213> Homo sapiens

<400> 155

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Lys Gly Asp Pro Gly Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro
1           5           10           15

Gly Ile Pro

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<210> 156

<211> 20

<212> PRT

<213> Homo sapiens

<400> 156

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

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Pro Gln Gly Val
20

<210> 157

<211> 21

<212> PRT

<213> Homo sapiens

<400> 157

Gly Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly
1 5 10 15

Ile Pro Gly Phe Pro
20

<210> 158

<211> 22

<212> PRT

<213> Homo sapiens

<400> 158

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly
1 5 10 15

Met Pro Gly Pro Arg Gly
20

<210> 159

<211> 23

<212> PRT

<213> Homo sapiens

<400> 159

Gly Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly
1 5 10 15

Ser Pro Gly Pro Ala Gly Gln
20

<210> 160

<211> 23

<212> PRT

<213> Homo sapiens

<400> 160

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

Pro Gly Pro Gln Gly Val Lys
20

<210> 161

<211> 25

<212> PRT

<213> Homo sapiens

<400> 161

Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro
1 5 10 15

Arg Gly Ser Pro Gly Pro Gln Gly Val
20 25

40

43

<210> 162

<211> 26

<212> PRT

<213> Homo sapiens

<400> 162

Ile	Thr	Gly	Ala	Arg	Gly	Leu	Ala	Gly	Pro	Pro	Gly	Met	Pro	Gly	Pro
1				5					10					15	
Arg	Gly	Ser	Pro	Gly	Pro	Gln	Gly	Val	Lys						
			20					25							

<210> 163

<211> 26

<212> PRT

<213> Homo sapiens

<400> 163

Gly	Ile	Thr	Gly	Ala	Arg	Gly	Leu	Ala	Gly	Pro	Pro	Gly	Met	Pro	Gly
1				5					10					15	
Pro	Arg	Gly	Ser	Pro	Gly	Pro	Gln	Gly	Val						
			20					25							

<210> 164

<211> 26

<212> PRT

<213> Homo sapiens

<400> 164

Gly	Val	Lys	Gly	Glu	Ser	Gly	Lys	Pro	Gly	Ala	Asn	Gly	Leu	Ser	Gly
1				5					10					15	
Glu	Arg	Gly	Pro	Pro	Gly	Pro	Gln	Gly	Leu						
			20					25							

<210> 165

<211> 26

<212> PRT

<213> Homo sapiens

<400> 165

Gly	Ser	Arg	Gly	Ala	Pro	Gly	Pro	Gln	Gly	Pro	Arg	Gly	Asp	Lys	Gly
1				5					10					15	
Glu	Thr	Gly	Glu	Arg	Gly	Ala	Ala	Gly	Ile						
			20					25							

<210> 166

<211> 28

<212> PRT

<213> Homo sapiens

<400> 166

Pro	Lys	Gly	Asp	Ala	Gly	Gln	Pro	Gly	Glu	Lys	Gly	Ser	Pro	Gly	Ala
1				5					10					15	
Gln	Gly	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Leu	Gly	Ile				
			20					25							

<210> 167

<211> 27

<212> PRT

<213> Homo sapiens

<400> 167

Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly
 1 5 10 15

Pro Arg Gly Ser Pro Gly Pro Gln Gly Val Lys
 20 25

<210> 168

<211> 32

<212> PRT

<213> Homo sapiens

<400> 168

Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu Gly Gly Lys Gly
 1 5 10 15

Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly Thr Pro Gly Leu
 20 25 30

<210> 169

<211> 35

<212> PRT

<213> Homo sapiens

<400> 169

Gly His Ala Gly Ala Gln Gly Pro Pro Gly Pro Pro Gly Ile Asn Gly
 1 5 10 15

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

Pro Gly Leu
 35

<210> 170

<211> 48

<212> PRT

<213> Homo sapiens

<400> 170

Ala Gly Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro Ala
 1 5 10 15

Gly Ala Pro Gly Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln Gly
 20 25 30

Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly Ile
 35 40 45

<210> 171

<211> 50

<212> PRT

<213> Homo sapiens

<400> 171

Gly Leu Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly
 1 5 10 15

Lys Pro Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala
20 25 30

Pro Gly Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro
35 40 45

Gly Leu
50

<210> 172

<211> 21

<212> PRT

<213> Homo sapiens

<400> 172

Gly Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly
1 5 10 15

Ile Pro Gly Phe Pro
20

<210> 173

<211> 24

<212> PRT

<213> Homo sapiens

<400> 173

Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly
1 5 10 15

Pro Pro Gly Pro Pro Gly Thr Ser
20

<210> 174

<211> 24

<212> PRT

<213> Homo sapiens

<400> 174

Lys Asp Gly Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro
1 5 10 15

Arg Gly Asn Arg Gly Glu Arg Gly
20

<210> 175

<211> 29

<212> PRT

<213> Homo sapiens

<400> 175

Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly
1 5 10 15

Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly Ser
20 25

<210> 176

<211> 29

<212> PRT

<213> Homo sapiens

<400> 176

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly
 1 5 10 15

Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
 20 25

<210> 177

<211> 31

<212> PRT

<213> Homo sapiens

<400> 177

Ala Pro Gly Ala Pro Gly Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu
 1 5 10 15

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

<210> 178

<211> 32

<212> PRT

<213> Homo sapiens

<400> 178

Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly
 1 5 10 15

Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly Ser Pro Gly Ser
 20 25 30

<210> 179

<211> 22

<212> PRT

<213> Homo sapiens

<400> 179

Ala Ile Gly Ser Pro Gly Pro Ala Gly Pro Arg Gly Pro Val Gly Pro
 1 5 10 15

Ser Gly Pro Pro Gly Lys
 20

<210> 180

<211> 23

<212> PRT

<213> Homo sapiens

<400> 180

Gly Ala Ile Gly Ser Pro Gly Pro Ala Gly Pro Arg Gly Pro Val Gly
 1 5 10 15

Pro Ser Gly Pro Pro Gly Lys
 20

<210> 181

<211> 15

<212> PRT

<213> Homo sapiens

<400> 181

Pro Ala Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala Gly

1 - 5 - 10 - 15

<210> 182

<211> 20

<212> PRT

<213> Homo sapiens

<400> 182

Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser Gly Pro Ala
1 5 10 15

Gly Pro Pro Gly
20

<210> 183

<211> 19

<212> PRT

<213> Homo sapiens

<400> 183

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

Gln Gly Val

<210> 184

<211> 19

<212> PRT

<213> Homo sapiens

<400> 184

Gly Leu Ser Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly
1 5 10 15

Leu Ala Gly

<210> 185

<211> 21

<212> PRT

<213> Homo sapiens

<400> 185

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

Gly Pro Gln Gly Val
20

<210> 186

<211> 21

<212> PRT

<213> Homo sapiens

<400> 186

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

Pro Gln Gly Val Lys
20

<210> 187

<211> 22

<212> PRT

<213> Homo sapiens

<400> 187

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

Gly	Pro	Gln	Gly	Val	Lys
			20		

<210> 188

<211> 21

<212> PRT

<213> Homo sapiens

<400> 188

Gly	Pro	Gln	Gly	Pro	Pro	Gly	Lys	Asn	Gly	Glu	Thr	Gly	Pro	Gln	Gly
1				5					10					15	

Pro	Pro	Gly	Pro	Thr
			20	

<210> 189

<211> 22

<212> PRT

<213> Homo sapiens

<400> 189

Gly	Val	Lys	Gly	Glu	Arg	Gly	Ser	Pro	Gly	Gly	Pro	Gly	Ala	Ala	Gly
1				5					10					15	

Phe	Pro	Gly	Ala	Arg	Gly
			20		

<210> 190

<211> 22

<212> PRT

<213> Homo sapiens

<400> 190

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

Pro	Gly	Pro	Gln	Gly	Val
			20		

<210> 191

<211> 23

<212> PRT

<213> Homo sapiens

<400> 191

Asn	Gly	Leu	Ser	Gly	Glu	Arg	Gly	Pro	Pro	Gly	Pro	Gln	Gly	Leu	Pro
1				5					10					15	

Gly	Leu	Ala	Gly	Thr	Ala	Gly
			20			

<210> 192

<211> 24

<212> PRT

<213> Homo sapiens

<400> 192

Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly
 1 5 10 15

Pro Pro Gly Pro Pro Gly Thr Ser
 20

<210> 193

<211> 24

<212> PRT

<213> Homo sapiens

<400> 193

Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro Ala Gly Ile Pro Gly
 1 5 10 15

Ala Pro Gly Leu Met Gly Ala Arg
 20

<210> 194

<211> 24

<212> PRT

<213> Homo sapiens

<400> 194

Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro Arg
 1 5 10 15

Gly Ser Pro Gly Pro Gln Gly Val
 20

<210> 195

<211> 25

<212> PRT

<213> Homo sapiens

<400> 195

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

Arg Gly Pro Pro Gly Pro Gln Gly Leu
 20 25

<210> 196

<211> 53

<212> PRT

<213> Homo sapiens

<400> 196

Gly Val Lys Gly Glu Arg Gly Ser Pro Gly Gly Pro Gly Ala Ala Gly
 1 5 10 15

Phe Pro Gly Ala Arg Gly Leu Pro Gly Pro Pro Gly Ser Asn Gly Asn
 20 25 30

Pro Gly Pro Pro Gly Pro Ser Gly Ser Pro Gly Lys Asp Gly Pro Pro
 35 40 45

Gly Pro Ala Gly Asn
 50

<210> 197

<211> 32

<212> PRT

<213> Homo sapiens

<400> 197

Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly
 1 5 10 15
 Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met
 20 25 30

<210> 198

<211> 32

<212> PRT

<213> Homo sapiens

<400> 198

Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly Val Ala
 1 5 10 15
 Gly Pro Pro Gly Gly Ser Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly
 20 25 30

<210> 199

<211> 32

<212> PRT

<213> Homo sapiens

<400> 199

Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly Val Ala
 1 5 10 15
 Gly Pro Pro Gly Gly Ser Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly
 20 25 30

<210> 200

<211> 29

<212> PRT

<213> Homo sapiens

<400> 200

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly
 1 5 10 15
 Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
 20 25

<210> 201

<211> 14

<212> PRT

<213> Homo sapiens

<400> 201

Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe Pro Gly Met
 1 5 10

<210> 202

<211> 14

<212> PRT

<213> Homo sapiens

<400> 202

Gly Gln Pro Gly Val Met Gly Phe Pro Gly Pro Lys Gly Asn
1 5 10

<210> 203

<211> 16

<212> PRT

<213> Homo sapiens

<400> 203

Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe Pro Gly Met Lys Gly
1 5 10 15

<210> 204

<211> 17

<212> PRT

<213> Homo sapiens

<400> 204

Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe Pro Gly Met Lys Gly
1 5 10 15

His

<210> 205

<211> 19

<212> PRT

<213> Homo sapiens

<400> 205

Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro Gly Pro
1 5 10 15

Ala Gly Ala

<210> 206

<211> 19

<212> PRT

<213> Homo sapiens

<400> 206

Gly Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly
1 5 10 15

Ile Pro Gly

<210> 207

<211> 20

<212> PRT

<213> Homo sapiens

<400> 207

Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro Gly
1 5 10 15

Pro Ala Gly Ala
20

<210> 208

<211> 20

<212> PRT

<213> Homo sapiens

<400> 208

Gly Phe Arg Gly Pro Ala Gly Pro Asn Gly Ile Pro Gly Glu Lys Gly
 1 5 10 15

Pro Ala Gly Glu
 20

<210> 209

<211> 20

<212> PRT

<213> Homo sapiens

<400> 209

Pro Gly Ile Pro Gly Gln Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro
 1 5 10 15

