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(74) Agent: ACOSTA, Melissa, W.; Fulbright & Jaworski
L.L.P., Fulbright Tower, 1301 McKinney, Suite 5100,
Houston, TX 77010-3095 (US).

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(71) Applicant (for all designated States except US): AGEN-
NIX INCORPORATED [US/US]; 8 Greenway Plaza
Suite 910, Houston, TX 77046 (US).

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(72) Inventors; and

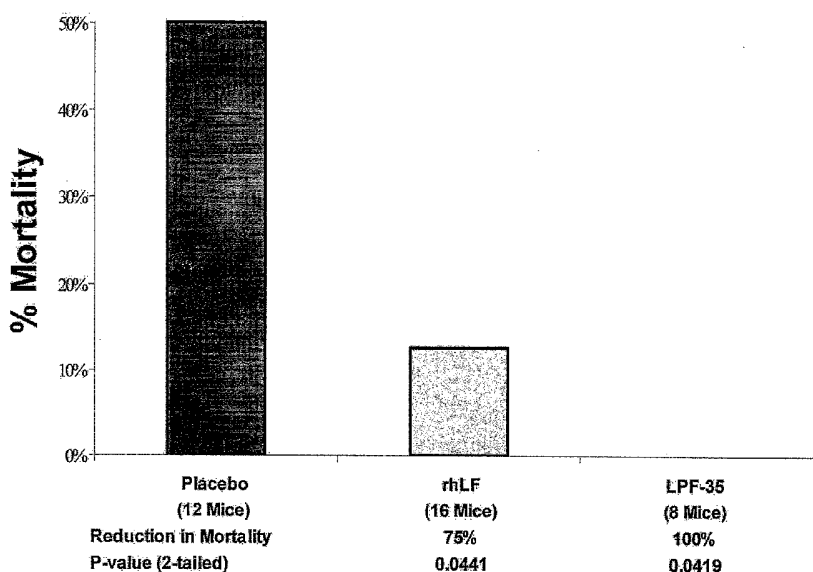
(75) Inventors/Applicants (for US only): VARAD-
HACHARY, Atul [IN/US]; 4328 Lula Street, Houston,
TX 77401 (US). GLYNN, Peter [US/US]; 3710 Bradley,
Houston, TX 77009 (US). PETRAK, Karel [GB/US];
707 Knox Street, Houston, Texas 77077 (US). ENGEL-
MAYER, Jose [MX/US]; 7315 Brompton, Apt. 250-B,
Houston, TX 77025 (US).

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(54) Title: COMPOSITIONS OF LACTOFERRIN RELATED PEPTIDES AND USES THEREOF



(57) Abstract: The present invention is directed to a composition consisting of a series of novel biologically active 33-mer peptides.

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COMPOSITIONS OF LACTOFERRIN RELATED PEPTIDES AND USES THEREOF RELATED APPLICATIONS

[0001] This Application claims priority to U.S. Provisional Application No. 60/622,172 filed October 26, 2004, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The present invention is directed to a composition consisting of a series of novel biologically active 33-mer peptides.

BACKGROUND OF THE INVENTION

[0003] Lactoferrin is a single chain metal binding glycoprotein. Many cell types, such as monocytes, macrophages, lymphocytes, and brush-border cells in the intestine, are known to have lactoferrin receptors. Lactoferrin is found mainly in external secretions of mucosal epithelia such as breast milk, saliva, tears, bile, and pancreatic fluid and has a wide array of functions related to host primary defense mechanisms. For example, lactoferrin has been reported to activate natural killer (NK) cells, induce colony stimulating activity, activate polymorphonuclear neutrophils (PMN), regulate granulopoiesis, enhance antibody-dependent cell cytotoxicity, stimulate lymphokine-activated killer (LAK) cell activity, and potentiate macrophage toxicity. Lactoferrins have been reported to have a number of beneficial effects including anti-infective, anti-inflammatory, immunomodulatory and anti-cancer activities.

[0004] Recombinant human lactoferrin has previously been described as being purified after expression in a variety of prokaryotic and eukaryotic organisms including aspergillus (US Patent No. 6,080,559), cattle (US Patent No. 5,919,913), rice, corn, *Sacharomcyes* (US Patent No. 6,228,614) and *Pichia pastoris* (US Patent No. 6,455,687, 6,277,817, 6,066,469). Also described are expression systems for the expression of full-length human lactoferrins (e.g. US Patent No. 6,100,054). In all cases, part of the teaching is expression of the full length cDNA and purification of the intact protein whose N-terminal, after processing of the leader peptide, is the amino acid glycine. Nuijens, et al. (US Patent No. 6,333,311) separately describe variants of human lactoferrin but their focus is limited to deletion or substitution of arginine residues found in the N-terminal domain of lactoferrin.

[0005] LF contains a strongly basic region close to its N-terminus and binds to a variety of anionic biological molecules including lipid A (Appelmelk et al., *Infect. Immun.* 62: 2628-2632 (1994)) and glycosaminoglycans which occur on the surface of most cells and in most extracellular matrices (Mann et al., *J. Biol. Chem.* 269: 23661-7 (1994)). Lactoferricin H (residues 1-47) and lactoferricin B (residue 17-41) are released by pepsinolysis of human or

bovine LF, respectively, and may have more potent antibacterial activity than the native proteins (Bellamy et al., *Biochim. Biophys. Acta.* 1121: 130-136 (1992)). A region composed of residues 28-34 is reported to contribute to the high affinity binding of human LF and lactoferricin H to endotoxin (Elass-Rochard et al., *Biochem. J.* 312: 839-845 (1995)). LF and lactoferricin B have been shown to inhibit the endotoxin-induced interleukin-6 response in human monocytic cells (Mattsby-Baltzer et al., *Pediatr. Res.* 40: 257-262 (1996)). Previously identified fragments of LF which exhibit antimicrobial activity were isolated from pepsin hydrolysates of LF (Tomita et al., (1993) U.S. Pat. No. 5,214,028; Tomita et al., (1994) U.S. Pat. No. 5,304,633; Tomita et al., (1994) U.S. Pat. No. 5,317,084; Tomita et al., (1997) U.S. Pat. No. 5,656,591).

[0006] Previous studies have established that the N-terminal 33 residues of human LF represent the minimal sequence that mediates binding of the protein to anionic polysaccharides such as glycosaminoglycans (Mann et al., *J. Biol. Chem.* 269: 23661-7 (1994)). This sequence contains a cationic head (residues 1-6) and tail (residues 28-33) which combine to form the glycosaminoglycan-binding site. In further studies described by Mann in U.S. Pat. No. 6,399,570, lactoferrin peptide fragments having up to the first 51 amino acids encompassed endotoxin neutralizing ability and antimicrobial activity. Mann further showed that up to 17 amino acids could be deleted from the C-terminus and up to 3 amino acids could be deleted N-terminus of the 51 amino acid long peptide while retaining the endotoxin neutralizing ability and antimicrobial activity.

[0007] The present invention is the first to describe a peptide composition that consists of lactoferrin related peptides which are at least 33 amino acids in length in which at least four amino acids at the C and/or N terminus are substituted for positive amino acids resulting in an enhancement of its biological activity.

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention is directed to a composition consisting of a series of biologically active peptides. The peptides of the present invention comprise at least 33 amino acids in which at least four amino acids at the C and/or N terminus are substituted for positive amino acids. These biologically active peptides can be used to treat a variety of pathological conditions, for example, but not limited to hyperproliferative disease, respiratory disorder, cardiovascular disease, neurological condition, autoimmune disorder, infectious disease, gastrointestinal disorder, endocrine and/or metabolism disorder, hematological disorder, ocular disorder, integument disorder, pain and a wound.

[0009] One embodiment of the present invention comprises a pharmaceutical composition that induces modulation of the immune system whereby the composition stimulates production of MIP-3alpha from hepatocytes. The composition can also inhibit bacterial growth as measured by minimum inhibitory concentration (MIC). More specifically, the composition comprises an amino acid sequence selected from the group consisting of SEQ.ID.NO.1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, and SEQ.ID.NO.11.

[0010] In certain embodiments, the pharmaceutical composition comprises at least four consecutive positively charged residues at the N-terminus or at least four positively charged residues at the C-terminus or at least four positively charged residues at each of the N- and C-termini. Thus, the pharmaceutical composition may comprise at least 25% positively charged residues or at least 33% positively charged residues. The positively charged residues are arginine, lysine or derivatives thereof.

[0011] In further embodiments, the pharmaceutical composition can further comprise a metal chelator. The metal chelator is selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), [ethylenebis (oxyethylenenitrilo)] tetraacetic acid (EGTA), 1,2-bis(2-aminophenoxy)ethane-N,N',N'-tetraacetic acid (BAPTA), and hydroxyethylene triamine diacetic acid, (HEDTA).

[0012] Another embodiment of the present invention comprises an isolated polypeptide having an amino acid sequence as defined in SEQ.ID.NO. 1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, or SEQ.ID.NO.11. The polypeptide is admixed with a pharmaceutically acceptable carrier.

[0013] Yet further, another embodiment comprises an expression vector comprising a nucleic acid sequence encoding an amino acid sequence selected from the group consisting of SEQ.ID.NO. 1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, and SEQ.ID.NO.11. The expression vector is further defined as a viral or plasmid vector. The viral vector is an adenoviral vector, an adeno-associated viral vector, a retroviral vector, a lentiviral vector, a herpes viral vector, polyoma viral vector, pox vector, or hepatitis B viral vector.

[0014] In certain embodiments, the present invention comprises a method of treating a pathological condition comprising the step of administering the pharmaceutical composition, or the polypeptide or the expression vector. It is understood that the

pharmaceutical composition or the polypeptide or the expression vector can be combined with a standard therapy to treat the pathological condition.

[0015] The pathological condition is selected from the group consisting of hyperproliferative disease, respiratory disorder, cardiovascular disease, neurological condition, autoimmune disorder, infectious disease, gastrointestinal disorder, endocrine and/or metabolism disorder, hematological disorder, ocular disorder, integument disorder, pain and a wound.

[0016] More specifically, the hyperproliferative disease is further defined as cancer. Exemplary cancers include, but are not limited to melanoma, non-small cell lung cancer, small-cell lung cancer, lung cancer, leukemia, hepatocarcinoma, retinoblastoma, astrocytoma, glioblastoma, gum cancer, tongue cancer, neuroblastoma, head cancer, neck cancer, breast cancer, pancreatic cancer, prostate cancer, renal cancer, bone cancer, testicular cancer, ovarian cancer, mesothelioma, cervical cancer, gastrointestinal cancer, lymphoma, myeloma, brain cancer, colon cancer, sarcoma or bladder cancer.

[0017] In certain embodiments the pharmaceutical composition or the polypeptide or the expression vector can be combined with a standard anti-cancer therapy to treat the cancer. The anti-cancer agent selected from the group consisting of chemotherapy, surgery, radiotherapy, an immunostimulant, anti-cancer biologic agent or a cancer vaccine

[0018] Yet further, hyperproliferative disease can also encompass rheumatoid arthritis, infectious arthritis, inflammatory bowel disease, osteoarthritis, leiomyomas, adenomas, lipomas, hemangiomas, fibromas, vascular occlusion, restenosis, atherosclerosis, pre-neoplastic lesions, carcinoma in situ, oral hairy leukoplakia, or psoriasis.

[0019] Exemplary neurological conditions that may be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to multiple sclerosis, Alzheimer's disease, Parkinson's disease, muscular dystrophy, sleep or depression.

[0020] Gastrointestinal disorders that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to Crohn's disease, colitis, necrotizing enterocolitis, endometriosis, irritable bowel syndrome, pancreatitis, periodontal disease, and ulcerative colitis.