Gly Ile Cys Glu
 20

<210> 210

<211> 21

<212> PRT

<213> Homo sapiens

<400> 210

Gly Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly
 1 5 10 15

Ile Pro Gly Phe Pro
 20

<210> 211

<211> 23

<212> PRT

<213> Homo sapiens

<400> 211

Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly
 1 5 10 15

Pro Pro Gly Pro Pro Gly Thr
 20

<210> 212

<211> 23

<212> PRT

<213> Homo sapiens

<400> 212

Gly Val Lys Gly Glu Arg Gly Ser Pro Gly Gly Pro Gly Ala Ala Gly
 1 5 10 15

Phe Pro Gly Ala Arg Gly Leu
 20

<210> 213

<211> 26

<212> PRT

<213> Homo sapiens

<400> 213

Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Gly Lys Gly Asp Ala Gly
 1 5 10 15

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

<210> 214

<211> 25

<212> PRT

<213> Homo sapiens

<400> 214

Gln Gly Pro Pro Gly Pro Thr Gly Pro Gly Gly Asp Lys Gly Asp Thr
 1 5 10 15

Gly Pro Pro Gly Pro Gln Gly Leu Gln
 20 25

<210> 215

<211> 25

<212> PRT

<213> Homo sapiens

<400> 215

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

Ile Pro Gly Ala Pro Gly Leu Met Gly
 20 25

<210> 216

<211> 26

<212> PRT

<213> Homo sapiens

<400> 216

Gln Gly Pro Pro Gly Glu Pro Gly Gln Ala Gly Pro Ser Gly Pro Pro
 1 5 10 15

Gly Pro Pro Gly Ala Ile Gly Pro Ser Gly
 20 25

<210> 217

<211> 26

<212> PRT

<213> Homo sapiens

<400> 217

Pro Gly Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met
 1 5 10 15

Gly Pro Ala Gly Ile Pro Gly Ala Pro Gly
 20 25

<210> 218

<211> 33

<212> PRT

<213> Homo sapiens

<400> 218

Arg Gly Leu Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro
 1 5 10 15

Gly Pro Ser Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly
 20 25 30

Asn

<210> 219

<211> 32

<212> PRT

<213> Homo sapiens

<400> 219

Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
 1 5 10 15

Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
 20 25 30

<210> 220

<211> 32

<212> PRT

<213> Homo sapiens

<400> 220

Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly
 1 5 10 15

Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly Gln
 20 25 30

<210> 221

<211> 35

<212> PRT

<213> Homo sapiens

<400> 221

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

Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro Gly Pro
 20 25 30

Ala Gly Ala
 35

<210> 222

<211> 36

<212> PRT

<213> Homo sapiens

<400> 222

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

Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro Gly
 20 25 30

Pro Gly Ala
 35

Pro Ala Gly Ala
35

<210> 223

<211> 40

<212> PRT

<213> Homo sapiens

<400> 223

Pro Pro Gly Glu Asn Gly Lys Pro Gly Glu Pro Gly Pro Lys Gly Asp
1 5 10 15
Ala Gly Ala Pro Gly Ala Pro Gly Gly Lys Gly Asp Ala Gly Ala Pro
20 25 30
Gly Glu Arg Gly Pro Pro Gly Leu
35 40

<210> 224

<211> 38

<212> PRT

<213> Homo sapiens

<400> 224

Gly Leu Lys Gly Glu Asn Gly Leu Pro Gly Glu Asn Gly Ala Pro Gly
1 5 10 15
Pro Met Gly Pro Arg Gly Ala Pro Gly Glu Arg Gly Arg Pro Gly Leu
20 25 30
Pro Gly Ala Ala Gly Ala
35

<210> 225

<211> 41

<212> PRT

<213> Homo sapiens

<400> 225

Gly Asn Thr Gly Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly
1 5 10 15
Asp Ala Gly Gln Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro
20 25 30
Pro Gly Ala Pro Gly Pro Leu Gly Ile
35 40

<210> 226

<211> 41

<212> PRT

<213> Homo sapiens

<400> 226

Gly Leu Met Gly Ala Arg Gly Pro Pro Gly Pro Ala Gly Ala Asn Gly
1 5 10 15
Ala Pro Gly Leu Arg Gly Gly Ala Gly Glu Pro Gly Lys Asn Gly Ala
20 25 30
Lys Gly Glu Pro Gly Pro Arg Gly Glu
35 40

<210> 227

<211> 50

<212> PRT

<213> Homo sapiens

<400> 227

Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu Gly Gly Lys Gly
 1 5 10 15

Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly Thr Pro Gly Leu
 20 25 30

Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser Pro Gly Pro Lys
 35 40 45

Gly Asp
 50

<210> 228

<211> 26

<212> PRT

<213> Homo sapiens

<400> 228

Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala Gly Pro Arg Gly
 1 5 10 15

Pro Val Gly Pro Ser Gly Pro Pro Gly Lys
 20 25

<210> 229

<211> 24

<212> PRT

<213> Homo sapiens

<400> 229

Lys Gly Asp Pro Gly Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro
 1 5 10 15

Gly Ile Pro Gly Gln Pro Gly Ser
 20

<210> 230

<211> 26

<212> PRT

<213> Homo sapiens

<400> 230

Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu Gly Gly Lys Gly
 1 5 10 15

Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala
 20 25

<210> 231

<211> 32

<212> PRT

<213> Homo sapiens

<400> 231

Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
 1 5 10 15

Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu

20

25

30

<210> 232

<211> 23

<212> PRT

<213> Homo sapiens

<400> 232

Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln Ala Gly Pro Ser Gly
 1 5 10 15

Pro Pro Gly Pro Pro Gly Ala
 20

<210> 233

<211> 20

<212> PRT

<213> Homo sapiens

<400> 233

Gly Val Ala Gly Pro Pro Gly Gly Ser Gly Pro Ala Gly Pro Pro Gly
 1 5 10 15

Pro Gln Gly Val
 20

<210> 234

<211> 35

<212> PRT

<213> Homo sapiens

<400> 234

Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp Gly Val Pro Gly
 1 5 10 15

Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly Pro Pro Gly Pro
 20 25 30

Ala Gly Gln
 35

<210> 235

<211> 17

<212> PRT

<213> Homo sapiens

<400> 235

Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly Pro Pro Gly Ile Asn
 1 5 10 15

Gly

<210> 236

<211> 11

<212> PRT

<213> Homo sapiens

<400> 236

Ala Gly Glu Arg Gly Ala Pro Gly Pro Ala Gly
 1 5 10

<210> 237

<211> 11

<212> PRT

<213> Homo sapiens

<400> 237

Ala	Gly	Ile	Pro	Gly	Phe	Pro	Gly	Met	Lys	Gly
1				5					10	

<210> 238

<211> 12

<212> PRT

<213> Homo sapiens

<400> 238

Phe	Pro	Gly	Met	Lys	Gly	His	Arg	Gly	Phe	Asp	Gly
1				5					10		

<210> 239

<211> 14

<212> PRT

<213> Homo sapiens

<400> 239

Gly	Phe	Pro	Gly	Ala	Arg	Gly	Leu	Pro	Gly	Pro	Pro	Gly	Ser
1				5					10				

<210> 240

<211> 15

<212> PRT

<213> Homo sapiens

<400> 240

Ala	Gly	Phe	Pro	Gly	Ala	Arg	Gly	Leu	Pro	Gly	Pro	Pro	Gly	Ser
1				5					10				15	

<210> 241

<211> 15

<212> PRT

<213> Homo sapiens

<400> 241

Pro	Pro	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Thr	Ser	Gly	His	Pro	Gly
1				5					10				15	

<210> 242

<211> 13

<212> PRT

<213> Homo sapiens

<400> 242

Gly	Phe	Pro	Gly	Met	Lys	Gly	His	Arg	Gly	Phe	Asp	Gly
1				5					10			

<210> 243

<211> 17

<212> PRT

<213> Homo sapiens

<400> 243

Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala Pro Gly Leu Pro Gly Ile

1 5 10 15

Ala

<210> 244

<211> 17

<212> PRT

<213> Homo sapiens

<400> 244

Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly Ile Lys

1 5 10 15

Gly

<210> 245

<211> 17

<212> PRT

<213> Homo sapiens

<400> 245

Asp Gly Arg Asn Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys

1 5 10 15

Gly

<210> 246

<211> 20

<212> PRT

<213> Homo sapiens

<400> 246

Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala Pro Gly Leu Pro

1 5 10 15

Gly Ile Ala Gly
20

<210> 247

<211> 19

<212> PRT

<213> Homo sapiens

<400> 247

Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro Gly Glu Pro Gly Pro Lys

1 5 10 15

Gly Asp Ala

<210> 248

<211> 17

<212> PRT

<213> Homo sapiens

<400> 248

Ala Gly Ile Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp

1 5 10 15

Gly

<210> 249

<211> 20

<212> PRT

<213> Homo sapiens

<400> 249

Arg	Gly	Gly	Ala	Gly	Glu	Pro	Gly	Lys	Asn	Gly	Ala	Lys	Gly	Glu	Pro
1				5					10					15	

Gly	Pro	Arg	Gly
			20

<210> 250

<211> 26

<212> PRT

<213> Homo sapiens

<400> 250

Lys	Gly	Glu	Arg	Gly	Ser	Pro	Gly	Gly	Pro	Gly	Ala	Ala	Gly	Phe	Pro
1				5					10					15	

Gly	Ala	Arg	Gly	Leu	Pro	Gly	Pro	Pro	Gly
			20				25		

<210> 251

<211> 27

<212> PRT

<213> Homo sapiens

<400> 251

Ile	Pro	Gly	Val	Pro	Gly	Ala	Lys	Gly	Glu	Asp	Gly	Lys	Asp	Gly	Ser
1				5					10					15	

Pro	Gly	Glu	Pro	Gly	Ala	Asn	Gly	Leu	Pro	Gly
			20					25		

<210> 252

<211> 28

<212> PRT

<213> Homo sapiens

<400> 252

Gly	Ala	Ala	Gly	Phe	Pro	Gly	Ala	Arg	Gly	Leu	Pro	Gly	Pro	Pro	Gly
1				5					10					15	

Ser	Asn	Gly	Asn	Pro	Gly	Pro	Pro	Gly	Pro	Ser	Gly
			20					25			

<210> 253

<211> 26

<212> PRT

<213> Homo sapiens

<400> 253

Arg	Pro	Gly	Pro	Pro	Gly	Pro	Ser	Gly	Pro	Arg	Gly	Gln	Pro	Gly	Val
1				5					10					15	

Met	Gly	Phe	Pro	Gly	Pro	Lys	Gly	Asn	Asp
			20					25	

<210> 254

<211> 29

<212> PRT

<213> Homo sapiens

<400> 254

Gln Gly Pro Pro Gly Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys
 1 5 10 15

Gly Glu Met Gly Pro Ala Gly Ile Pro Gly Ala Pro Gly
 20 25

<210> 255

<211> 26

<212> PRT

<213> Homo sapiens

<400> 255

Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly Glu Arg
 1 5 10 15

Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly
 20 25

<210> 256

<211> 30

<212> PRT

<213> Homo sapiens

<400> 256

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

Gly Pro Pro Gly Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser
 20 25 30