[0021] Exemplary autoimmune disorders that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to graft versus host disease (GVHD), organ transplant rejection, autoimmune hepatitis, primary biliary cirrhosis, autoimmune cholangitis, primary sclerosing

cholangitis, irritable bowel syndrome (IBS), multiple sclerosis (MS), chronic granulomatous disease, ankylosing spondylitis, scleroderma, polymyositis, (dermato)myositis, systemic vasculitis, systemic lupus erythematosus (SLE), Crohn's disease, insulin-dependent diabetes (type 1) or ulcerative colitis.

[0022] Endocrine and/or metabolism disorder that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to diabetes mellitus, thyroid disorder, or osteoporosis.

[0023] Hematological disorders that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to anaemia, sickle cell anemia or cachexia.

[0024] Infectious diseases that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to a disease that result from infection of either a virus, a bacterium or a fungus or a combination thereof. Exemplary viruses include, but are not limited to herpes simplex, labilis zoster, HIV, hepatitis A, hepatitis B, or hepatitis C. Infectious disease can include HIV, hepatitis, West Nile Virus bacterial meningitis, paramenigeal infections, septic thrombophlebitis, candidiasis, myocarditis, bacteremia, sepsis, or septic shock.

[0025] Ocular disorder that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to conjunctivitis, dry eye disease, glaucoma, allergic eye disease, uveitis or ocular infection.

[0026] Cardiovascular disease that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to congestive heart failure, hypertension, cardiomyopathy, myocarditis, atherosclerosis, chronic venous disease, or heart arrhythmia.

[0027] In further embodiments, the pathological condition is elevated cholesterol or dyslipidemia.

[0028] The wound that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to skin wound, internal wound, gastrointestinal wound, oral wound, ophthalmic wound, surgical wound and fractures.

[0029] The respiratory disorder that can be treated using the pharmaceutical composition or the polypeptide or the expression vector of the present invention can include, but are not limited to atopic asthma, non-atopic asthma, emphysema, bronchitis, chronic obstructive

pulmonary disease (COPD), sinusitis, allergic rhinitis, fibrotic lung disease, ARDS, pulmonary vascular disease/pulmonary hypertension, Cor Pulmonale, or cystic fibrosis.

[0030] In further embodiments, the composition stimulates the production of IL-18. Yet further, the composition stimulates the production of IL-12, GM-CSF, or IFN- γ . Still further, composition stimulates or supplements immune cells, exemplary immune cells are T lymphocytes, B-lymphocytes, dendritic cells (DCs), other antigen presenting cells (APCs), natural killer (NK) cells, macrophages or monocytes. The T lymphocytes are selected from the group consisting of CD4+, CD8+, CD3+ and CD40+ cells and the B-lymphocytes are CD40+ cells.

[0031] In certain embodiments, the composition is administered orally, inhalation, nasally, topically or parenterally. Parenterally can include subcutaneously, intramuscularly, intraperitoneally, intravenously, intraarterially, intramyocardially, transendocardially, transepically, intrathecally or intra-tumorally.

[0032] The foregoing has outlined rather broadly the features and technical advantages of the present invention in order that the detailed description of the invention that follows may be better understood. Additional features and advantages of the invention will be described hereinafter which form the subject of the claims of the invention. It should be appreciated by those skilled in the art that the conception and specific embodiment disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present invention. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the invention as set forth in the appended claims. The novel features which are believed to be characteristic of the invention, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] For a more complete understanding of the present invention, reference is now made to the following descriptions taken in conjunction with the accompanying drawing, in which:

[0034] FIG. 1 shows in vitro NK cell activation, as measured by the percent killing of target cells, by peptide LPF-35.

[0035] FIG. 2 shows T cell stimulation by peptide LPF-35 for various cell surface cluster markers including CD3/CD4, CD3/CD8, CD4/CD69 and CD8/CD69.

[0036] FIG. 3 shows the reduction in mortality achieved with peptide LPF-35 in a mouse model of sepsis versus placebo and a positive control using recombinant human lactoferrin.

[0037] FIG. 4 shows the reduction in eye damage achieved using various concentrations of peptide LPF-35 versus saline control in a rabbit model of dry eye disease.

[0038] FIGS. 5A and 5B show the effects of a single oral dose of either peptide LPF-32 or peptide LPF-35 on lung resistance (FIG. 5A) and airway hyperresponsiveness (FIG. 5B) to carbachol in a sheep model of asthma.

[0039] FIGS. 6A and 6B show the effects of peptide LPF-35, at various doses after 3 days of oral administration, on lung resistance (FIG. 6A) and airway hyperresponsiveness (FIG. 6B) to carbachol in a sheep model of asthma.

[0040] FIGS. 7A and 7B show that the rate and incidence of wound healing are increased following topical treatment with different concentrations of peptide LPF-35 in a mouse model of chronic wounds. FIG. 7A shows the effects on acceleration of wound closure. FIG. 7B shows the increase in incidence of wound healing.

[0041] FIGS. 8A and 8B show the effect of oral administration of peptide LPF-35, at different doses, on decreasing the blood levels of glucose (FIG. 8A) and insulin (FIG. 8B) in a mouse model of diabetes.

[0042] FIG. 9 shows the effect of peptide LPF-35, at different doses and time points, on the expression of MIP-3-alpha in hepatocytes.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0043] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. For purposes of the present invention, the following terms are defined below.

[0044] As used herein, the use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." Still further, the terms "having", "containing", "including" and "comprising" are interchangeable and one of skill in the art is cognizant that these terms are open ended terms.

[0045] The term “acute pain” as used herein includes tissue injury or pathology. For example, acute pain includes, but is not limited to pain following surgery (e.g., surgery), pain following trauma (e.g., blunt or sharp injury, bullet wounds), pain associated with athletic injury, and the occasional headache. Medically, acute pain can have a diagnostic value; that is, it leads to the discovery of a pathological condition. Yet further, acute pain lasts or is anticipated to last for a short period of time, typically less than one to two months. Acute pain is associated with hyperactivity of the sympathetic nervous system, for example, tachycardia, increased respiratory rate, increased blood pressure, increased cortisol release, diaphoresis and dilated pupils.

[0046] The term “antibiotic” as used herein is defined as a substance that inhibits the growth of microorganisms without damage to the host. For example, the antibiotic may inhibit cell wall synthesis, protein synthesis, nucleic acid synthesis, or alter cell membrane function. Classes of antibiotics that can possibly be used include, but are not limited to, macrolides (e.g., erythromycin), penicillins (e.g., nafcillin), cephalosporins (e.g., cefazolin), carbapenems (e.g., imipenem, aztreonam), other beta-lactam antibiotics, beta-lactam inhibitors (e.g., sulbactam), oxalines (i.e. linezolid), aminoglycosides (e.g., gentamicin), chloramphenicol, sulfonamides (e.g., sulfamethoxazole), glycopeptides (e.g., vancomycin), quinolones (e.g., ciprofloxacin), tetracyclines (e.g., minocycline), fusidic acid, trimethoprim, metronidazole, clindamycin, mupirocin, rifamycins (e.g., rifampin), streptogramins (e.g., quinupristin and dalfopristin) lipoprotein (e.g., daptomycin), polyenes (e.g., amphotericin B), azoles (e.g., fluconazole), and echinocandins (e.g., caspofungin acetate). The term “morbidity” as used herein is the state or condition of being diseased. Yet further, morbidity can also refer to the ratio of incidence, for example the number of sick subjects or cases of diseases in relationship to a specific population.

[0047] The term “anti-depressant drug” as used herein includes compounds that provide pain relief by reducing side-effects including anxiety. Anti-depressant drugs include, for example, but are not limited to tricyclic antidepressants, sedatives, tranquilizers, hypnotics, anti-histamines, and amphetamines.

[0048] The term “antimicrobial” as used herein is defined as a substance that inhibits the growth of microorganisms without damage to the host, for example antibiotics, anti-fungal and antiseptics.

[0049] The term “atherosclerosis” as used herein includes a form of arteriosclerosis characterized by a combination of changes in the intima of arteries, such changes include, but are not limited to accumulation of lipids, complex carbohydrates, blood and blood products, fibrous

tissue and calcium deposits. Yet further, atherosclerotic plaques can be characterized into at least two areas. One type is characterized by prominent proliferation of cells with small accumulations of lipids. The second type consists mostly of intracellular and extracellular lipid accumulation and a small amount of cellular proliferation.

[0050] The term “bacteremia” as used herein is defined as having a focus of bacterial infection or bacteria in the blood of the subject.

[0051] The term “cancer” as used herein is defined as a hyperproliferation of cells whose unique trait—loss of normal control—results in unregulated growth, lack of differentiation, local tissue invasion, and metastasis. Examples include but are not limited to, melanoma, non-small cell lung, small-cell lung, lung, hepatocarcinoma, leukemia, retinoblastoma, astrocytoma, glioblastoma, gum, tongue, neuroblastoma, head, neck, breast, pancreatic, prostate, renal, bone, testicular, ovarian, mesothelioma, cervical, gastrointestinal, lymphoma, brain, colon, sarcoma or bladder cancer.

[0052] The term “cardiovascular disease or disorder” as used herein refers to disease and disorders related to the cardiovascular or circulatory system. Cardiovascular disease and/or disorders include, but are not limited to, diseases and/or disorders of the pericardium, heart valves (e.g., incompetent valves, stenosed valves, rheumatic heart disease, mitral valve prolapse, aortic regurgitation), myocardium (e.g., coronary artery disease, myocardial infarction, heart failure, ischemic heart disease, angina), blood vessels (e.g., hypertension, arteriosclerosis, aneurysm) or veins (e.g., varicose veins, hemorrhoids). Yet further, one skilled in the art recognizes that cardiovascular diseases and/or disorders can result from congenital defects, genetic defects, environmental influences (e.g., dietary influences, lifestyle, stress, etc.), and other defects or influences.

[0053] The term “cell,” “cell line,” and “cell culture” as used herein may be used interchangeably. All of these terms also include their progeny, which are any and all subsequent generations. It is understood that all progeny may not be identical due to deliberate or inadvertent mutations.

[0054] The term “chemokine” as used herein refers to small cytokines that are involved in the migration and activation of cells, for example phagocytic cells and lymphocytes. One of skill in the art realizes that chemokines play a central role in inflammatory and immune response processes.

[0055] The term “cholesterol” as used herein refers to the monohydric alcohol form, which is a white, powdery substance that is found in all animal cells and in animal-based

foods (not in plants). Cholesterol is an essential nutrient necessary for many functions, including the following: repairing cell membranes, manufacturing vitamin D on the skin's surface, production of hormones, such as estrogen and testosterone, and possibly helping cell connections in the brain that are important for learning and memory.

[0056] The term "chronic pain" as used herein refers to pain that lasts longer than 1 month or beyond the resolution of an acute tissue injury or is recurring or is associated with tissue injury and/or chronic diseases that are expected to continue or progress, for example, cancer, arthritis, inflammatory disease, chronic wounds, cardiovascular accidents, spinal cord disorders, central nervous system disorder or recovery from surgery. Chronic pain can be associated with several factors that include, but are not limited to lassitude, sleep disturbance, decreased appetite, loss of taste for food, weight loss, diminished libido, constipation, or depression.

[0057] The term "chylomicron" as used herein refers to the largest in size and lowest in density of the triglyceride carrying lipoproteins.

[0058] The term "cytokine" as used herein refers to proteins that are made by cells that affect the behavior of other cells, for example stimulate or inhibit cell proliferation. For example, cytokines that are made by lymphocytes are often called lymphokines or interleukins. One of skill in the art realizes that the term cytokine is a generic term used in the literature to refer to proteins that are made by cells that can affect the behavior of other cells.