<210> 257

<211> 31

<212> PRT

<213> Homo sapiens

<400> 257

Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln Pro Gly Glu
 1 5 10 15

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

<210> 258

<211> 32

<212> PRT

<213> Homo sapiens

<400> 258

Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly Pro Pro Gly Thr Ala
 1 5 10 15

Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu Val Gly Pro Ala Gly
 20 25 30

<210> 259

<211> 32

<212> PRT

<213> Homo sapiens

<400> 259

Gln Gly Pro Pro Gly Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys
 1 5 10 15

Gly Glu Met Gly Pro Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly
 20 25 30

<210> 260

<211> 33

<212> PRT

<213> Homo sapiens

<400> 260

Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro
 1 5 10 15

Gly Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly
 20 25 30

Gln

<210> 261

<211> 33

<212> PRT

<213> Homo sapiens

<400> 261

Phe Pro Gly Ala Pro Gly Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu
 1 5 10 15

Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly Val Ala
 20 25 30

Gly

<210> 262

<211> 33

<212> PRT

<213> Homo sapiens

<400> 262

Ala Gly Phe Pro Gly Ala Pro Gly Gln Asn Gly Glu Pro Gly Gly Lys
 1 5 10 15

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

Val

<210> 263

<211> 41

<212> PRT

<213> Homo sapiens

<400> 263

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

Gly Pro Pro Gly Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly
 20 25 30

20 20 30
 Ala Lys Gly Glu Val Gly Pro Ala Gly
 35 40

<210> 264

<211> 53

<212> PRT

<213> Homo sapiens

<400> 264

Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly Val Pro Gly Gly Pro
 1 5 10 15

Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly Pro Gly Ser Asp Gly
 20 25 30

Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser Gly Arg Pro Gly Pro
 35 40 45

Pro Gly Pro Ser Gly
 50

<210> 265

<211> 12

<212> PRT

<213> Homo sapiens

<400> 265

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala
 1 5 10

<210> 266

<211> 18

<212> PRT

<213> Homo sapiens

<400> 266

Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly Thr Pro Gly Leu Gln
 1 5 10 15

Gly Met

<210> 267

<211> 18

<212> PRT

<213> Homo sapiens

<400> 267

Asn Gly Leu Ser Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Leu Pro
 1 5 10 15

Gly Leu

<210> 268

<211> 20

<212> PRT

<213> Homo sapiens

<400> 268

Met Gly Ala Arg Gly Pro Pro Gly Pro Ala Gly Ala Asn Gly Ala Pro
 1 5 10 15

Gly Leu Arg Gly
20

<210> 269

<211> 20

<212> PRT

<213> Homo sapiens

<400> 269

Asn Gly Leu Ser Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Leu Pro
1 5 10 15

Gly Leu Ala Gly
20

<210> 270

<211> 23

<212> PRT

<213> Homo sapiens

<400> 270

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly
1 5 10 15

Met Pro Gly Pro Arg Gly Ser
20

<210> 271

<211> 29

<212> PRT

<213> Homo sapiens

<400> 271

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly
1 5 10 15

Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
20 25

<210> 272

<211> 32

<212> PRT

<213> Homo sapiens

<400> 272

Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu Gly Gly Lys Gly Ala Ala
1 5 10 15

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

<210> 273

<211> 30

<212> PRT

<213> Homo sapiens

<400> 273

Ser Gly Pro Lys Gly Asp Ala Gly Gln Pro Gly Glu Lys Gly Ser Pro
1 5 10 15

Gly Ala Gln Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly Ile
20 25 30

<210> 274

<211> 31

<212> PRT

<213> Homo sapiens

<400> 274

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly
 1 5 10 15

Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val Lys Gly
 20 25 30

<210> 275

<211> 37

<212> PRT

<213> Homo sapiens

<400> 275

Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala Gly Pro Pro Gly
 1 5 10 15

Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly Ser Pro Gly Ser
 20 25 30

Pro Gly Tyr Gln Gly
 35

<210> 276

<211> 40

<212> PRT

<213> Homo sapiens

<400> 276

Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly Pro
 1 5 10 15

Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro Ala
 20 25 30

Gly Ile Pro Gly Ala Pro Gly Leu
 35 40

<210> 277

<211> 12

<212> PRT

<213> Homo sapiens

<400> 277

Ile Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly
 1 5 10

<210> 278

<211> 17

<212> PRT

<213> Homo sapiens

<400> 278

Arg Gly Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg
 1 5 10 15

Gly

<210> 279

<211> 17

<212> PRT

<213> Homo sapiens

<400> 279

Lys Gly Pro Ala Gly Ile Pro Gly Phe Pro Gly Met Lys Gly His Arg
 1 5 10 15

Gly

<210> 280

<211> 20

<212> PRT

<213> Homo sapiens

<400> 280

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

Gly Pro Gln Gly
 20

<210> 281

<211> 20

<212> PRT

<213> Homo sapiens

<400> 281

Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro
 1 5 10 15

Gly Pro Arg Gly
 20

<210> 282

<211> 23

<212> PRT

<213> Homo sapiens

<400> 282

Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro
 1 5 10 15

Gly Met Pro Gly Pro Arg Gly
 20

<210> 283

<211> 23

<212> PRT

<213> Homo sapiens

<400> 283

Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro Arg
 1 5 10 15

Gly Ser Pro Gly Pro Gln Gly
 20

<210> 284

<211> 24

<212> PRT

<213> Homo sapiens

<400> 284

Gln Gly Pro Pro Gly Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys
 1 5 10 15

Gly Glu Met Gly Pro Ala Gly Ile
 20

<210> 285

<211> 24

<212> PRT

<213> Homo sapiens

<400> 285

Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe
 1 5 10 15

Pro Gly Met Lys Gly His Arg Gly
 20

<210> 286

<211> 26

<212> PRT

<213> Homo sapiens

<400> 286

Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro
 1 5 10 15

Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly
 20 25

<210> 287

<211> 26

<212> PRT

<213> Homo sapiens

<400> 287

Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro Arg
 1 5 10 15

Gly Ser Pro Gly Pro Gln Gly Val Lys Gly
 20 25

<210> 288

<211> 26

<212> PRT

<213> Homo sapiens

<400> 288

Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile Pro
 1 5 10 15

Gly Phe Pro Gly Met Lys Gly His Arg Gly
 20 25

<210> 289

<211> 29

<212> PRT

<213> Homo sapiens

<400> 289

Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg Gly Asn Asp Gly
 1 5 10 15

Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly Pro
 20 25

<210> 290

<211> 29

<212> PRT

<213> Homo sapiens

<400> 290

Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala Pro Gly Glu Arg
 1 5 10 15

Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg Gly
 20 25

<210> 291

<211> 29

<212> PRT

<213> Homo sapiens

<400> 291

Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln Gly Pro Arg Gly Asp Lys
 1 5 10 15

Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly Ile Lys Gly

20

25

<210> 292

<211> 32

<212> PRT

<213> Homo sapiens

<400> 292

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

Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly
 20 25 30

<210> 293

<211> 34

<212> PRT

<213> Homo sapiens

<400> 293

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

Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly
 20 25 30

Leu Ser

<210> 294

<211> 37

<212> PRT

<213> Homo sapiens

<400> 294

```

Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
1           5           10           15

Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly
                20           25           30

Ala Pro Gly Ser Pro
          35

```

<210> 295

<211> 35

<212> PRT

<213> Homo sapiens

<400> 295

```

Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro Arg
1           5           10           15

Gly Ser Pro Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys Pro Gly
                20           25           30

Ala Asn Gly
          35

```

<210> 296

<211> 38

<212> PRT

<213> Homo sapiens

<400> 296

```

Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly Val Ala
1           5           10           15

Gly Pro Pro Gly Gly Ser Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly
                20           25           30

Val Lys Gly Glu Arg Gly
          35

```

<210> 297

<211> 40

<212> PRT

<213> Homo sapiens

<400> 297

```

Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser Gly Pro Ala
1           5           10           15

Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly Ser Pro Gly
                20           25           30

Gly Pro Gly Ala Ala Gly Phe Pro
          35           40

```

<210> 298

<211> 48

<212> PRT

<213> Homo sapiens

<400> 298

```

Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro Ala Gly Ala
1           5           10           15

Pro Gly Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln Gly Pro Arg
           20           25           30

Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly Ile Lys Gly
           35           40           45

```

<210> 299

<211> 12

<212> PRT

<213> Homo sapiens

<400> 299

```

Ile Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly
1           5           10

```

<210> 300

<211> 14

<212> PRT

<213> Homo sapiens

<400> 300

```

Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro Arg Gly
1           5           10

```

<210> 301

<211> 16

<212> PRT

<213> Homo sapiens

<400> 301

```

Gly Pro Gln Gly Leu Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly
1           5           10           15

```

<210> 302

<211> 17

<212> PRT

<213> Homo sapiens

<400> 302

```

Lys Gly Pro Ala Gly Ile Pro Gly Phe Pro Gly Met Lys Gly His Arg
1           5           10           15

```

Gly

<210> 303

<211> 21

<212> PRT

<213> Homo sapiens

<400> 303

```

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

```

```

Gly Pro Gln Gly Val
           20

```

<210> 304

<211> 23

<212> PRT

<213> Homo sapiens

<400> 304

Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro Gly Glu Pro Gly Pro Lys
 1 5 10 15

Gly Asp Ala Gly Ala Pro Gly
 20

<210> 305

<211> 24

<212> PRT

<213> Homo sapiens

<400> 305

Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro Asn Gly Ile Pro Gly Glu
 1 5 10 15

Lys Gly Pro Ala Gly Glu Arg Gly
 20

<210> 306

<211> 27

<212> PRT

<213> Homo sapiens

<400> 306

Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro Gly Pro
 1 5 10 15

Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly
 20 25

<210> 307

<211> 27

<212> PRT

<213> Homo sapiens

<400> 307

Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro Gly Pro
 1 5 10 15

Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly
 20 25

<210> 308

<211> 26

<212> PRT

<213> Homo sapiens

<400> 308

Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro Asn Gly Ile Pro
 1 5 10 15

Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly
 20 25

<210> 309

<211> 26

<212> PRT

<213> Homo sapiens

<400> 309

```

Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile Pro
1           5           10           15
Gly Phe Pro Gly Met Lys Gly His Arg Gly
                20           25

```

<210> 310

<211> 29

<212> PRT

<213> Homo sapiens

<400> 310

```

Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly Thr Ser
1           5           10           15
Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly
                20           25

```

<210> 311

<211> 27

<212> PRT

<213> Homo sapiens

<400> 311

```

Ala Pro Gly Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu
1           5           10           15
Arg Gly Ala Ala Gly Ile Lys Gly His Arg Gly
                20           25

```

<210> 312

<211> 29

<212> PRT

<213> Homo sapiens

<400> 312

```

Arg Gly Ala Pro Gly Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr
1           5           10           15
Gly Glu Arg Gly Ala Ala Gly Ile Lys Gly His Arg Gly
                20           25

```

<210> 313

<211> 32

<212> PRT

<213> Homo sapiens

<400> 313

```

Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser Pro Gly Pro Ala
1           5           10           15
Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala Gly Pro Arg Gly
                20           25           30

```

<210> 314

<211> 29

<212> PRT

<213> Homo sapiens

<400> 314

Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe
 1 5 10 15

Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
 20 25

<210> 315

<211> 33

<212> PRT

<213> Homo sapiens

<400> 315

Asp Ala Gly Gln Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro
 1 5 10 15

Pro Gly Ala Pro Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg
 20 25 30

Gly

<210> 316

<211> 35

<212> PRT

<213> Homo sapiens

<400> 316

Arg Gly Pro Thr Gly Pro Ile Gly Pro Pro Gly Pro Ala Gly Gln Pro
 1 5 10 15

Gly Asp Lys Gly Glu Gly Gly Ala Pro Gly Leu Pro Gly Ile Ala Gly
 20 25 30

Pro Arg Gly
 35

<210> 317

<211> 35

<212> PRT

<213> Homo sapiens

<400> 317

Lys Gly Asp Ala Gly Gln Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln
 1 5 10 15

Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly
 20 25 30

Ala Arg Gly
 35

<210> 318

<211> 33

<212> PRT

<213> Homo sapiens

<400> 318

Arg Asn Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu
 1 5 10 15

Asn Gly Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg

20

25

30

Gly

<210> 319

<211> 35

<212> PRT

<213> Homo sapiens

<400> 319

Ala	Pro	Gly	Phe	Arg	Gly	Pro	Ala	Gly	Pro	Asn	Gly	Ile	Pro	Gly	Glu
1			5					10					15		

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

Gly	Ala	Ala
		35

<210> 320

<211> 35

<212> PRT

<213> Homo sapiens

<400> 320

Arg	Gly	Ala	Pro	Gly	Phe	Arg	Gly	Pro	Ala	Gly	Pro	Asn	Gly	Ile	Pro
1			5					10					15		

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

Pro	Arg	Gly
		35

<210> 321

<211> 35

<212> PRT

<213> Homo sapiens

<400> 321

Arg	Gly	Ser	Pro	Gly	Glu	Arg	Gly	Glu	Thr	Gly	Pro	Pro	Gly	Pro	Ala
1			5					10					15		

Gly	Phe	Pro	Gly	Ala	Pro	Gly	Gln	Asn	Gly	Glu	Pro	Gly	Gly	Lys	Gly
			20				25					30			

Glu	Arg	Gly
		35

<210> 322

<211> 38

<212> PRT

<213> Homo sapiens

<400> 322

Gly	His	Ala	Gly	Ala	Gln	Gly	Pro	Pro	Gly	Pro	Pro	Gly	Ile	Asn	Gly
1			5					10					15		

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

Pro	Gly	Leu	Met	Gly	Ala
					35

<210> 323

<211> 38

<212> PRT

<213> Homo sapiens

<400> 323

```

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

Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly
                20           25           30

Leu Ser Gly Glu Arg Gly
                35

```

<210> 324

<211> 13

<212> PRT

<213> Homo sapiens

<400> 324

```

Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala
1           5           10

```

<210> 325

<211> 12

<212> PRT

<213> Homo sapiens

<400> 325

```

Ile Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly
1           5           10

```

<210> 326

<211> 14

<212> PRT

<213> Homo sapiens

<400> 326

```

Arg Gly Leu Ala Gly Pro Pro Gly Met Pro Gly Pro Arg Gly
1           5           10

```

<210> 327

<211> 20

<212> PRT

<213> Homo sapiens

<400> 327

```

Gln Gly Pro Pro Gly Ala Pro Gly Pro Leu Gly Ile Ala Gly Ile Thr
1           5           10           15

Gly Ala Arg Gly
                20

```

<210> 328

<211> 20

<212> PRT

<213> Homo sapiens

<400> 328

```

Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro
..          ..          ..          ..

```

1 5 10 15

Gly Pro Arg Gly
20

<210> 329

<211> 23

<212> PRT

<213> Homo sapiens

<400> 329

Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
1 5 10 15

Gly Pro Ala Gly Ala Asn Gly
20

<210> 330

<211> 24

<212> PRT

<213> Homo sapiens

<400> 330

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

Gly Pro Gln Gly Val Lys Gly Glu
20

<210> 331

<211> 26

<212> PRT

<213> Homo sapiens

<400> 331

Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro Gly Pro Leu
1 5 10 15

Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly
20 25

<210> 332

<211> 24

<212> PRT

<213> Homo sapiens

<400> 332

Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile Pro Gly Phe
1 5 10 15

Pro Gly Met Lys Gly His Arg Gly
20

<210> 333

<211> 24

<212> PRT

<213> Homo sapiens

<400> 333

Lys Asp Gly Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro
1 5 10 15

- - - - -

Arg Gly Asn Arg Gly Glu Arg Gly
20

<210> 334

<211> 26

<212> PRT

<213> Homo sapiens

<400> 334

Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Pro Pro Gly Met Pro
1 5 10 15

Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly
20 25

<210> 335

<211> 27

<212> PRT

<213> Homo sapiens

<400> 335

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

Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys
20 25

<210> 336

<211> 32

<212> PRT

<213> Homo sapiens

<400> 336

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

Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly
20 25 30

<210> 337

<211> 34

<212> PRT

<213> Homo sapiens

<400> 337

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

Gly Pro Gln Gly Val Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly
20 25 30

Leu Ser

<210> 338

<211> 37

<212> PRT

<213> Homo sapiens

<400> 338

Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
1 5 10 15

Glv Ser Pro Glv Lvs Asp Glv Pro Pro Glv Pro Ala Glv Asn Thr Glv

```

-----
      20      25      30
-----
Ala Pro Gly Ser Pro
      35

<210> 339
<211> 38
<212> PRT
<213> Homo sapiens

<400> 339
Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly Val Ala
1          5          10          15
Gly Pro Pro Gly Gly Ser Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly
      20      25      30
Val Lys Gly Glu Arg Gly
      35

<210> 340
<211> 44
<212> PRT
<213> Homo sapiens

<400> 340
Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro Ala Gly Ala
1          5          10          15
Pro Gly Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln Gly Pro Arg
      20      25      30
Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala
      35      40

<210> 341
<211> 53
<212> PRT
<213> Homo sapiens

<400> 341
Arg Gly Ala Pro Gly Glu Lys Gly Glu Gly Gly Pro Pro Gly Val Ala
1          5          10          15
Gly Pro Pro Gly Gly Ser Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly
      20      25      30
Val Lys Gly Glu Arg Gly Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe
      35      40      45
Pro Gly Ala Arg Gly
      50

<210> 342
<211> 6
<212> PRT
<213> Homo sapiens

<400> 342
Ala Ile Gly Pro Ser Gly
1          5

<210> 343
<211> 6