[0059] The term "diabetes mellitus" as used herein refers to a disorder of carbohydrate metabolism that is typically characterized by hyperglycemia and glycosuria, which results from inadequate production or utilization of insulin. Diabetes mellitus includes several syndromes or disorders, for example, but not limited to, primary diabetes mellitus (e.g., insulin-dependent (Type I) and non-insulin-dependent (Type II)); secondary diabetes [for example: pancreatic diabetes (e.g., destruction of the pancreas, removal of the pancreas, etc.); extrapancreatic/endocrine diabetes (e.g., hypersomatotropism, hyperadrenalism, hyperthyroidism, glucagonoma, etc.); drug-induced diabetes (e.g., steroid diabetes, thiazides, etc.)] and rare/exceptional forms of diabetes (e.g., lipoatrophic diabetes, myatonic diabetes, disturbance of insulin receptors, genetic syndromes, etc). Long-term complications of diabetes include neuropathy, retinopathy, nephropathy, generalized degenerative changes in the blood vessels and increased susceptibility to infection.

[0060] The term “effective amount” or “therapeutically effective amount” as used herein refers to an amount that results in an improvement or remediation of the symptoms of the disease or condition.

[0061] The term “expression construct” or “transgene” is defined as any type of genetic construct containing a nucleic acid coding for gene products in which part or all of the nucleic acid encoding sequence is capable of being transcribed can be inserted into the vector. The transcript is translated into a protein, but it need not be. In certain embodiments, expression includes both transcription of a gene and translation of mRNA into a gene product. In other embodiments, expression only includes transcription of the nucleic acid encoding genes of interest. In the present invention, the term “therapeutic construct” may also be used to refer to the expression construct or transgene.

[0062] The term “expression vector” refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. In some cases, RNA molecules are then translated into a protein, polypeptide, or peptide. Expression vectors can contain a variety of control sequences, which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operatively linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described infra. In the present invention, the term “therapeutic vector” may also be used to refer to the expression vector.

[0063] The term “fragile bone condition” or “fragile bone disease” as used herein refers to a condition or disease characterized by low bone mass or structural deterioration of bone tissue, leading to bone fragility and increased susceptibility to fractures.

[0064] The term “gastrointestinal disorder or conditions” as used herein includes gastrointestinal disorders in which one or more of the symptoms and conditions affect the gastrointestinal tract from the mouth to the anus, as well as any organ that may play a role in digestion, for example, but not limited to the pancreas, or the gall bladder. Gastrointestinal disorders include, but are not limited to, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, early satiety, epigastric pain, nausea, vomiting, burbulence, regurgitation, intestinal pseudoobstruction, anal incontinence, gastroesophageal reflux disease, irritable bowel syndrome, ulcerative colitis, Crohn's disease, renal disorders, menstrual cramps, pancreatitis, spastic and interstitial cystitis and ulcers and the visceral pain associated therewith.

[0065] The term "Grade 3 neutropenia" refers to the reduction of the absolute neutrophil cell count (ANC) to less than about 1000 cells/ μ L. The term "neutropenia" generally refers to a condition in which the ANC is reduced to 1000 cells/ μ L or less. Such a condition may be caused by depressed production, increased peripheral destruction of neutrophils. The most common neutropenias are iatrogenic, resulting from the widespread use of cytotoxic or immunosuppressive therapies for cancer treatment or control of autoimmune disorders. Other causes of neutropenia include induction by drugs, hematological diseases including idiopathic, cyclic neutropenia, Chediak-Higashi syndrome, aplastic anemia, infantile genetic disorders, tumor invasion such as myelofibrosis, nutritional deficiency; infections such as tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis, AIDS, antineutrophil antibodies and/or splenic or lung trapping, autoimmune disorders, Wegner's granulomatosis, acute endotoxemia, hemodialysis, and cardiopulmonary bypass. The present invention applies to any acquired and inherited neutropenic conditions.

[0066] The term "graft-versus-host-disease" or "GVHD" as used herein is the pathological reaction that occurs between the host and grafted tissue. The grafted or donor tissue dominates the pathological reaction. Graft-versus-host-disease (GVHD) can be seen following stem cell and/or solid organ transplantation. GVHD occurs in immunocompromised subjects, who when transplanted, receive "passenger" lymphocytes in the transplanted stem cells or solid organ. These lymphocytes recognize the recipient's tissue as foreign. Thus, they attack and mount an inflammatory and destructive response in the recipient. GVHD has a predilection for epithelial tissues, especially skin, liver, and mucosa of the gastrointestinal tract. GVHD subjects are immunocompromised due to the fact that prior to transplant of the graft, the subject receives immunosuppressive therapy.

[0067] The term "gram-negative bacteria" or "gram-negative bacterium" as used herein is defined as bacteria which have been classified by the Gram stain as having a red stain. Gram-negative bacteria have thin walled cell membranes consisting of a single layer of peptidoglycan and an outer layer of lipopolysaccharide, lipoprotein, and phospholipid. Exemplary organisms include, but are not limited to, Enterobacteriaceae consisting of Escherichia, Shigella, Edwardsiella, Salmonella, Citrobacter, Klebsiella, Enterobacter, Hafnia, Serratia, Proteus, Morganella, Providencia, Yersinia, Erwinia, Buttlauxella, Cedecea, Ewingella, Kluyvera, Tatumella and Rahnella. Other exemplary gram-negative organisms not in the family Enterobacteriaceae include, but are not limited to, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia, Cepacia, Gardenerella, Vaginalis, and Acinetobacter species.

[0068] The term “gram-positive bacteria” or “gram-positive bacterium” as used herein refers to bacteria, which have been classified using the Gram stain as having a blue stain. Gram-positive bacteria have a thick cell membrane consisting of multiple layers of peptidoglycan and an outside layer of teichoic acid. Exemplary organisms include, but are not limited to, *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, enterococci, corynebacteria, and *Bacillus* species.

[0069] The term “high-density lipoprotein” or “HDL” as used herein is the smallest and most dense type of cholesterol-carrying lipoprotein and is often referred to as the “good” cholesterol.

[0070] The term “hyperproliferative disease” is defined as a disease that results from a hyperproliferation of cells. Exemplary hyperproliferative diseases include, but are not limited to cancer or autoimmune diseases. Other hyperproliferative diseases may include vascular occlusion, restenosis, atherosclerosis, or inflammatory bowel disease.

[0071] The term “immunocompromised” as used herein is defined as a subject who is, at the time of pathogen exposure, has a pre-existing condition that reduces one or more mechanisms for normal defense against infection. The immunocompromised condition may be due to a defect or dysfunction of the immune system or to other factors that heighten susceptibility to infection, for example immunosuppressive agents. Although such a categorization allows a conceptual basis for evaluation, immunocompromised individuals with infection often do not fit completely into one group or the other. More than one defect in the body’s defense mechanisms may be affected. For example, an immunocompromised state can result from indwelling central lines or other types of impairment due to intravenous drug abuse; or be caused by secondary malignancy, malnutrition, or having been infected with other infectious agents such as tuberculosis, influenza, *Staphylococcus aureus* or sexually transmitted diseases, e.g., syphilis or hepatitis.

[0072] The term “insulin-dependent diabetes mellitus”; “IDDM” or “Type I” refer to diabetes that is characterized by a hyperglycemia, glycosuria, and low blood insulin levels. Type I diabetes can develop at any age. It typically has an abrupt onset during the first two decades of life. Insulin therapy is usually required.

[0073] The term “intermediate density lipoprotein” or “IDL” as used herein refers to a triglyceride-carrying lipoprotein.

[0074] The term “lactoferrin composition” as used herein refers to a composition having a lactoferrin related peptide.

[0075] The term “lactoferrin” or “LF” as used herein refers to native or recombinant lactoferrin. Native lactoferrin can be obtained by purification from mammalian milk or colostrum or from other natural sources. Recombinant lactoferrin (rLF) can be made by recombinant expression or direct production in genetically altered animals, plants, fungi, bacteria, or other prokaryotic or eukaryotic species, or through chemical synthesis.

[0076] The term “lipid” as used herein refers to the building blocks of any of the fats or fatty substances found in animals and plants, which are characterized by their insolubility in water and solubility in fat solvents such as alcohol, ether and chloroform. Lipids include fats (e.g., esters of fatty acids and glycerol); lipoids (e.g., phospholipids, cerebrosides, waxes) and sterols (e.g., cholesterol).

[0077] The term “lipoproteins” as used herein are protein spheres that transport cholesterol, triglyceride, or other lipid molecules through the bloodstream. Lipoproteins are categorized into five types according to size and density. They can be further defined by whether they carry cholesterol [the two smaller lipoproteins (HDL and LDL)] or triglycerides [the three largest lipoproteins (IDL, VLDL, and chylomicrons)].

[0078] The term “low density lipoprotein” or “LDL” as used herein is a type of cholesterol-carrying lipoprotein which is often called the "bad" cholesterol.

[0079] The term “metal chelator” as used herein refers to a compound which binds metal. Metal chelators that can be used in the present invention include the divalent metal chelators, for example, ethylenediaminetetraacetic acid (EDTA), [ethylenebis(oxyethylenenitrilo)] tetraacetic acid (EGTA), 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), hydroxyethylene triamine diacetic acid (HEDTA), or salts thereof.

[0080] The term “morbidity” as used herein is the state of being diseased. Yet further, morbidity can also refer to the disease rate or the ratio of sick subjects or cases of disease in to a given population.

[0081] The term “mortality” as used herein is the state of being mortal or causing death. Yet further, mortality can also refer to the death rate or the ratio of number of deaths to a given population.

[0082] The term “neurology” or “neurological” refers to conditions, disorders, and/or diseases that are associated with the nervous system. Thus, any condition, disorder and/or disease that effects any component or aspect of the nervous system (either central or peripheral) is referred to as a neurological condition, disorder and/or disease. As used herein, the term “neurological” or “neurology” encompasses the terms “neuropsychiatric” or “neuropsychiatry”

and “neuropsychological” or “neuropsychological”. Thus, a neurological disease, condition, or disorder includes, but is not limited to cognitive disorders, affective disorders (e.g., depression disorders and/or anxiety disorders), movement disorders, mental disorders, pain disorders, sleep disorders, etc.

[0083] The term “neutropenia” as used herein refers to an a decrease or small number of neutrophils in the blood compared to normal. For example, the World Health Organization defines neutropenia as a subject having an absolute neutrophil cell count (ANC) of about 2000 cells/ μ L or less. Thus, as used herein a subject suffering from neutropenia is one having an ANC of about 2000 cells/ μ L or less, for example 1000 cells/ μ L or even less than 500 cells/ μ L.

[0084] The term “non-insulin-dependent diabetes mellitus”; “NIDDM” or Type II” refer to diabetes that is characterized by hyperglycemia and insulin levels being normal to high. Typically, Type II diabetes is a form of diabetes mellitus that has gradual onset in obese individuals over the age of 35. Insulin therapy is usually not required; however, Type II diabetics can be destined or prone to become fully insulin-dependent.

[0085] The term “oral administration” as used herein includes oral, buccal, enteral or intragastric administration.

[0086] The term “organ or tissue transplant rejection” as used herein refers to a consequence of organ or tissue transplantation caused by the recipient's or host's immune system in response to the transplanted organ/tissue, which can damage or destroy it. Thus, one of skill in the art realizes that “organ or tissue transplant rejection” is controlled by the host subject.

[0087] The term “osteoporosis” as used herein is defined as a general term for describing any disease process that results in reduction in the mass of bone.

[0088] The term “pain” as used herein refers to an unpleasant sensation. For example, the subject experiences discomfort, distress or suffering. Pain of a moderate or high intensity is typically accompanied by anxiety. Thus, one of skill in the art is cognizant that pain may have dual properties, for example sensation and emotion.

[0089] The term “parenteral administration” as used herein includes any form of administration in which the compound is absorbed into the subject without involving absorption via the intestines. Exemplary parenteral administrations that are used in the present invention include, but are not limited to intramuscular, intravenous, intraperitoneal, intraocular, subcutaneous, or intraarticular or intratumoral administration. Yet further, parenteral administration also includes administration into a surgical field.