```

<212> PRT

<213> Homo sapiens

<400> 343

Gly Ile Pro Gly Ala Pro
1 5

<210> 344

<211> 6

<212> PRT

<213> Homo sapiens

<400> 344

Ile Lys Gly His Arg Gly
1 5

<210> 345

<211> 6

<212> PRT

<213> Homo sapiens

<400> 345

Val Lys Gly Glu Ser Gly
1 5

<210> 346

<211> 6

<212> PRT

<213> Homo sapiens

<400> 346

His Ala Gly Ala Gln Gly
1 5

<210> 347

<211> 6

<212> PRT

<213> Homo sapiens

<400> 347

Asp Gly Thr Ser Gly His
1 5

<210> 348

<211> 6

<212> PRT

<213> Homo sapiens

<400> 348

Ile Gly Ser Pro Gly Pro
1 5

<210> 349

<211> 6

<212> PRT

<213> Homo sapiens

<400> 349

Leu Ser Gly Glu Arg Gly
1 5

<210> 350

<211> 6

<212> PRT

<213> Homo sapiens

<400> 350

Val Lys Gly Glu Arg Gly
1 5

<210> 351

<211> 6

<212> PRT

<213> Homo sapiens

<400> 351

Gly Ala Arg Gly Leu Ala
1 5

<210> 352

<211> 6

<212> PRT

<213> Homo sapiens

<400> 352

Gly Ala Pro Gly Glu Lys
1 5

<210> 353

<211> 6

<212> PRT

<213> Homo sapiens

<400> 353

Ile Lys Gly Pro Ala Gly
1 5

<210> 354

<211> 6

<212> PRT

<213> Homo sapiens

<400> 354

Gly Ile Pro Gly Gln Pro
1 5

<210> 355

<211> 6

<212> PRT

<213> Homo sapiens

<400> 355

Gly Pro Pro Gly Pro Thr
1 5

<210> 356

<211> 6

<212> PRT

<213> Homo sapiens

<400> 356

Lys Asn Gly Glu Thr Gly
1 5

<210> 357

<211> 6

<212> PRT

<213> Homo sapiens

<400> 357

Leu Lys Gly Glu Asn Gly
1 5

<210> 358

<211> 6

<212> PRT

<213> Homo sapiens

<400> 358

Gly Asp Pro Gly Pro Pro
1 5

<210> 359

<211> 6

<212> PRT

<213> Homo sapiens

<400> 359

Gly Asp Pro Gly Pro Pro
1 5

<210> 360

<211> 6

<212> PRT

<213> Homo sapiens

<400> 360

Phe Pro Gly Ala Arg Gly
1 5

<210> 361

<211> 6

<212> PRT

<213> Homo sapiens

<400> 361

Gly Asp Lys Gly Glu Thr
1 5

<210> 362

<211> 6

<212> PRT

<213> Homo sapiens

<400> 362

Gly Gly Ala Gly Glu Pro
1 5

<210> 363

<400> 363

000

<210> 364

<211> 6

<212> PRT

<213> Homo sapiens

<400> 364

Gly Pro Pro Gly Pro Pro
1 5

<210> 365

<211> 6

<212> PRT

<213> Homo sapiens

<400> 365

Gly Ala Ala Gly Glu Pro
1 5

<210> 366

<211> 6

<212> PRT

<213> Homo sapiens

<400> 366

Gly Leu Ser Gly Glu Arg
1 5

<210> 367

<211> 6

<212> PRT

<213> Homo sapiens

<400> 367

Ile Ala Gly Ile Thr Gly
1 5

<210> 368

<211> 6

<212> PRT

<213> Homo sapiens

<400> 368

Pro Gly Phe Pro Gly Met
1 5

<210> 369

<211> 6

<212> PRT

<213> Homo sapiens

<400> 369

Gly Ile Ala Gly Ile Thr
1 5

<210> 370

<211> 6

<212> PRT

<213> Homo sapiens

<400> 370

Gly Ala Arg Gly Leu Ala
1 5

<210> 371

<211> 6

<212> PRT

<213> Homo sapiens

<400> 371

Gly Leu Ala Gly Pro Pro
1 5

<210> 372

<211> 6

<212> PRT

<213> Homo sapiens

<400> 372

Gly Pro Pro Gly Val Ala
1 5

<210> 373

<211> 6

<212> PRT

<213> Homo sapiens

<400> 373

Gly Pro Ala Gly Ile Pro
1 5

<210> 374

<211> 6

<212> PRT

<213> Homo sapiens

<400> 374

Pro Gly Pro Pro Gly Ile
1 5

<210> 375

<211> 6

<212> PRT

<213> Homo sapiens

<400> 375

Gly Ala Pro Gly Pro Gln
1 5

<210> 376

<211> 6

<212> PRT

<213> Homo sapiens

<400> 376

Gly Asp Ala Gly Gln Pro
1 5

<210> 377

<211> 6

<212> PRT

<213> Homo sapiens

<400> 377

His Ala Gly Ala Gln Gly
1 5

<210> 378

<211> 6

<212> PRT

<213> Homo sapiens

<400> 378

Gly Pro Pro Gly Ala Pro
1 5

<210> 379

<211> 6

<212> PRT

<213> Homo sapiens

<400> 379

Gly Leu Ala Gly Pro Pro
1 5

<210> 380

<211> 6

<212> PRT

<213> Homo sapiens

<400> 380

Ala Ile Gly Pro Ser Gly
1 5

<210> 381

<211> 6

<212> PRT

<213> Homo sapiens

<400> 381

Gly Pro Pro Gly Pro Ala
1 5

<210> 382

<211> 6

<212> PRT

<213> Homo sapiens

<400> 382

Ser Pro Gly Pro Ala Gly
1 5

<210> 383

<211> 6

<212> PRT

<213> Homo sapiens

<400> 383

Ala Ala Gly Thr Pro Gly
1 5

<210> 384

<211> 6

<212> PRT

<213> Homo sapiens

<400> 384

Thr Ser Gly His Pro Gly
1 5

<210> 385

<211> 6

<212> PRT

<213> Homo sapiens

<400> 385

Pro Ser Gly Pro Pro Gly
1 5

<210> 386

<211> 6

<212> PRT

<213> Homo sapiens

<400> 386

Pro Gly Leu Met Gly Ala
1 5

<210> 387

<211> 6

<212> PRT

<213> Homo sapiens

<400> 387

Ser Pro Gly Pro Gln Gly
1 5

<210> 388

<211> 6

<212> PRT

<213> Homo sapiens

<400> 388

Pro Pro Gly Pro Pro Gly
1 5

<210> 389

<211> 6

<212> PRT

<213> Homo sapiens

<400> 389

Gly Ala Ile Gly Pro Ser
1 5

<210> 390

<211> 6

<212> PRT

<213> Homo sapiens

<400> 390

Pro Pro Gly Pro Ala Gly
1 5

<210> 391

<211> 6

<212> PRT

<213> Homo sapiens

<400> 391

Ser Pro Gly Pro Lys Gly
1 5

<210> 392

<211> 6

<212> PRT

<213> Homo sapiens

<400> 392

Pro Pro Gly Pro Ala Gly
1 5

<210> 393

<211> 6

<212> PRT

<213> Homo sapiens

<400> 393

Leu Pro Gly Pro Pro Gly
1 5

<210> 394

<211> 6

<212> PRT

<213> Homo sapiens

<400> 394

Gly Ala Pro Gly Leu Lys

1 5

<210> 395
<211> 6
<212> PRT
<213> Homo sapiens

<400> 395
Gly Leu Pro Gly Pro Pro
1 5

<210> 396
<211> 6
<212> PRT
<213> Homo sapiens

<400> 396
Gly Pro Pro Gly Ile Lys
1 5

<210> 397
<211> 6
<212> PRT
<213> Homo sapiens

<400> 397
Gly Pro Pro Gly Val Ala
1 5

<210> 398
<211> 6
<212> PRT
<213> Homo sapiens

<400> 398
Thr Pro Gly Leu Gln Gly
1 5

<210> 399
<211> 6
<212> PRT
<213> Homo sapiens

<400> 399
Gly Thr Pro Gly Leu Gln
1 5

<210> 400
<211> 6
<212> PRT
<213> Homo sapiens

<400> 400
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Lys Gly Ser Pro Gly Ala

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

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Pro Gly Ala Asn Gly Leu
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Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe Val Phe Pro Lys Glu
20 25 30
Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys Pro Leu
35 40 45
Lys Ala Phe Thr Val Cys Leu His Phe Tyr Thr Glu Leu Ser Ser Thr
50 55 60
Arg Gly Thr Val Phe Ser Arg Met Pro Pro Arg Asp Lys Thr Met Arg
65 70 75 80
Phe Phe Ile Phe Trp Ser Lys Asp Ile Gly Tyr Ser Phe Thr Val Gly
85 90 95
Gly Ser Glu Ile Leu Phe Glu Val Pro Glu Val Thr Val Ala Pro Val
100 105 110
His Ile Cys Thr Ser Trp Glu Ser Ala Ser Gly Ile Val Glu Phe Trp
115 120 125
Val Asp Gly Lys Pro Arg Val Arg Lys Ser Leu Lys Lys Gly Tyr Thr
130 135 140
Val Gly Ala Glu Ala Ser Ile Ile Leu Gly Gln Glu Gln Asp Ser Phe
145 150 155 160
Gly

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Met Lys Val Leu Trp Ala Ala Leu Leu Val Thr Phe Leu Ala Gly Cys
1 5 10 15
Gln Ala Lys Val Glu Gln Ala Val Glu Thr Glu Pro Glu Pro Glu Leu
20 25 30
Arg Gln Gln Thr Glu Trp Gln Ser Gly Gln Arg Trp Glu Leu Ala Leu
35 40 45
Gly Arg Phe Trp Asp Tyr Leu Arg Trp Val Gln Thr Leu Ser Glu Gln
50 55 60
Val Gln Glu Glu Leu Leu Ser Ser Gln Val Thr Gln Glu Leu Arg Ala
65 70 75 80

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Leu Met Asp Glu Thr Met Lys Glu Leu Lys Ala Tyr Lys Ser Glu Leu
      85                      90                      95
Glu Glu Gln Leu Thr Pro Val Ala Glu Glu Thr Arg Ala Arg Leu Ser
      100                      105                      110
Lys Glu Leu Gln Ala Ala Gln Ala Arg Leu Gly Ala Asp Met Glu Asp
      115                      120                      125
Val Cys Gly Arg Leu Val Gln Tyr Arg Gly Glu Val Gln Ala Met Leu
      130                      135                      140
Gly Gln Ser Thr Glu Glu Leu Arg Val Arg Leu Ala Ser His Leu Arg
      145                      150                      155                      160
Lys Leu Arg Lys Arg Leu Leu Arg Asp Ala Asp Asp Leu Gln Lys Arg
      165                      170                      175
Leu Ala Val Tyr Gln Ala Gly Ala Arg Glu Gly Ala Glu Arg Gly Leu
      180                      185                      190
Ser Ala Ile Arg Glu Arg Leu Gly Pro Leu Val Glu Gln Gly Arg Val
      195                      200                      205
Arg Ala Ala Thr Val Gly Ser Leu Ala Gly Gln Pro Leu Gln Glu Arg
      210                      215                      220
Ala Gln Ala Trp Gly Glu Arg Leu Arg Ala Arg Met Glu Glu Met Gly
      225                      230                      235                      240
Ser Arg Thr Arg Asp Arg Leu Asp Glu Val Lys Glu Gln Val Ala Glu
      245                      250                      255
Val Arg Ala Lys Leu Glu Glu Gln Ala Gln Gln Ile Arg Leu Gln Ala
      260                      265                      270
Glu Ala Phe Gln Ala Arg Leu Lys Ser Trp Phe Glu Pro Leu Val Glu
      275                      280                      285
Asp Met Gln Arg Gln Trp Ala Gly Leu Val Glu Lys Val Gln Ala Ala
      290                      295                      300
Val Gly Thr Ser Ala Ala Pro Val Pro Ser Asp Asn His
      305                      310                      315

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

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Gln

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

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1                      5                      10                      15

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Gln

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Val	Ala	Glu	Val	Arg	Ala	Lys	Leu	Glu	Glu	Gln	Ala	Gln	Gln	Ile	Arg
1				5					10					15	

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

Gln

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Ala	Met	Leu	Gly	Gln	Ser	Thr	Glu	Glu	Leu	Arg	Val	Arg
1				5					10			

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Glu	Gln	Ala	Val	Glu	Thr	Glu	Pro	Glu	Pro	Glu	Leu	Arg	Gln
1				5					10				

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Arg	Gln	Gln	Thr	Glu	Trp	Gln	Ser	Gly	Gln	Arg	Trp	Glu	Leu
1				5					10				

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<400> 667

Leu	Ala	Val	Tyr	Gln	Ala	Gly	Ala	Arg	Glu	Gly	Ala	Glu	Arg	Gly	Leu
1				5					10					15	

Ser Ala

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Arg	Ala	Lys	Leu	Glu	Gln	Ala	Gln	Gln	Ile	Arg	Leu
1			5					10			

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<400> 669

Ala	Lys	Leu	Glu	Gln	Ala	Gln	Gln	Ile	Arg	Leu	Gln	Ala
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Ala	Lys	Val	Glu	Gln	Ala	Val	Glu	Thr	Glu	Pro	Glu	Pro	Glu	Leu	Arg
1			5						10					15	

Gln

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<400> 671

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

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Glu	Gln	Ala	Val	Glu	Thr	Glu	Pro	Glu	Pro	Glu	Leu	Arg	Gln
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Asp	Glu	Val	Lys	Glu	Gln	Val	Ala	Glu	Val	Arg	Ala	Lys	Leu	Glu	Glu
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Lys Glu Ser Asp Thr Ser Tyr Val Ser Leu Lys Ala Pro Leu Thr Lys
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Gly Gly Asn Phe Glu Gly Ser Gln Ser Leu Val Gly Asp Ile Gly Asn
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Ala Leu Lys Tyr Glu Val Gln Gly Glu Val Phe Thr Lys Pro Gln Leu
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Gly Ile Val Glu Phe Trp Val Asp Gly Lys Pro Arg Val Arg
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Arg Lys Ala Phe Val Phe Pro Lys Glu Ser
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Lys Tyr Glu Val Gln Gly Glu Val Phe Thr Lys Pro Gln Leu Trp Pro
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Asp Ser Phe Gly Gly Asn Phe Glu Gly Ser Gln Ser Leu

1 5 10

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

1 5 10

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Ser Leu Lys Lys Gly Tyr Thr Val Gly Ala Glu Ala Ser

1 5 10

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Ala Phe Gly Gln Thr Asp Met Ser Arg Lys Ala Phe

1 5 10

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Ser Leu Lys Lys Gly Tyr Thr Val Gly Ala Glu Ala Ser Ile

1 5 10

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Gly Glu Val Phe Thr Lys Pro Gln Leu Trp Pro

1 5 10

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Ser Ile Ile Leu Gly Gln Glu Gln Asp Ser Phe Gly Gly Asn Phe

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Lys Tyr Glu Val Gln Gly Glu Val Phe Thr Lys Pro Gln Leu
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Lys Val Glu Gln Ala Val
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Ala Glu Val Arg Ala Lys
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Met Leu Gly Gln Ser Thr
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Gln Ala Val Glu Thr Glu
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Gln Gln Thr Glu Trp Gln
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Ala Val Tyr Gln Ala Gly
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Ala Lys Leu Glu Glu Gln
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Lys Leu Glu Glu Gln Ala
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Val Glu Gln Ala Val Glu
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Gln Ala Val Glu Thr Glu
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Glu Val Lys Glu Gln Val
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Ala Phe Val Phe Pro Lys
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Tyr Glu Val Gln Gly Glu
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Lys Ala Phe Val Phe Pro
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Ser Phe Gly Gly Asn Phe
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Phe Val Leu Ser Pro Asp
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Ile Ile Leu Gly Gln Glu
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Tyr Glu Val Gln Gly Glu
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Gly Asn Phe Glu Gly Ser

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Glu Gly Ala Glu Arg Gly
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Glu Val Arg Ala Lys Leu
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20 25 30