[0090] The term “peptide composition” as used herein refers to a composition comprising at least one of the lactoferrin related peptides of the present invention. Such peptides include, but are not limited to SEQ.ID.NO.1 (LFP-21), SEQ.ID.NO.2 (LFP-22), SEQ.ID.NO.3 (LFP-23), SEQ.ID.NO.4 (LFP-24), SEQ.ID.NO.5 (LFP-25), SEQ.ID.NO.6 (LFP-31), SEQ.ID.NO.7 (LFP-32), SEQ.ID.NO.8 (LFP-33), SEQ.ID.NO.9 (LFP-34), SEQ.ID.NO.10 (LFP-35), and SEQ.ID.NO.11 (LFP-36).

[0091] The term “pharmaceutically acceptable carrier” as used herein includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the vectors or cells of the present invention, its use in therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

[0092] The term “polynucleotide” is defined as a chain of nucleotides. Furthermore, nucleic acids are polymers of nucleotides. Thus, nucleic acids and polynucleotides as used herein are interchangeable. One skilled in the art has the general knowledge that nucleic acids are polynucleotides, which can be hydrolyzed into the monomeric “nucleotides.” The monomeric nucleotides can be hydrolyzed into nucleosides. As used herein polynucleotides include, but are not limited to, all nucleic acid sequences which are obtained by any means available in the art, including, without limitation, recombinant means, i.e., the cloning of nucleic acid sequences from a recombinant library or a cell genome, using ordinary cloning technology and PCRTM, and the like, and by synthetic means. Furthermore, one skilled in the art is cognizant that polynucleotides include mutations of the polynucleotides, include but are not limited to, mutation of the nucleotides, or nucleosides by methods well known in the art.

[0093] The term “polypeptide” is defined as a chain of amino acid residues, usually having a defined sequence. As used herein the term polypeptide is interchangeable with the terms “peptides” and “proteins”.

[0094] The term “preventing” as used herein refers to minimizing, reducing or suppressing the risk of developing a disease state or parameters relating to the disease state or progression or other abnormal or deleterious conditions.

[0095] The term “respiratory disorder” refers to any condition and/or disorder relating to respiration and/or the respiratory system. The respiratory disorder can be an allergic or non-allergic respiratory disorder. More specifically, the respiratory disorder includes, but is

not limited to atopic asthma, non-atopic asthma, emphysema, bronchitis, chronic obstructive pulmonary disease, sinusitis and allergic rhinitis.

[0096] The term “sepsis” as used herein is defined as a Systemic Inflammatory Response Syndrome to an infective process in which severe derangement of the host immune system fails to prevent extensive ‘spill over’ of inflammatory mediators from a local infection focus into the systemic circulation.

[0097] The term “septic shock” as used herein is a consequence of sepsis in which the systemic inflammatory response leads to the failure of vital organs’ function (for example of the lungs as in ARDS).

[0098] The term “subject” as used herein, is taken to mean any mammalian subject to which a lactoferrin composition is administered according to the methods described herein. Thus, a skilled artisan realizes that a mammalian subject, includes, but is not limited to humans, monkeys, horses, pigs, cows, dogs, cats, rats and mice. In a specific embodiment, the methods of the present invention are employed to treat a human subject.

[0099] The term “Th₂ cells” as used herein is defined as a subset of CD4 T-cells that are characterized by the cytokines they produce. These cells are mainly involved in stimulating B cells to produce antibody and are often called helper T-cells. It is also known that extracellular antigens tend to stimulate the production of Th₂ cells. Thus, as used herein, “Th₂ cells” is interchangeable with “helper T-cells”.

[0100] The term “topical administration” as used herein includes, but is not limited to topical, dermal, or epidermal.

[0101] The term “total cholesterol” as used herein refers to the sum of three kinds of lipids: high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. Levels of serum total cholesterol of > 200 mg/dl are levels that are an indicating risk factor for atherosclerosis and cardiovascular disease.

[0102] The term “treating” and “treatment” as used herein refers to administering to a subject a therapeutically effective amount of a recombinant human lactoferrin composition so that the subject has an improvement in the said disease condition. The improvement is any observable or measurable improvement. Thus, one of skill in the art realizes that a treatment may improve the patient condition, but may not be a complete cure of the disease.

[0103] The term “triglycerides” as used herein are composed of fatty acid molecules and are the basic chemicals contained in fats in both animals and plants.

[0104] The term “type I osteoporosis” or “postmenopausal osteoporosis” as used herein is usually found in women after the beginning of menopause. The incidence in women is six to eight times higher than that in men. It has been postulated that the cause of this osteoporosis is accelerated bone resorption. The increased bone turnover results in a secondary decrease in parathyroid hormone (PTH) secretion as well as a secondary reduction in the renal production of calcitriol. Patients present with trabecular bone loss with vertebral fractures or distal forearm fractures.

[0105] The term “type II osteoporosis” or “age-associated osteoporosis” or “senile osteoporosis” occurs in men or women over the age of 70. The mechanisms of this bone mass loss are thought to be increased PTH secretion resulting from decreased gastrointestinal calcium absorption and decreased osteoblast function. Patients usually present with fractures of the hip or vertebrae, sites that contain cortical and trabecular bone, although fractures of the pelvis, ribs, and tibia can also occur.

[0106] The term “very low density lipoprotein” or “VLDL” as used herein refers to a triglyceride carrying lipoprotein.

[0107] The term “wound” as used herein refers to any injury, such as an ulcer, as a result of disease or disorder, or as a result of an accident, incident, or surgical procedure. Wound can be further defined as acute and/or chronic.

II. Lactoferrin

[0108] The lactoferrin can be obtained through isolation and purification from natural sources, for example, but not limited to mammalian milk. The lactoferrin is preferably mammalian lactoferrin, such as bovine or human lactoferrin. In preferred embodiments, the lactoferrin is produced recombinantly using genetic engineering techniques well known and used in the art, such as recombinant expression or direct production in genetically altered animals, plants or eukaryotes, or chemical synthesis. See, *e.g.*, U.S. Patent Nos. 5,571,896; 5,571,697 and 5,571,691, which are herein incorporated by reference.

[0109] In certain aspects, the present invention provides lactoferrin variants having enhanced biological activities over natural LF and or rLF, *e.g.*, the ability to stimulate and/or inhibit cytokines or chemokines. In particular, the invention provides peptides related to lactoferrin, including deletional, substitutional or replacement variants.

A. Lactoferrin Related Peptides

[0110] In certain embodiments, the present invention concerns novel peptide compositions. As used herein, a “peptide,” “amino acid molecule,” “polypeptide,” “peptide

composition” generally refers, but is not limited to, a peptide of about 33 amino acids. As used herein, all the terms related to “peptide” are interchangeable.

[0111] More particularly, the peptides of the present invention are derived from lactoferrin. Thus, a lactoferrin related peptide includes related-compounds of the respective molecules that exhibit at least some biological activity in common with their native counterparts, for example lactoferrin. Such related-compounds include, but are not limited to, truncated polypeptides and polypeptides having fewer amino acids than the native polypeptide. The full length lactoferrin protein, which includes polypeptide sequences, for example, but are not limited to SEQ.ID.NO.12 (GenBank accession AAA36159.1), SEQ.ID.NO.13 (GenBank accession CAA38572.1); SEQ.ID.NO.14 (GenBank accession NP_032548.2); SEQ.ID.NO.15 (GenBank accession NP_002334.1); SEQ.ID.NO.16 (GenBank accession NP_851341.1); SEQ.ID.NO.17 (GenBank accession AAN11304.1); SEQ.ID.NO.18 (GenBank accession AAN75578.2); SEQ.ID.NO.19 (GenBank accession CAA06441.1); SEQ.ID.NO.20 (GenBank accession BAA13633.1); SEQ.ID.NO.21 (GenBank accession AAG48753.1); SEQ.ID.NO.22 (GenBank accession BAB03470.1); SEQ.ID.NO.23 (GenBank accession AAF82241.1); SEQ.ID.NO.24 (GenBank accession CAB53387.1); SEQ.ID.NO.25 (GenBank accession BAA07458.1); SEQ.ID.NO.26 (GenBank accession CAA09407.1); SEQ.ID.NO.27 (GenBank accession AAB60324.1); SEQ.ID.NO.28 (GenBank accession CAA55517.1); SEQ.ID.NO.29 (GenBank accession CAA40366.1); SEQ.ID.NO.30 (GenBank accession CAA37914.1); SEQ.ID.NO.31 (GenBank accession CAA37116.1); SEQ.ID.NO.32 (GenBank accession AAA97958.1); SEQ.ID.NO.33 (GenBank accession AAA59479.1); SEQ.ID.NO.34 (GenBank accession AAA59511.1); SEQ.ID.NO.35 (GenBank accession AAA30610.1); SEQ.ID.NO.36 (GenBank accession AAA31102.1); SEQ.ID.NO.37 (GenBank accession AAA31059.1); SEQ.ID.NO.38 (GenBank accession AAA30617.1); and SEQ.ID.NO.39 (GenBank accession AAA30609.1), more fully described in U.S. Patent Nos. 6,399,570; 5,304,633; 5,317,084; 5,656,591; 5,849,885; 5,849,881; 5,766,939 which are incorporated herein by reference in its entirety. More specifically, the lactoferrin related peptides may include the following sequences, but are not limited to these sequences, SEQ.ID.NO.1 (LFP-21), SEQ.ID.NO.2 (LFP-22), SEQ.ID.NO.3 (LFP-23), SEQ.ID.NO.4 (LFP-24), SEQ.ID.NO.5 (LFP-25), SEQ.ID.NO.6 (LFP-31), SEQ.ID.NO.7 (LFP-32), SEQ.ID.NO.8 (LFP-33), SEQ.ID.NO.9 (LFP-34), SEQ.ID.NO.10 (LFP-35), and SEQ.ID.NO.11 (LFP-36).

[0112] In certain embodiments the size of the peptide composition or amino acid molecule may comprise, but is not limited to, about 1, about 2, about 3, about 4, about 5, about 6,

about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, about 50, about 60 or greater amino molecule residues, and any range derivable therein.

[0113] As used herein, an "amino molecule" refers to any amino acid, amino acid derivative or amino acid mimic as would be known to one of ordinary skill in the art. In certain embodiments, the residues of the peptide are sequential or contiguous, without any non-amino molecule interrupting the sequence of amino molecule residues. In other embodiments, the sequence may comprise one or more non-amino molecule moieties. In particular embodiments, the sequence of residues of the peptide may be interrupted by one or more non-amino molecule moieties.

[0114] Accordingly, the term "peptide" encompasses amino molecule sequences comprising at least one of the 20 common amino acids in naturally synthesized proteins, or at least one modified or unusual amino acid, including but not limited to those shown on Table 1 below.

TABLE 1			
Modified and Unusual Amino Acids			
Abbr.	Amino Acid	Abbr.	Amino Acid
Aad	2-Aminoadipic acid	EtAsn	N-Ethylasparagine
Baad	3- Aminoadipic acid	Hyl	Hydroxylysine
Bala	β -alanine, β -Amino-propionic acid	AHyl	allo-Hydroxylysine
Abu	2-Aminobutyric acid	3Hyp	3-Hydroxyproline
4Abu	4- Aminobutyric acid, piperidinic acid	4Hyp	4-Hydroxyproline
Acp	6-Aminocaproic acid	Ide	Isodesmosine
Ahe	2-Aminoheptanoic acid	Alle	allo-Isoleucine
Aib	2-Aminoisobutyric acid	MeGly	N-Methylglycine, sarcosine
Baib	3-Aminoisobutyric acid	MeIle	N-Methylisoleucine
Apm	2-Aminopimelic acid	MeLys	6-N-Methyllysine
Dbu	2,4-Diaminobutyric acid	MeVal	N-Methylvaline
Des	Desmosine	Nva	Norvaline
Dpm	2,2'-Diaminopimelic acid	Nle	Norleucine

TABLE 1			
Modified and Unusual Amino Acids			
Abbr.	Amino Acid	Abbr.	Amino Acid
Dpr	2,3-Diaminopropionic acid	Orn	Ornithine
EtGly	N-Ethylglycine		

[0115] Peptide compositions may be made by any technique known to those of skill in the art, including the expression of proteins, polypeptides or peptides through standard molecular biological techniques, the isolation of peptide compounds from natural sources, or the chemical synthesis of peptides. The nucleotide and protein, polypeptide and peptide sequences for various genes have been previously disclosed, and may be found at computerized databases known to those of ordinary skill in the art. One such database is the National Center for Biotechnology Information's Genbank and GenPept databases. The coding regions for these known genes may be amplified and/or expressed using the techniques disclosed herein or as would be known to those of ordinary skill in the art. Alternatively, various commercial preparations of polypeptides and peptides are known to those of skill in the art.

[0116] In certain embodiments a peptide composition may be purified. Generally, "purified" will refer to a specific polypeptide, or peptide composition that has been subjected to fractionation to remove various other proteins, polypeptides, or peptides, and which composition substantially retains its activity, as may be assessed, for example, by the protein assays, as would be known to one of ordinary skill in the art for the specific or desired polypeptide or peptide.

B. Peptide Variants

[0117] Deletional variants can be produced by proteolysis of lactoferrin and/or expression of a polynucleotide encoding a truncated lactoferrin as described in U.S. Patent 6,333,311, which is incorporated herein by reference.

[0118] Substitutional variants or replacement variants typically contain the exchange of one amino acid for another at one or more sites within the protein. Substitutions can be conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine;

serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine.

[0119] In making such changes, the hydrophatic index of amino acids may be considered. The importance of the hydrophatic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982). It is accepted that the relative hydrophatic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like.

[0120] Each amino acid has been assigned a hydrophatic index on the basis of their hydrophobicity and charge characteristics (Kyte and Doolittle, 1982), these are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

[0121] It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydrophatic index or score and still result in a protein with similar biological activity, *e.g.*, still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydrophatic indices are within ± 2 is preferred, those that are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

[0122] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U.S. Patent 4,554,101, incorporated herein by reference, states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein. As detailed in U.S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 \pm 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4).

[0123] Still further, it is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtains a biologically equivalent and immunologically equivalent protein. In such changes, the substitution of amino acids whose

hydrophilicity values are within ± 2 is preferred, those that are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

[0124] Thus, in the present invention, substitutional variants or replacement can be produced using standard mutagenesis techniques, for example, site-directed mutagenesis as disclosed in U.S. Patents 5,220,007; 5,284,760; 5,354,670; 5,366,878; 5,389,514; 5,635,377; 5,789,166, and 6,333,311, which are incorporated herein by reference. It is envisioned that at least the N-terminal glycine amino acid residue can be replaced or substituted with any of the twenty natural occurring amino acids, for example a positively charged amino acid (arginine, lysine, or histidine), a neutral amino acid (alanine, asparagine, cysteine, glutamine, glycine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine) and/or a negatively charged amino acid (aspartic acid or glutamic acid).

[0125] In terms of functional equivalents, it is well understood by the skilled artisan that, inherent in the definition of a "biologically functional equivalent" protein is the concept that there is a limit to the number of changes that may be made within a defined portion of the molecule while retaining a molecule with an acceptable level of equivalent biological activity and/or enhancing the biological activity of the lactoferrin molecule. Biologically functional equivalents are thus defined herein as those proteins in which selected amino acids (or codons) may be substituted. Functional activity is defined as the ability of the lactoferrin related peptide to stimulate or inhibit various cytokines or chemokines. In particular, a biological functional equivalent will be able to stimulate production of macrophage inflammatory protein 3 alpha (MIP-3 α).

[0126] Yet further, the lactoferrin peptides of this invention can be in glycosylated or unglycosylated form, can be modified post-translationally (e.g., acetylation, and phosphorylation) or can be modified synthetically (e.g., the attachment of a labeling group). Fragments of lactoferrin molecules that retain the prophylactic efficacy can also be used (see, e.g. PCT/IB00/00271, which is incorporated herein in reference in its entirety).

C. Production of Lactoferrin Related Peptides

1. Synthetic Variants

[0127] The present invention also describes lactoferrin related peptides for use in various embodiments of the present invention. Because of their relatively small size, the peptides of the invention can also be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and Young (1984); Tam et al. (1983); Merrifield (1986); and Barany and Merrifield (1979), each incorporated herein

by reference. Short peptide sequences, or libraries of overlapping peptides, usually from about 6 up to about 35 to 50 amino acids, which correspond to the selected regions described herein, can be readily synthesized and then screened in screening assays designed to identify reactive peptides. Alternatively, recombinant DNA technology may be employed wherein a nucleotide sequence which encodes a peptide of the invention is inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression.

2. Recombinant Synthesis

a) Nucleic Acid Compositions

[0128] Certain embodiments of the present invention concern a nucleic acid composition having a nucleic acid sequence of lactoferrin. In certain aspects, a lactoferrin nucleic acid comprises a wild-type or a mutant lactoferrin nucleic acid. In particular aspects, a lactoferrin nucleic acid sequence encodes for or comprises a transcribed nucleic acid. In other aspects, a lactoferrin nucleic acid sequence comprises a nucleic acid segment of SEQ.ID.NO.40 (GenBank accession M93150); SEQ.ID.NO.41 (GenBank accession X54801); SEQ.ID.NO.42 (GenBank accession NM_008522); SEQ.ID.NO.43 (GenBank accession NM_002343); SEQ.ID.NO.44 (GenBank accession NM_180998); SEQ.ID.NO.45 (GenBank accession AY137470); SEQ.ID.NO.46 (GenBank accession AY178998); SEQ.ID.NO.47 (GenBank accession AJ005203); SEQ.ID.NO.48 (GenBank accession D88510); SEQ.ID.NO.49 (GenBank accession AF332168); SEQ.ID.NO.50 (GenBank accession AB046664); SEQ.ID.NO.51 (GenBank accession AAF82241.1); SEQ.ID.NO.52 (GenBank accession AJ131674); SEQ.ID.NO.53 (GenBank accession D38380); SEQ.ID.NO.54 (GenBank accession AJ010930); SEQ.ID.NO.55 (GenBank accession U07643); SEQ.ID.NO.56 (GenBank accession X78902); SEQ.ID.NO.57 (GenBank accession X57084); SEQ.ID.NO.58 (GenBank accession X53961); SEQ.ID.NO.59 (GenBank accession X52941); SEQ.ID.NO.60 (GenBank accession U53857); SEQ.ID.NO.61 (GenBank accession M73700); SEQ.ID.NO.62 (GenBank accession M83202); SEQ.ID.NO.63 (GenBank accession L19981); SEQ.ID.NO.64 (GenBank accession M92089); SEQ.ID.NO.65 (GenBank accession M81327); SEQ.ID.NO.66 (GenBank accession M63502); and SEQ.ID.NO.67 (GenBank accession L08604) or a biologically functional equivalent thereof. In particular aspects, the nucleic acid sequence of the present invention encodes a polypeptide, peptide, for example, but not limited to SEQ.ID.NO.1 (LFP-21), SEQ.ID.NO.2 (LFP-22), SEQ.ID.NO.3 (LFP-23), SEQ.ID.NO.4 (LFP-24), SEQ.ID.NO.5 (LFP-25), SEQ.ID.NO.6 (LFP-31), SEQ.ID.NO.7 (LFP-32), SEQ.ID.NO.8 (LFP-33), SEQ.ID.NO.9 (LFP-34), SEQ.ID.NO.10 (LFP-35), and SEQ.ID.NO.11 (LFP-36). Thus, nucleic acid compositions encoding lactoferrin

and/or lactoferrin related peptides are herein provided and are also available to a skilled artisan at accessible databases, including the National Center for Biotechnology Information's GenBank database and/or commercially available databases, such as from Celera Genomics, Inc. (Rockville, MD).

[0129] The term "nucleic acid" is well known in the art. A "nucleic acid" as used herein will generally refer to a molecule (i.e., a strand) of DNA, RNA or a derivative or analog thereof, comprising a nucleobase. A nucleobase includes, for example, a naturally occurring purine or pyrimidine base found in DNA (e.g., an adenine "A," a guanine "G," a thymine "T" or a cytosine "C") or RNA (e.g., an A, a G, an uracil "U" or a C). The term "nucleic acid" encompass the terms "oligonucleotide" and "polynucleotide," each as a subgenus of the term "nucleic acid." The term "oligonucleotide" refers to a molecule of between about 3 and about 100 nucleobases in length. The term "polynucleotide" refers to at least one molecule of greater than about 100 nucleobases in length.

[0130] These definitions generally refer to a single-stranded molecule, but in specific embodiments will also encompass an additional strand that is partially, substantially or fully complementary to the single-stranded molecule. Thus, a nucleic acid may encompass a double-stranded molecule or a triple-stranded molecule that comprises one or more complementary strand(s) or "complement(s)" of a particular sequence comprising a molecule. As used herein, a single stranded nucleic acid may be denoted by the prefix "ss," a double stranded nucleic acid by the prefix "ds," and a triple stranded nucleic acid by the prefix "ts."

[0131] The nucleic acids of the present invention encompass biologically functional equivalent lactoferrin proteins, polypeptides, or lactoferrin related peptides. Examples of such peptides include, but are not limited to SEQ.ID.NO.1 (LFP-21), SEQ.ID.NO.2 (LFP-22), SEQ.ID.NO.3 (LFP-23), SEQ.ID.NO.4 (LFP-24), SEQ.ID.NO.5 (LFP-25), SEQ.ID.NO.6 (LFP-31), SEQ.ID.NO.7 (LFP-32), SEQ.ID.NO.8 (LFP-33), SEQ.ID.NO.9 (LFP-34), SEQ.ID.NO.10 (LFP-35), and SEQ.ID.NO.11 (LFP-36). Such sequences may arise as a consequence of codon redundancy or functional equivalency that is known to occur naturally within nucleic acid sequences or the proteins, polypeptides or peptides thus encoded. Alternatively, functionally equivalent proteins, polypeptides or peptides may be created via the application of recombinant DNA technology, in which changes in the protein, polypeptide or peptide structure may be engineered, based on considerations of the properties of the amino acids being exchanged. Changes designed by man may be introduced, for example, through the application of site-

directed mutagenesis techniques as discussed herein below, e.g., to introduce improvements or alterations to the antigenicity of the protein, polypeptide or peptide.

[0132] Encompassed by the invention are nucleic acid sequences encoding relatively small peptides, such as, for example, peptides of from about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, about 47, about 48, about 49, to about 50 amino acids in length, or more preferably, of from about 1 to about 33 amino acids in length; as set forth in SEQ.ID.NO. 1, SEQ.ID.NO.2, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, and SEQ.ID.NO.11 and also larger peptides up to and from about 1 to about 34 amino acids in length; as set forth in SEQ.ID.NO.3.

3. Expression Vectors

[0133] The present invention may involve using expression constructs as the pharmaceutical composition. In certain embodiments, it is contemplated that the expression construct comprises polynucleotide sequences encoding polypeptides which can enhance the immune system, for example the expression construct may comprise a nucleic acid sequence encoding the amino acid sequence of SEQ.ID.NO.1 (LFP-21), SEQ.ID.NO.2 (LFP-22), SEQ.ID.NO.3 (LFP-23), SEQ.ID.NO.4 (LFP-24), SEQ.ID.NO.5 (LFP-25), SEQ.ID.NO.6 (LFP-31), SEQ.ID.NO.7 (LFP-32), SEQ.ID.NO.8 (LFP-33), SEQ.ID.NO.9 (LFP-34), SEQ.ID.NO.10 (LFP-35), SEQ.ID.NO.11 (LFP-36), SEQ.ID.NO.12.