Ile Pro Gly Gly Val Pro Gly Gly Val Phe Tyr Pro Gly Ala Gly Leu
35 40 45

Gly Ala Leu Gly Gly Gly Ala Leu Gly Pro Gly Gly Lys Pro Leu Lys
50 55 60

Pro Val Pro Gly Gly Leu Ala Gly Ala Gly Leu Gly Ala Gly Leu Gly
65 70 75 80

Ala Phe Pro Ala Val Thr Phe Pro Gly Ala Leu Val Pro Gly Gly Val
85 90 95

Ala Asp Ala Ala Ala Tyr Lys Ala Ala Lys Ala Gly Ala Gly Leu
100 105 110

Gly Gly Val Pro Gly Val Gly Gly Leu Gly Val Ser Ala Gly Ala Val
115 120 125

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

Gly Leu Pro Gly Val Tyr Pro Gly Gly Val Leu Pro Gly Ala Arg Phe
145 150 155 160

Pro Gly Val Gly Val Leu Pro Gly Val Pro Thr Gly Ala Gly Val Lys
165 170 175

Pro Lys Ala Pro Gly Val Gly Gly Ala Phe Ala Gly Ile Pro Gly Val
 180 185 190
 Gly Pro Phe Gly Gly Pro Gln Pro Gly Val Pro Leu Gly Tyr Pro Ile
 195 200 205
 Lys Ala Pro Lys Leu Pro Gly Gly Tyr Gly Leu Pro Tyr Thr Thr Gly
 210 215 220
 Lys Leu Pro Tyr Gly Tyr Gly Pro Gly Gly Val Ala Gly Ala Ala Gly
 225 230 235 240
 Lys Ala Gly Tyr Pro Thr Gly Thr Gly Val Gly Pro Gln Ala Ala Ala
 245 250 255
 Ala Ala Ala Ala Lys Ala Ala Ala Lys Phe Gly Ala Gly Ala Ala Gly
 260 265 270
 Val Leu Pro Gly Val Gly Gly Ala Gly Val Pro Gly Val Pro Gly Ala
 275 280 285
 Ile Pro Gly Ile Gly Gly Ile Ala Gly Val Gly Thr Pro Ala Ala Ala
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 Ala Ala Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Ala
 305 310 315 320
 Gly Leu Val Pro Gly Gly Pro Gly Phe Gly Pro Gly Val Val Gly Val
 325 330 335
 Pro Gly Ala Gly Val Pro Gly Val Gly Val Pro Gly Ala Gly Ile Pro
 340 345 350
 Val Val Pro Gly Ala Gly Ile Pro Gly Ala Ala Val Pro Gly Val Val
 355 360 365
 Ser Pro Glu Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Lys Tyr Gly
 370 375 380
 Ala Arg Pro Gly Val Gly Val Gly Gly Ile Pro Thr Tyr Gly Val Gly
 385 390 395 400
 Ala Gly Gly Phe Pro Gly Phe Gly Val Gly Val Gly Gly Ile Pro Gly
 405 410 415
 Val Ala Gly Val Pro Ser Val Gly Gly Val Pro Gly Val Gly Gly Val
 420 425 430
 Pro Gly Val Gly Ile Ser Pro Glu Ala Gln Ala Ala Ala Ala Lys
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 Ala Ala Lys Tyr Gly Val Gly Thr Pro Ala Ala Ala Ala Lys Ala
 450 455 460
 Ala Ala Lys Ala Ala Gln Phe Gly Leu Val Pro Gly Val Gly Val Ala
 465 470 475 480
 Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly Val Gly
 485 490 495
 Leu Ala Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly
 500 505 510
 Val Gly Val Ala Pro Gly Ile Gly Pro Gly Gly Val Ala Ala Ala Ala
 515 520 525
 Lys Ser Ala Ala Lys Val Ala Ala Lys Ala Gln Leu Arg Ala Ala Ala
 530 535 540
 Gly Leu Gly Ala Gly Ile Pro Gly Leu Gly Val Gly Val Gly Val Pro
 545 550 555 560
 Gly Leu Gly Val Gly Ala Gly Val Pro Gly Leu Gly Val Gly Ala Gly
 565 570 575
 Val Pro Gly Phe Gly Ala Gly Ala Asp Glu Gly Val Arg Arg Ser Leu
 580 585 590
 Ser Pro Glu Leu Arg Glu Gly Asp Pro Ser Ser Ser Gln His Leu Pro
 595 600 605

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Ser Thr Pro Ser Ser Pro Arg Val Pro Gly Ala Leu Ala Ala Ala Lys
 610                      615                      620

Ala Ala Lys Tyr Gly Ala Ala Val Pro Gly Val Leu Gly Gly Leu Gly
625                      630                      635                      640

Ala Leu Gly Gly Val Gly Ile Pro Gly Gly Val Val Gly Ala Gly Pro
                      645                      650                      655

Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Gln Phe
                      660                      665                      670

Gly Leu Val Gly Ala Ala Gly Leu Gly Gly Leu Gly Val Gly Gly Leu
675                      680                      685

Gly Val Pro Gly Val Gly Gly Leu Gly Gly Ile Pro Pro Ala Ala Ala
690                      695                      700

Ala Lys Ala Ala Lys Tyr Gly Ala Ala Gly Leu Gly Gly Val Leu Gly
705                      710                      715                      720

Gly Ala Gly Gln Phe Pro Leu Gly Gly Val Ala Ala Arg Pro Gly Phe
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Gly Leu Ser Pro Ile Phe Pro Gly Gly Ala Cys Leu Gly Lys Ala Cys
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Gly Arg Lys Arg Lys
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Ala Gly Gly Phe
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<210> 738

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Gly Ile Gly Pro Gly Gly Val Ala Ala
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<400> 739

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1			5					10					15		

Gly	Ile	Ala	Gly	Val	Gly	Thr
			20			

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1			5					10					15		

Gly	Ile	Ala	Gly	Val	Gly	Thr
			20			

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1			5					10					15	

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Gly	Val	Gly	Ile	Ser	Pro	Glu	Ala	Gln	Ala	Ala	Ala	Ala	Lys	Ala
1			5					10					15	

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Arg	Pro	Gly	Val	Gly	Val
1			5		

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<212> PRT

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<400> 744

Leu	Pro	Tyr	Thr	Thr	Gly
1			5		

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<400> 745

Val Ala Pro Gly Val Gly
1 5

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<400> 746

Gly Ala Gly Val Pro Gly
1 5

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<400> 747

Val Gly Ile Ser Pro Glu
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<210> 748

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<213> Homo sapiens

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Arg Pro Gly Val Gly Val
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<213> Homo sapiens

<400> 749

Leu Pro Tyr Thr Thr Gly
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Gly Val Gly Ala Gly Gly
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Tyr Gly Tyr Gly Pro Gly
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<213> Homo sapiens

<400> 752

Gly Pro Gly Gly Val Ala
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Gly Ile Ala Gly Val Gly
1 5

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<212> PRT

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Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Gly Gly Cys
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<400> 755

Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Lys
1 5 10

<210> 756

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<400> 756

Lys Asp Gly Glu Thr Gly Ala Ala Gly Pro Pro Gly Lys
1 5 10

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<400> 757

Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Lys

1 5 10

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Pro Gly Lys Asn Gly Glu Thr Pro Gly Pro Gln Gly Pro Lys
1 5 10

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Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Gly Gly Cys
1 5 10

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1 5 10

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Ile Ala Gly Leu Thr Gly Ala Arg Gly Leu Ala Gly Lys
1 5 10

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Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly Lys
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Lys Asp Gly Thr Ser Gly
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Lys	Asp	Gly	Thr	Ser	Gly	His	Pro	Gly	Pro	Gly	Gly	Cys
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<213> Homo sapiens

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Lys	Asp	Gly	Thr	Ser	Gly	His	Pro	Gly	Pro	Ile	Gly	Lys
1				5					10			

<210> 766

<211> 13

<212> PRT

<213> Homo sapiens

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Lys	Asp	Gly	Ser	Ser	Gly	His	Pro	Gly	Pro	Ile	Gly	Lys
1				5					10			

<210> 767

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<212> PRT

<213> Homo sapiens

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Pro	Gly	Lys	Asp	Gly	Thr	Ser	Gly	His	Pro	Gly	Pro	Lys
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<210> 768

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<213> Homo sapiens

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Cys	Gly	Gly	Gly	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Leu	Gly
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<213> Homo sapiens

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Ala	Gln	Gly	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Leu	Gly
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<210> 770

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Ala	Gln	Gly	Pro	Pro	Gly	Ser	Pro	Gly	Pro	Leu	Gly
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<210> 771

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Asp	Asp	Gly	Pro	Ser	Gly	Ala	Glu	Gly	Pro	Pro	Gly
1				5						10	

<210> 772

<211> 12

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<213> Homo sapiens

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Gly	Pro	Pro	Gly	Ala	Pro	Gly	Pro	Leu	Gly	Ile	Ala
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<211> 13

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<213> Homo sapiens

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Asn	Thr	Gly	Ala	Pro	Gly	Ser	Pro	Gly	Val	Cys	Gly	Gly
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<210> 774

<211> 13

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<213> Homo sapiens

<400> 774

Asn	Thr	Gly	Ala	Pro	Gly	Ser	Pro	Gly	Val	Ser	Gly	Lys
1				5					10			

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<212> PRT

<213> Homo sapiens

<400> 775

Asn	Ser	Gly	Ser	Pro	Gly	Asn	Pro	Gly	Val	Ala	Gly	Lys
1				5					10			

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<400> 776

Ala	Gly	Asn	Thr	Gly	Ala	Pro	Gly	Ser	Pro	Gly	Val
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<210> 777

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<212> PRT

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<400> 777

Ala	Ile	Gly	Pro	Ser	Gly	Pro	Ala	Gly	Lys	Gly	Gly	Cys
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<210> 778

<211> 13

<212> PRT

<213> Homo sapiens

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Ala	Ile	Gly	Pro	Ser	Gly	Pro	Ala	Gly	Lys	Asp	Gly	Lys
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<210> 779

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<400> 779

Ala	Ile	Gly	Pro	Ala	Gly	Pro	Ala	Gly	Lys	Asp	Gly	Lys
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<210> 780

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<213> Homo sapiens

<400> 780

Pro	Gly	Ala	Ile	Gly	Pro	Ser	Gly	Pro	Ala	Gly	Lys	Asp
1				5					10			

<210> 781

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<213> Homo sapiens

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Ala	Gly	Gly	Phe	Ala	Pro
1				5	

<210> 782

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<213> Homo sapiens

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Cys	Gly	Gly	Glu	Lys	Ala	Gly	Gly	Phe	Ala	Pro
1				5					10	

<210> 783

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<212> PRT

<213> Homo sapiens

<400> 783

Cys Gly Glu Lys Ala Gly Gly Phe Ala Pro
1 5 10

<210> 784

<211> 10

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<400> 784

Cys Gly Glu Lys Ser Gly Gly Phe Ser Pro
1 5 10

<210> 785

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<212> PRT

<213> Homo sapiens

<400> 785

Gly Gly Glu Lys Ala Gly Gly Phe Ala Pro Tyr Tyr
1 5 10

<210> 786

<211> 6

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<400> 786

Gln Asn Gly Asn Ile Lys
1 5

<210> 787

<211> 13

<212> PRT

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<400> 787

Ile Val Ile Glu Leu Gly Thr Asn Pro Leu Gly Gly Cys
1 5 10

<210> 788

<211> 13

<212> PRT

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Ile Val Ile Glu Leu Gly Thr Asn Pro Leu Lys Ser Lys
1 5 10

<210> 789

<211> 13

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Leu Val Ile Glu Leu Gly Gly Asn Pro Leu Lys Asn Lys

1 5 10

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 1 5 10

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 1 5 10

<210> 792
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 1 5 10

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 1 5 10

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 Thr Leu Leu Asp Leu Gln Asn Asn Asp Ile Ser Glu
 1 5 10

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 1 5 10

<210> 796
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<212> PRT

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<400> 796

Gln	Asn	Gly	Asn	Ile	Lys	Ile	Gly	Gln	Asp	Gly	Gly	Cys	Lys	Leu	His
1				5					10					15	