[0134] In certain embodiments, the present invention involves the manipulation of genetic material to produce expression constructs that encode the peptides of the present invention. Thus, the peptides are contained in an expression vector. Such methods involve the generation of expression constructs containing, for example, a heterologous nucleic acid sequence encoding the peptide of interest and a means for its expression, replicating the vector in an appropriate cell, obtaining viral particles produced therefrom, and infecting cells with the recombinant virus particles.

[0135] As used in the present invention, the term "expression vector" refers to any type of genetic construct comprising a nucleic acid coding for a lactoferrin related peptide, for example, but not limited to SEQ.ID.NO.1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, and

SEQ.ID.NO.11. In some cases, DNA molecules are then translated into a protein, polypeptide, or peptide. Expression vectors can contain a variety of "control sequences," which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operably linked coding sequence in a particular host cell. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described infra. It is contemplated in the present invention, that virtually any type of vector may be employed in any known or later discovered method to deliver nucleic acids encoding a lactoferrin related peptide. An expression vector comprising a nucleic acid encoding a lactoferrin related peptide may comprise a virus or engineered construct derived from a viral genome.

[0136] In particular embodiments of the invention, a plasmid vector is contemplated for use to transform a host cell. In general, plasmid vectors containing replicon and control sequences that are derived from species compatible with the host cell are used in connection with these hosts. The vector ordinarily carries a replication site, as well as marking sequences that are capable of providing phenotypic selection in transformed cells. Plasmid vectors are well known and are commercially available. Such vectors include, but are not limited to, the commercially available pSupervector (OligoEngine, Seattle, WA), and pSuppressorNeo vector (IMGENEX Corporation). Other vectors that may be employed in the present invention include, but are not limited to, the following eukaryotic vectors: pWLNEO, pSV2CAT, pOG44, PXT1, pSG (Stratagene) pSVK3, pBSK, pBR322, pUC vectors, vectors that contain markers that can be selected in mammalian cells, such as pCDNA3.1, episomally replicating vectors, such as the pREP series of vectors, pBPV, pMSG, pSVL (Pharmacia), adenovirus vector (AAV; pCWRSV, Chatterjee et al. (1992)); retroviral vectors, such as the pBABE vector series, a retroviral vector derived from MoMuLV (pGINa, Zhou et al., (1994)); and pTZ18U (BioRad, Hercules, CA).

[0137] In one embodiment, a gene encoding a lactoferrin related peptide is introduced in vivo in a viral vector. The ability of certain viruses to enter cells via receptor-mediated endocytosis and to integrate into the host cell genome and express viral genes stably and efficiently have made them attractive candidates for the transfer of foreign genes into mammalian cells (Ridgeway, 1988; Nicolas and Rubenstein, 1988; Baichwal and Sugden, 1986; Temin, 1986). Such vectors include an attenuated or defective DNA virus, such as but not limited to herpes simplex virus (HSV), papilloma virus, Epstein Barr virus (EBV), adenovirus, adeno-associated virus (AAV), lentivirus and the like. Defective viruses, which entirely or

almost entirely lack viral genes, are preferred. Defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Thus, any tissue can be specifically targeted. Examples of particular vectors include, but are not limited to, a defective herpes virus 1 (HSV1) vector (Kaplitt et al., 1991) an attenuated adenovirus vector, (Stratford-Perricaudet et al., 1992), a defective adeno-associated virus vector (Samulski et al., 1987 and Samulski et al., 1989) or pox-vector. Such vectors may be used to (i) transform cell lines in vitro for the purpose of expressing the a lactoferrin related peptide or (ii) to transform cells in vitro or in vivo to provide therapeutic molecules for gene therapy. Thus, the present invention contemplates viral vectors such as, but not limited to, an adenoviral vector, an adeno-associated viral vector, a retroviral vector, a lentiviral vector, a herpes viral vector, polyoma viral vector, pox-vector or hepatitis B viral vector.

[0138] Preferably, for in vivo administration, an appropriate immunosuppressive treatment is employed in conjunction with the viral vector, e.g., adenovirus vector, to avoid immunodeactivation of the viral vector and transfected cells. For example, immunosuppressive cytokines, such as interleukin-12 (IL-12), interferon- γ (IFN- γ), or anti-CD4 antibody, can be administered to block humoral or cellular immune responses to the viral vectors (Wilson, Nature Medicine (1995). In addition, it is advantageous to employ a viral vector that is engineered to express a minimal number of antigens.

[0139] In another embodiment the gene can be introduced in a retroviral vector, e.g., as described in U.S. Pat. No. 5,399,346; Mann et al., 1983; U.S. Pat. No. 4,650,764; U.S. Pat. No. 4,980,289; Markowitz et al., 1988; U.S. Pat. No. 5,124,263; International Patent Publication No. WO 95/07358; and Kuo et al., 1993, each of which is incorporated herein by reference in its entirety. Targeted gene delivery is described in International Patent Publication WO 95/28494.

[0140] Alternatively, the vector can be introduced in vivo by lipofection. For the past decade, there has been increasing use of liposomes for encapsulation and transfection of nucleic acids in vitro. Synthetic cationic lipids designed to limit the difficulties and dangers encountered with liposome mediated transfection can be used to prepare liposomes for in vivo transfection of a gene encoding a marker. The use of cationic lipids may promote encapsulation of negatively charged nucleic acids, and also promote fusion with negatively charged cell membranes. The use of lipofection to introduce exogenous genes into the specific organs in vivo has certain practical advantages. Molecular targeting of liposomes to specific cells represents

one area of benefit. Lipids may be chemically coupled to other molecules for the purpose of targeting. Targeted peptides, e.g., hormones or neurotransmitters, and proteins such as antibodies, or non-peptide molecules could be coupled to liposomes chemically.

[0141] It is also possible to introduce the vector in vivo as a naked DNA plasmid. Naked DNA vectors for gene therapy can be introduced into the desired host cells by methods known in the art, e.g., transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter (Wu and Wu, 1988).

[0142] As used herein, the terms "cell," "cell line," and "cell culture" may be used interchangeably. All of these terms also include their progeny, which is any and all subsequent generation formed by cell division. It is understood that all progeny may not be identical due to deliberate or inadvertent mutations. A host cell may be "transfected" or "transformed," which refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A transformed cell includes the primary subject cell and its progeny. As used herein, the terms "engineered" and "recombinant" cells or host cells are intended to refer to a cell into which an exogenous nucleic acid sequence, such as, for example, a lactoferrin related peptide. Therefore, recombinant cells are distinguishable from naturally occurring cells that do not contain a recombinantly introduced nucleic acid.

[0143] Host cells may be derived from prokaryotes or eukaryotes, depending upon whether the desired result is replication of the vector or expression of part or all of the vector encoded nucleic acid sequences. Numerous cell lines and cultures are available for use as a host cell, and they can be obtained through the American Type Culture Collection (ATCC), which is an organization that serves as an archive for living cultures and genetic materials. In certain embodiments, a cell may comprise, but is not limited to, at least one skin, bone, neuron, axon, cartilage, blood vessel, cornea, muscle, fascia, brain, prostate, breast, endometrium, lung, pancreas, small intestine, blood, liver, testes, ovaries, cervix, colon, skin, stomach, esophagus, spleen, lymph node, bone marrow, kidney, peripheral blood, embryonic or ascite cell, and all cancers thereof. An appropriate host can be determined by one of skill in the art based on the vector backbone and the desired result. Bacterial cells used as host cells for vector replication and/or expression include DH5 α , JM109, and KC8, as well as a number of commercially available bacterial hosts such as SURE[®] Competent Cells and SOLOPACK[™] Gold Cells (STRATAGENE[®], La Jolla).

[0144] Examples of eukaryotic host cells for replication and/or expression of a vector include HeLa, NIH3T3, Jurkat, 293, Cos, CHO, Saos, and PC12. Other eukaryotic cells include yeast cells, such as *Aspergillus* species and *Saccharomyces* species. Many host cells from various cell types and organisms are available and would be known to one of skill in the art. In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, and/or modifies and/or processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and/or processing (e.g., cleavage) of protein products may be important for the function of the protein.

III. Pharmaceutical Compositions

[0145] The present invention is drawn to a composition comprising a lactoferrin that is dispersed in a pharmaceutical carrier. The lactoferrin that is contained in the composition of the present invention comprises lactoferrin related peptides, for example, SEQ.ID.NO. 1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, and SEQ.ID.NO.11 and/or expression vectors encoding a lactoferrin related peptide.

[0146] Yet further, the composition comprises lactoferrin related peptides in combination with a metal chelator dispersed in a pharmaceutical carrier. Thus, the present invention is drawn to a composition with or without a metal chelator that is dispersed in a pharmaceutical carrier. One of skill in the art understands that both compositions (e.g., lactoferrin related peptides alone or in combination with a metal chelator) are within the scope of the present invention and can be used interchangeably depending upon the type of response that is desired. It is envisioned that the addition of a metal chelator to the composition enhances the sequestering of metal ions and thus strengthens the immune system or enhances the effect of the lactoferrin related peptides.

[0147] Metal chelators that can be used in combination with lactoferrin, include the divalent metal chelators, for example, ethylenediaminetetraacetic acid (EDTA), [ethylenebis(oxyethylenenitrilo)] tetraacetic acid (EGTA), 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), hydroxyethylene triamine diacetic acid, (HEDTA) or any salts thereof. The amount of the metal chelator in the composition may vary from about 0.01 μg to about 20 g. More preferably, EDTA is used in combination with lactoferrin.

[0148] The lactoferrin composition of the present invention may comprise different types of carriers depending on whether it is to be administered in solid, liquid or aerosol form, and whether it need to be sterile for such routes of administration as injection. The present

invention can be administered intravenously, intradermally, transdermally, intrathecally, intraarterially, intraperitoneally, intranasally, intravaginally, intrarectally, topically, intramuscularly, subcutaneously, mucosally, orally, topically, locally, inhalation (e.g., aerosol inhalation), injection, infusion, continuous infusion, localized perfusion bathing target cells directly, via a catheter, via a lavage, in cremes, in lipid compositions (e.g., liposomes), or by other method or any combination of the forgoing as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, incorporated herein by reference).

[0149] The composition of the present invention suitable for administration is provided in a pharmaceutically acceptable carrier with or without an inert diluent. The carrier should be assimilable and includes liquid, semi-solid, e.g., pastes, or solid carriers. Except insofar as any conventional media, agent, diluent or carrier is detrimental to the recipient or to the therapeutic effectiveness of the composition contained therein, its use in administrable composition for use in practicing the methods of the present invention is appropriate. Examples of carriers or diluents include fats, oils, water, saline solutions, lipids, liposomes, resins, binders, fillers and the like, or combinations thereof.

[0150] Sterile injectable solutions are prepared by incorporating the lactoferrin in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0151] In a specific embodiment of the present invention, the composition is combined or mixed thoroughly with a semi-solid or solid carrier. The mixing can be carried out in any convenient manner such as grinding. Stabilizing agents can be also added in the mixing process in order to protect the composition from loss of therapeutic activity, i.e., denaturation in the stomach or in the open wound environment. Examples of stabilizers for use in an the composition include buffers, amino acids such as glycine and lysine, carbohydrates such as dextrose, mannose, galactose, fructose, lactose, sucrose, maltose, sorbitol, mannitol, etc., proteolytic enzyme inhibitors, and the like. Yet further, it is envisioned that divalent metal

chelators, for example EDTA, can also be used to stabilize the composition of the present invention. More preferably, for an orally administered composition, the stabilizer can also include antagonists to the secretion of stomach acids. Yet further, for a topically administered composition, the stabilizer can also include antagonists to skin acids.

[0152] In further embodiments, the present invention may concern the use of a pharmaceutical lipid vehicle compositions that include lactoferrin or lactoferrin related peptides, one or more lipids, and an aqueous solvent. As used herein, the term "lipid" will be defined to include any of a broad range of substances that is characteristically insoluble in water and extractable with an organic solvent. This broad class of compounds are well known to those of skill in the art, and as the term "lipid" is used herein, it is not limited to any particular structure. Examples include compounds which contain long-chain aliphatic hydrocarbons and their derivatives. A lipid may be naturally occurring or synthetic (i.e., designed or produced by man). However, a lipid is usually a biological substance. Biological lipids are well known in the art, and include for example, neutral fats, phospholipids, phosphoglycerides, steroids, terpenes, lysolipids, glycosphingolipids, glycolipids, sulphatides, lipids with ether and ester-linked fatty acids and polymerizable lipids, and combinations thereof. Of course, compounds other than those specifically described herein that are understood by one of skill in the art as lipids are also encompassed by the compositions and methods of the present invention.

[0153] One of ordinary skill in the art would be familiar with the range of techniques that can be employed for dispersing a composition in a lipid vehicle. For example, the lactoferrin or lactoferrin related peptides may be dispersed in a solution containing a lipid, dissolved with a lipid, emulsified with a lipid, mixed with a lipid, combined with a lipid, covalently bonded to a lipid, contained as a suspension in a lipid, contained or complexed with a micelle or liposome, or otherwise associated with a lipid or lipid structure by any means known to those of ordinary skill in the art. The dispersion may or may not result in the formation of liposomes.

[0154] The composition for oral administration which is combined with a semi-solid or solid carrier can be further formulated into hard or soft shell gelatin capsules, tablets, or pills. More preferably, gelatin capsules, tablets, or pills are enterically coated. Enteric coatings prevent denaturation of the composition in the stomach or upper bowel where the pH is acidic. See, e.g., U.S. Pat. No. 5,629,001. Upon reaching the small intestines, the basic pH therein dissolves the coating and permits the lactoferrin composition to be released and absorbed by specialized cells, e.g., epithelial enterocytes and Peyer's patch M cells.

[0155] Oral administration of the composition includes oral, buccal, enteral or intragastric administration. It is also envisioned that the composition may be used as a food additive. For example, the composition is sprinkled on food or added to a liquid prior to ingestion. In further embodiments, the oral composition is administered in conjunction with an antacid. Thus, an antacid is administered prior or substantially simultaneously with or after oral administration of the composition. The administration of an antacid just prior or immediately following the administration of the composition may help to reduce the degree of inactivation of the lactoferrin in the digestive tract. Examples of appropriate antacids include, but are not limited to, sodium bicarbonate, magnesium oxide, magnesium hydroxide, calcium carbonate, magnesium trisilicate, magnesium carbonate and aluminum hydroxide gel.

[0156] In another embodiment, a powdered composition is combined with a liquid carrier such as, i.e., water or a saline solution, with or without a stabilizing agent.

[0157] In other preferred embodiments of the invention, lactoferrin or lactoferrin related peptides may be formulated for administration via various miscellaneous routes, for example, topical (i.e., transdermal) administration, mucosal administration (intranasal, vaginal, etc.) and/or inhalation.

[0158] Pharmaceutical compositions for topical administration may include the active compound formulated for a medicated application such as an ointment, paste, cream or powder. Ointments include all oleaginous, adsorption, emulsion and water-solubly based compositions for topical application, while creams and lotions are those compositions that include an emulsion base only. Topically administered medications may contain a penetration enhancer to facilitate adsorption of the active ingredients through the skin. Suitable penetration enhancers include glycerin, alcohols, alkyl methyl sulfoxides, pyrrolidones and luarocapram. Possible bases for compositions for topical application include polyethylene glycol, lanolin, cold cream and petrolatum as well as any other suitable absorption, emulsion or water-soluble ointment base. Topical preparations may also include emulsifiers, gelling agents, and antimicrobial preservatives as necessary to preserve the active ingredient and provide for a homogenous mixture. Transdermal administration of the present invention may also comprise the use of a "patch". For example, the patch may supply one or more active substances at a predetermined rate and in a continuous manner over a fixed period of time.

[0159] In certain embodiments, the pharmaceutical compositions may be delivered by eye drops, intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering compositions directly to the lungs via nasal aerosol sprays have been described e.g., in

U.S. Pat. Nos. 5,756,353 and 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga et al., 1998) and lysophosphatidyl-glycerol compounds (U.S. Pat. No. 5,725, 871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroethylene support matrix is described in U.S. Pat. No. 5,780,045 (specifically incorporated herein by reference in its entirety).

[0160] The term aerosol refers to a colloidal system of finely divided solid or liquid particles dispersed in a liquefied or pressurized gas propellant. The typical aerosol of the present invention for inhalation will consist of a suspension of active ingredients in liquid propellant or a mixture of liquid propellant and a suitable solvent. Suitable propellants include hydrocarbons and hydrocarbon ethers. Suitable containers will vary according to the pressure requirements of the propellant. Administration of the aerosol will vary according to subject's age, weight and the severity and response of the symptoms.

[0161] In further embodiments, the compositions of this invention, can be incorporated into various types of ophthalmic formulations for delivery to the eye (e. g., topically, intracamerally, or via an implant). The compositions are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compositions may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a composition in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the composition. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the composition in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

[0162] Further, the composition for topical administration which is combined with a semi-solid carrier can be further formulated into a gel ointment. A preferred carrier for the formation of a gel ointment is a gel polymer. Gel polymers prevent denaturation of the composition in the open skin by serum proteases. The gel formulation of the present invention also provides a controlled delivery system for lactoferrin or its activity on a wound site. Controlled delivery refers to drug release or activity release sufficient to maintain a therapeutic level over an extended period of time, such as up to 24 hours or more, preferably in the range of 1 to 12 hours. The present gel formulation increases the contact time of the lactoferrin at the wound site and provides a sustained release dosage form necessary to achieve a significant increase in the rate of wound healing. This is an important advantage because it permits less frequent application of the formulation to the wound and thereby permits fewer disturbances to the wound and its cellular components.

[0163] The gel formulation of the present invention has the advantage of adhering to a wound and conforming to irregular body or wound contours. The gels may be applied directly to a wound site or in conjunction with a compliant porous or microporous substrate, for example in the form of a coating, to be applied to the wound site. Gels have the further advantages of having a high water content (which keeps the wound moist), the ability to absorb wound exudate, easy application to a wound and easy removal by washing. Gels have a cool feeling when applied to a wound and thus can increase patient comfort and acceptance of the formulation, especially on sensitive wounds.

[0164] The aqueous gels of the present invention have different viscosities depending on the intended application of the gel. Viscosity is a measure of the resistance of a liquid to flow. It is defined as the ratio of the shearing stress to the rate of shearing. The shear stress is the resistance of the liquid to flow under the influence of an applied force, i.e., the molecular resistance within a body opposing an external force. The shear stress is defined as the ratio of the force to the area sheared. When a liquid is sheared, assuming laminar flow, the layers of the liquid move at different rates. The relative rate of motion of the layers is only one factor in the rate of shear. The other is the distance, or clearance between the shearing planes. Thus, shear rate is defined as the ratio of the velocity of the gel to the clearance. Viscosity has the dimensions of dynes/sec/cm². These dimensions are referred to as poise. The dimensions of viscosity referred to herein, unless otherwise indicated, are in centipoise (cP) as measured using a Brookfield viscometer. All viscosity values are at room temperature, e.g., 22°C- 25°C, unless otherwise indicated.

[0165] The gel forming materials of the present invention may be water-soluble polymers capable of forming a viscous aqueous solution or non-water soluble, water swellable polymers (e.g., collagen), which can also form a viscous solution. Swellable polymers are those that absorb water rather than dissolve in water. Cross-linked forms of the polymer described herein may not be water soluble but may be water-swellable. Therefore, cross-linked forms of the polymer are within the scope of the present invention. Cross-linking refers to covalently bonding polymer chains together with a bifunctional reagent such as glutaraldehyde. Also, it is understood by those skilled in the art that certain polymers may have to be used in the salt form or partially neutralized in order to be made water soluble. For example, it is preferable to use hyaluronic acid as sodium hyaluronate to provide suitable water solubility.

[0166] In the aqueous gel formulations for topical or incisional wound healing, the polymer may be selected from the group consisting of vinyl polymers, polyoxyethylene-polyoxypropylene copolymers, polysaccharides, proteins, poly(ethylene oxide), acrylamide polymers and derivatives or salts thereof. It is understood that poly(ethyleneoxide) includes polyethylene glycol. In the gel formulations for use in healing wounds in the anterior chamber of the eye, the polymers may be the same except that it is not preferred to use the polyoxyethylene-polyoxypropylene copolymers or poly(ethylene oxide). Also, for anterior chamber use, it is preferred that the polymer is biodegradable, i.e., it will break down into harmless constituents that can be drained from or metabolized in the anterior chamber. In the low viscosity, aqueous formulations for use in ophthalmic wound healing, the gel forming polymers may be the same as for topical or incisional wound healing, except that poly(ethylene oxide) is not preferred to be used.

[0167] The vinyl polymers useful in the present invention may be selected from the group consisting of polyacrylic acid, polymethacrylic acid, polyvinyl pyrrolidone and polyvinyl alcohol. The polysaccharides useful in the present invention are selected from the group consisting of cellulose or cellulose derivatives, glycosaminoglycans, agar, pectin, alginic acid, dextran, starch, and chitosan. Starch occurs in two forms, α -amylose and amylopectin. The more water-soluble α -amylose is preferred. The glycosaminoglycans are selected from the group consisting of hyaluronic acid, chondroitin, chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, keratan sulfate, heparin sulfate and heparin. The glycosaminoglycans are used to enhance wound healing in combination with any other gel-forming polymer. The proteins useful in the present invention are selected from the group consisting of collagen, gelatin and fibronectin. The acrylamide polymers are polyacrylamide or polymethacrylamide polymers. Biocompatible

polyacrylamide polymers are preferred. In further embodiments, carbomers are the preferred polyacrylamide polymer. Carbomers are synthetic high molecular weight polymers of acrylic acid cross linked with either alkyl esters of sucrose or pentaerythritol. Suitable commercially available grades of carbomer include Carbopol 910, Carbopol 934P, Carbopol 940, Carbopol 941, Carbopol 971P, Carbopol 974P, Carbopol 980, Carbopol 981, Carbopol 1342, Rheogic 252L, Rheogic 250H, and Hostacerin PN73.

[0168] In the gel formulation for topical or incisional wound healing, the viscosity may be within the range 1,000-12,000,000 cps at room temperature. It is preferred that the viscosity range be 50,000-2,000,000. In one embodiment of the present invention, the topical gel formulation may comprise 0.01-5% by weight polyacrylic acid having an average molecular weight of about 450,000-4,000,000. In a preferred embodiment, the polyacrylic acid is present at 0.5-1.5% by weight and has an average molecular weight of 2,000,000-4,000,000. The pH of the polyacrylic acid gel should be within the range 4.5-8 and more preferably in the range 6.5-7.5.

[0169] In another embodiment, the topical and incisional gel of the present invention may comprise 15-60% by weight of a polyoxyethylene-polyoxypropylene block copolymer having an average molecular weight of about 500-50,000. In a preferred embodiment, the block copolymer is present at 15-40% by weight and has an average molecular weight in the range 1,000-15,000. The block copolymers used in the present invention are commonly known as Pluronics. Preferred Pluronics are Pluronic F88 and F127.

[0170] In a further embodiment, the topical or incisional gel may comprise 1 to 20% by weight of a cellulose polymer having a molecular weight of about 50,000 to 700,000. In a preferred embodiment, the cellulose polymer is present at 2-8% by weight and has an average molecular weight in the range 80,000-240,000. Preferred cellulose polymers are hydroxypropylmethyl cellulose (HPMC), carboxymethyl cellulose (CMC) and methyl cellulose (MC).