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Gln	Asn	Gly	Asn	Ile	Lys	Ile	Gly	Gln	Asp	Tyr	Lys
1				5					10		

<210> 798

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<400> 798

Gln	Asp	Gly	Asn	Ile	Lys	Ile	Gly	Gln	Asp	Tyr	Lys
1				5					10		

<210> 799

<211> 13

<212> PRT

<213> Homo sapiens

<400> 799

Val	Ala	Gln	Asn	Gly	Asn	Ile	Lys	Ile	Gly	Gln	Asp	Lys
1				5					10			

<210> 800

<211> 13

<212> PRT

<213> Homo sapiens

<400> 800

Val	Ala	Gln	Asp	Gly	Asn	Ile	Lys	Ile	Gly	Gln	Asp	Lys
1				5					10			

REFERENCES CITED IN THE DESCRIPTION

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PATENTKRAV

1. Fremgangsmåde til bioassay til kvantificering af peptidfragmenter, der omfatter en neo-epitop, som er dannet ved spaltning af kollagen type III ved hjælp af MMP-1, MMP-3, MMP-8, MMP-9, MMP-13, cathepsin K, cathepsin S, ADAMTS1, ADAMTS4 eller ADAMTS8,
5 hvilken fremgangsmåde omfatter, at en prøve, der omfatter peptidfragmenterne, bringes i kontakt med et monoklonalt antistof, som har specifik bindingsaffinitet for neo-epitopet, og at niveauet for det monoklonale antistofs binding til peptidfragmenter i prøven, hvor det monoklonale antistof ikke er reaktivt med intakt kollagen type III, bestemmes, hvor det monoklonale antistof har specifik bindingsaffinitet for den N-terminale neo-
10 epitopsekvens KNGETG og er ikke-reaktivt med en N-prolongeret version af et sådant peptid.
2. Fremgangsmåde ifølge krav 1, hvor fremgangsmåden udføres som et kompetitivt immunassay, hvor det monoklonale antistof og et kompetitivt middel inkuberes i nærværelse af prøven, og det kompetitive middel konkurrerer med peptidfragmenterne i prøven om at binde
15 til det monoklonale antistof.
3. Fremgangsmåde ifølge krav 2, hvor det kompetitive middel er et syntetisk peptid eller er et oprenset nativt peptid, som er dannet ved spaltning af det protein, hvorfra epitopen kommer, med henblik på at afdække neo-epitopen.
20
4. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 3, hvor prøven er en prøve af urin, serum, blod eller plasma.
5. Fremgangsmåde ifølge et hvilket som helst foregående krav, hvor prøven er en patientafledt
25 prøve, hvilken fremgangsmåde endvidere omfatter sammenligning af det bestemte niveau for peptidfragmenternes binding med værdier, som er karakteristiske for (a) sammenlignelige sunde individer og/eller (b) en patologisk aterosklerotisk tilstand.
6. Monoklonalt antistof mod en N-terminal neo-epitop, som er dannet ved proteinasespaltning
30 af kollagen type III, idet antistoffet specifikt er immunreaktivt med den N-terminale neo-epitopsekvens KNGETG og er ikke-reaktivt med en N-prolongeret version af et sådant peptid.
7. Cellelinje, der producerer et monoklonalt antistof ifølge krav 6.

8. Immunassaykit, der omfatter et monoklonalt antistof ifølge krav 6 og et kompetitivt middel, som binder det monoklonale antistof, og valgfrit ét eller flere af et vaskereagens, en buffer, et stopreagens, et enzymmærke, et enzymmærkesubstrat, kalibreringsstandarder, et anti-murint antistof og instruktioner til udførelse af et assay under anvendelse af kittet.

DRAWINGS

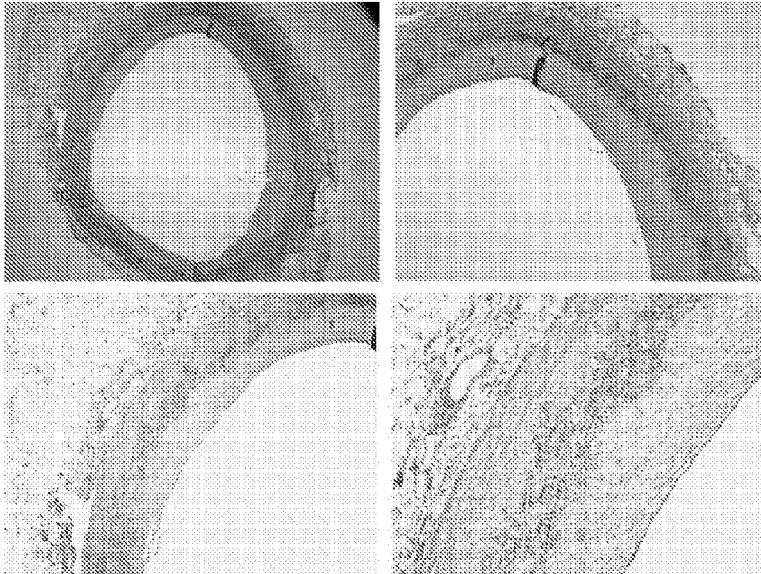


Figure 1

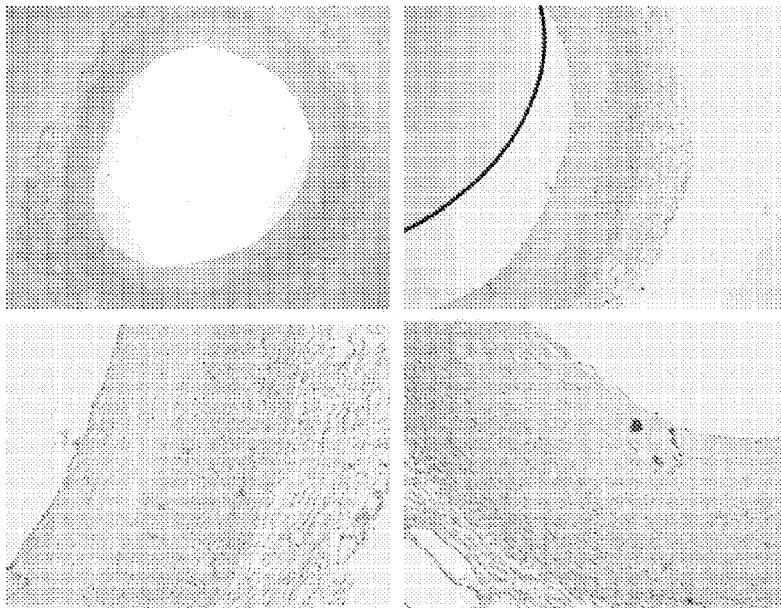


Figure 2

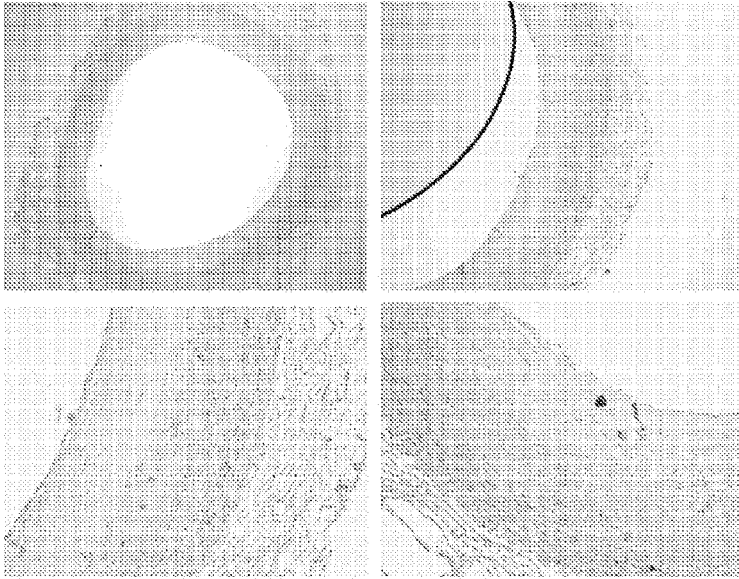


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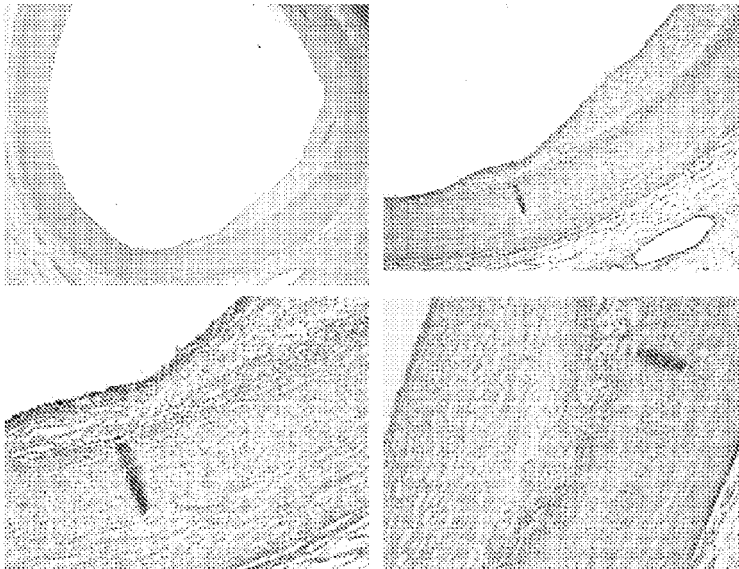


Figure 4

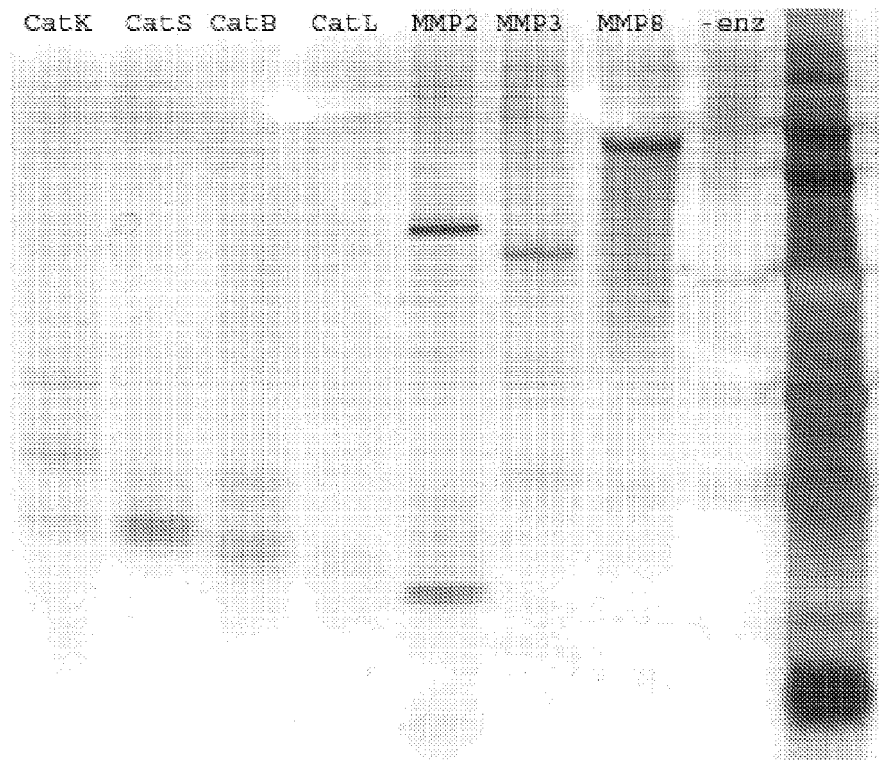


Figure 5

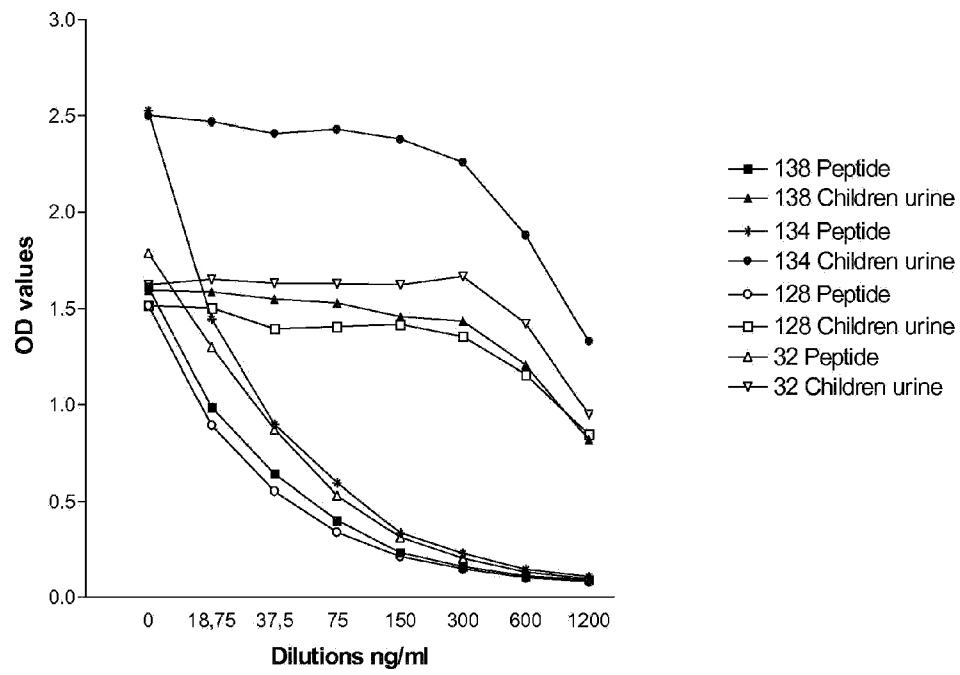


Figure 6

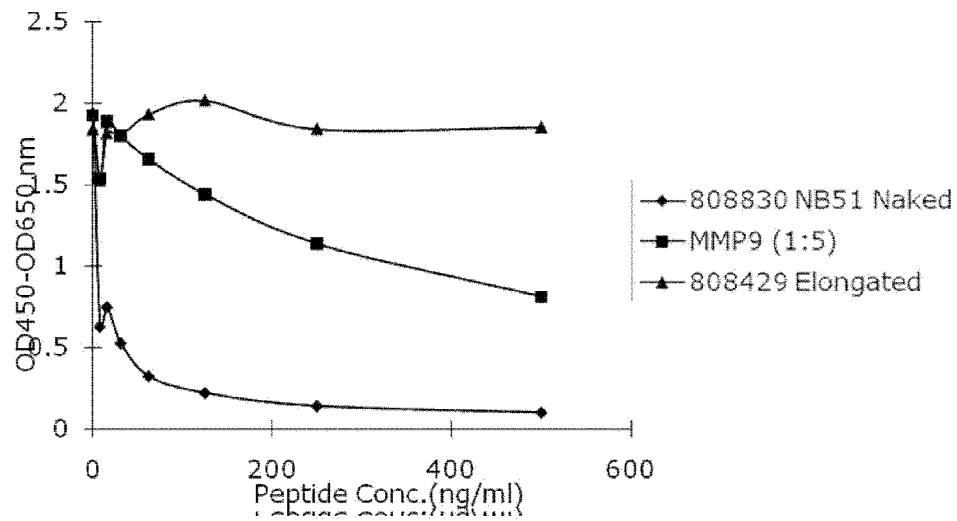


Figure 7

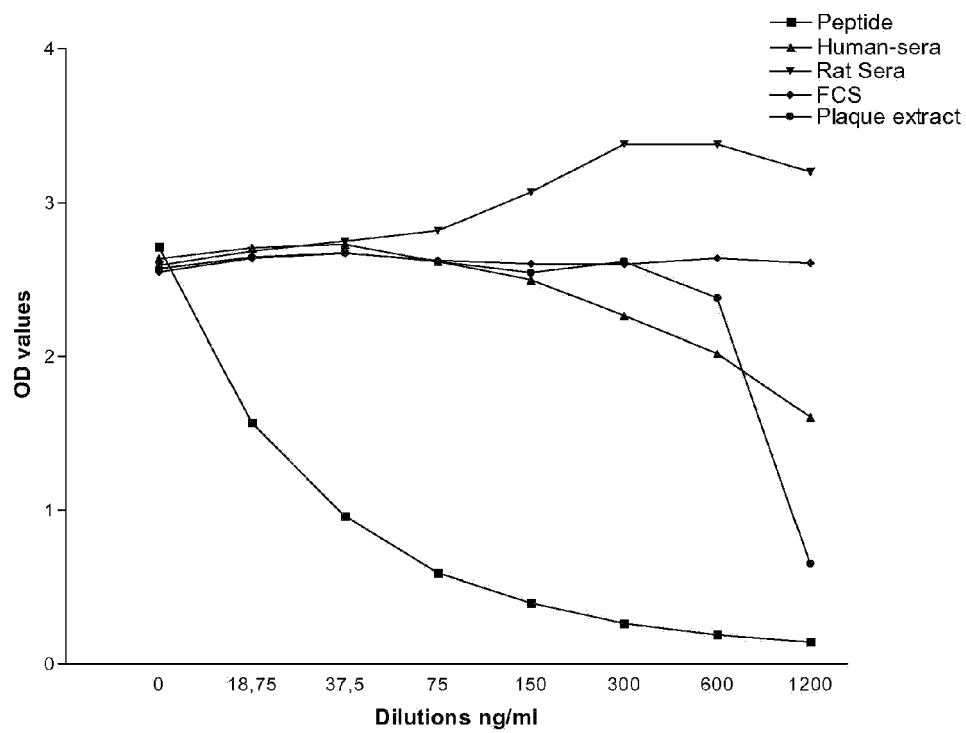


Figure 8

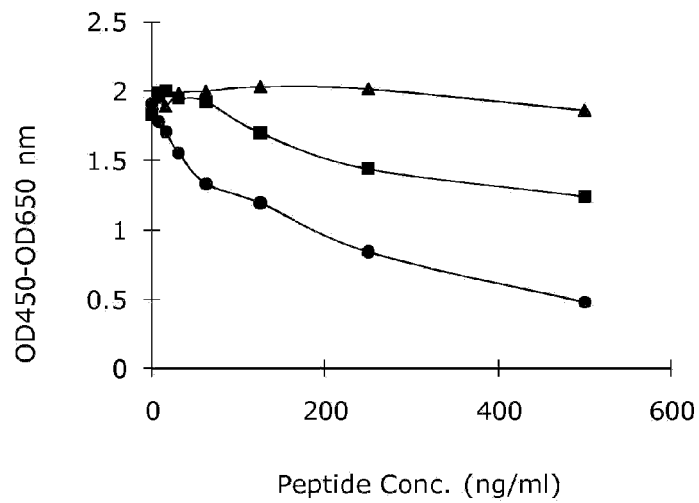


Figure 9

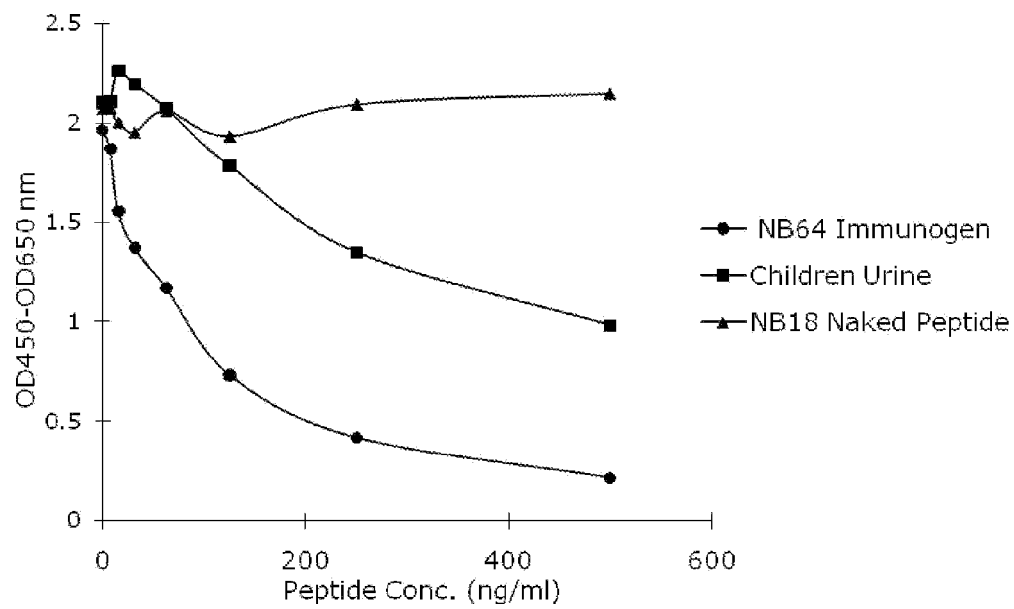


Fig 10

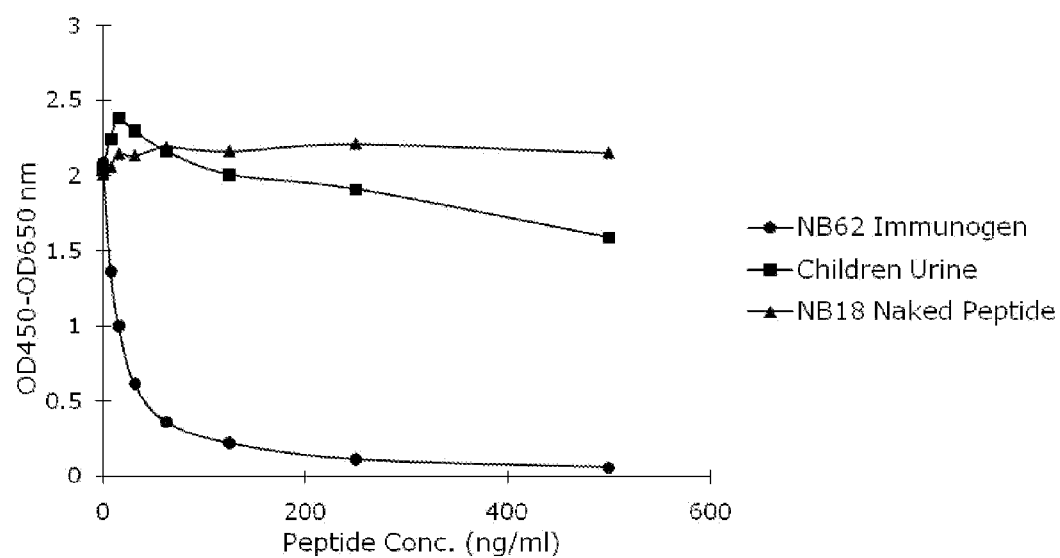


Fig 11