[0171] In a further embodiment, the topical and incisional gel may comprise 0.5-10% by weight of hyaluronic acid having an average molecular weight in the range 500,000 to 8,000,000. In a preferred embodiment, the hyaluronic acid is present at 1.5-6.0% by weight and the average molecular weight is greater than 1,000,000.

[0172] Acrylamide polymers may be useful for all types of wound healing, particularly in the anterior chamber of the eye. An absorbable acrylamide polymer, such as polyacrylamide, may be a good substitute for present carrier systems used in ophthalmic applications, such as hyaluronic acid. The acrylamide polymers may have an average molecular

weight in the range 1-13 million, preferably about 4-6 million. The weight percent of the acrylamide polymer in the gel may be 2-5%, preferably 3.5-4.5%. Substituted acrylamide polymers, such as methyl and alkyl substituted polymers are also within the scope of the present invention.

[0173] For use in the anterior chamber of the eye, an acrylamide gel delivery system has the following characteristics: any products of the dissolution or degradation of the delivery matrix are nontoxic and do not clog the trabecular mesh work; the gel is optically transparent; and the gel can be left in the anterior chamber without causing adverse clinical effects such as an unacceptable increase in ocular pressure.

[0174] It will be readily apparent to one skilled in the art that the desired viscosity range may be achieved by varying the molecular weight and percent concentration of the polymer in the formulation. For example, a gel having a low viscosity may be achieved by using a low molecular weight polymer or a lower percent concentration or a combination of the two. A high viscosity gel may be achieved by using a higher molecular weight polymer and a higher percent concentration. Intermediate viscosities may be achieved by varying the molecular weight and percent concentration accordingly.

[0175] The low viscosity solution may comprise 0.01-2.0% by weight polyacrylic acid having an molecular weight of about 100,000-4,000,000. In a preferred embodiment, the polymer is present at 0.05-0.5%. In another embodiment, this dilute viscous solution may comprise 2-40% by weight of a polyoxyethylene-polyoxypropylene copolymer having an average molecular weight of 500-500,000. Preferably, the concentration is 2-20% and the molecular weight is 1,000-15,000. Alternatively, the dilute viscous solution may comprise a cellulose polymer at 1-20% and having a molecular weight of about 80,000-240,000. It is preferred that the concentration be in the range of 1-10%. In a further embodiment, the dilute viscous solution may comprise 0.5-5.0% by weight hyaluronic acid having an average molecular weight of about 500,000-8,000,000. Preferably, the concentration is 0.5-2.0% and the average molecular weight is 1,000,000-6,000,000. If the dilute viscous solution is to be used as eye drops, it is preferred that the viscosity be in the range 1-100 cps. If it is used for other applications, such as soaking a bandage, then any viscosity in the range 1.0-5,000 will be suitable.

[0176] Upon formulation, solutions are administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective to result in an improvement or remediation of the symptoms. The formulations are easily administered in a

variety of dosage forms such as ingestible solutions, drug release capsules, gel ointments and the like. Some variation in dosage can occur depending on the condition of the subject being treated. The person responsible for administration can, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations meet sterility, general safety and purity standards as required by FDA Office of Biologics standards.

IV. Methods of Treatment Using the Lactoferrin related peptides

[0177] In certain aspects of the present invention, a peptide composition comprising lactoferrin related peptides or related-compounds thereof is administered to treat a pathological condition, for example such conditions, include, but are not limited to hyperproliferative disease, respiratory disease, cardiovascular disease, neurological condition, autoimmune disorder, infectious disease, gastrointestinal disorder, endocrine and/or metabolism disorder, hematological disorder, ocular disorder, integument disorder, pain and a wound.

[0178] It is envisioned that the immune system, whether local, systemic or mucosal, is enhanced by lactoferrin related peptides stimulating cytokines and/or chemokines. Exemplary cytokines include interleukin-18 and GM-CSF in the gastrointestinal tract, which are known to enhance immune cells or stimulate production of immune cells. For example, interleukin-18 enhances natural killer cells or T lymphocytes, which can kill bacteria infecting a wound. In specific embodiments, interleukin-18 (IL-18) enhances CD4+, CD8+ and CD3+ cells. It is known by those of skill in the art that IL-18 is a Th1 cytokine that acts in synergy with interleukin-12 and interleukin-2 in the stimulation of lymphocyte IFN-gamma production. Other cytokines or chemokines may also be enhanced for example, but not limited to IL-12, IL-1b, MIP-3 α , MIP-1 α or IFN-gamma. Other cytokines or enzymes may be inhibited for example, but not limited to IL-2, IL-4, IL-5, IL-10, TNF- α , or matrix metalloproteinases.

[0179] In further embodiments, cytokines, for example, interleukin-18 or granulocyte/macrophage colony-stimulating factor, can stimulate the production or activity of immune cells. The immune cells include, but are not limited to T lymphocytes, natural killer cells, macrophages, dendritic cells, and polymorphonuclear cells. More specifically, the polymorphonuclear cells are neutrophils and the T lymphocytes are selected from the group consisting of CD4+, CD8+ and CD3+ T cells.

[0180] Still further, it is envisioned that lactoferrin related peptides stimulate production of MIP-3 α from hepatocytes. Lactoferrin is known to contribute to the defense systems of the body through its anti-microbial properties. In addition, evidence suggests that recombinant human lactoferrin (rhLF) elicits a more general innate-like immune response when

administered orally. The innate immune system is the 'first line of defense' of the body against hostile environments and comprise of a variety of effector and cellular mechanisms. This innate immune response is initially likely mediated by the 'detection system' of receptors known to be present on the surface of the gut epithelial cells, such as pattern recognition receptors, IL-1 receptor and general 'scavenger' receptors. These receptors recognize and respond to specific structural features of the presented molecules. As a result, various intracellular signaling pathways may be initiated (e.g., NF κ B, Wnt, etc.) that result in the overall orchestration of the cellular response of the body to the prevailing biological situation (e.g., infection). RhLF and peptides derived from rhLF elicit a similar response of human hepatocytes *in vitro* in terms of producing an important chemokine – namely MIP-3-alpha. It is surmised that some general structural features that are responsible for the biological response to rhLF are retained in peptides that are structurally related to the parent molecule (rhLF).

[0181] The route of administration will vary, naturally, with the location and nature of the lesion, and include, for example parentally, orally or topically. Parenteral administrations include, but are not limited to intradermal, transdermal, intravenous, intramuscular, intranasal, subcutaneous, percutaneous, intratracheal, intraocular, intraperitoneal, intratumoral, perfusion, lavage, direct injection U.S. Pat. Nos. 6,613,308, 5,466,468, 5,543,158; 5,641,515; and 5,399,363 (each specifically incorporated herein by reference in its entirety). Alimentary administrations include, but are not limited to orally, buccally, rectally, or sublingually.

[0182] Treatment methods will involve treating an individual with an effective amount of a peptide composition as defined in the present invention. An effective amount is described, generally, as that amount sufficient to detectably and repeatedly ameliorate, reduce, minimize or limit the extent of a disease or its symptoms.

[0183] The effective amount or "therapeutically effective amounts" of the peptide composition to be used are those amounts effective to produce beneficial results, particularly with respect to cancer treatment, in the recipient animal or patient. Such amounts may be initially determined by reviewing the published literature, by conducting *in vitro* tests or by conducting metabolic studies in healthy experimental animals. Before use in a clinical setting, it may be beneficial to conduct confirmatory studies in an animal model, preferably a widely accepted animal model of the particular disease to be treated. Preferred animal models for use in certain embodiments are rodent models, which are preferred because they are economical to use and, particularly, because the results gained are widely accepted as predictive of clinical value.

[0184] As is well known in the art, a specific dose level of active compounds such as the peptide composition for any particular patient depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The person responsible for administration will determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[0185] A therapeutically effective amount of a peptide composition as a treatment varies depending upon the host treated and the particular mode of administration. In one embodiment of the invention the dose range of a peptide composition will be about 0.5 mg/kg body weight to about 500 mg/kg body weight. The term "body weight" is applicable when an animal is being treated. When isolated cells are being treated, "body weight" as used herein should read to mean "total cell body weight". The term "total body weight" may be used to apply to both isolated cell and animal treatment. All concentrations and treatment levels are expressed as "body weight" or simply "kg" in this application are also considered to cover the analogous "total cell body weight" and "total body weight" concentrations. However, those of skill will recognize the utility of a variety of dosage range, for example, 0.1 µg/kg body weight to 1 µg/kg body weight, 1 µg/kg to 1 mg/kg body weight, 1 mg/kg body weight to 450 mg/kg body weight, 2 mg/kg body weight to 400 mg/kg body weight, 3 mg/kg body weight to 350 mg/kg body weight, 4 mg/kg body weight to 300 mg/kg body weight, 5 mg/kg body weight to 250 mg/kg body weight, 6 mg/kg body weight to 200 mg/kg body weight, 7 mg/kg body weight to 150 mg/kg body weight, 8 mg/kg body weight to 100 mg/kg body weight, or 9 mg/kg body weight to 50 mg/kg body weight. Further, those of skill will recognize that a variety of different dosage levels will be of use, for example, 0.1 µg/kg, 1 µg/kg, 10 µg/kg, 100 µg/kg, 200 µg/kg; 300 µg/kg; 400 µg/kg, 500 µg/kg, 600 µg/kg, 700 µg/kg, 800 µg/kg, 900 µg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 12.5 mg/kg, 15 mg/kg, 17.5 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, 40 mg/kg, 45 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, 120 mg/kg, 140 mg/kg, 150 mg/kg, 160 mg/kg, 180 mg/kg, 200 mg/kg, 225 mg/kg, 250 mg/kg, 275 mg/kg, 300 mg/kg, 325 mg/kg, 350 mg/kg, 375 mg/kg, 400 mg/kg, 450 mg/kg, 500 mg/kg, 550 mg/kg, 600 mg/kg, 700 mg/kg, 750 mg/kg, 800 mg/kg, 900 mg/kg, 1000 mg/kg, 1250 mg/kg, 1500 mg/kg, 1750 mg/kg, 2000 mg/kg, 2500 mg/kg, and/or 3000 mg/kg. Of course, all of these dosages are exemplary, and any dosage in-between these points is also

expected to be of use in the invention. Any of the above dosage ranges or dosage levels may be employed for the peptide composition of the present invention.

[0186] The treatments may include various "unit doses." Unit dose is defined as containing a predetermined quantity of the therapeutic composition (lactoferrin related peptides or its related-compounds thereof) calculated to produce the desired responses in association with its administration, i.e., the appropriate route and treatment regimen. The quantity to be administered, and the particular route and formulation, are within the skill of those in the clinical arts. Also of import is the subject to be treated, in particular, the state of the subject and the protection desired. A unit dose need not be administered as a single injection but may comprise continuous infusion over a set period of time.

[0187] In certain embodiments, the composition is given in a single dose or multiple doses. The single dose may be administered daily, or multiple times a day, or multiple times a week, or monthly or multiple times a month. In a further embodiment, the composition is given in a series of doses. The series of doses may be administered daily, or multiple times a day, weekly, or multiple times a week, or monthly, or multiple times a month.

A. Hyperproliferative Disease

[0188] The hyperproliferative disease, includes but is not limited to neoplasms. A neoplasm is an abnormal tissue growth, generally forming a distinct mass that grows by cellular proliferation more rapidly than normal tissue growth. Neoplasms show partial or total lack of structural organization and functional coordination with normal tissue. These can be broadly classified into three major types. Malignant neoplasms arising from epithelial structures are called carcinomas, malignant neoplasms that originate from connective tissues such as muscle, cartilage, fat or bone are called sarcomas and malignant tumors affecting hematopoietic structures (structures pertaining to the formation of blood cells) including components of the immune system, are called leukemias, lymphomas and myelomas. A tumor is the neoplastic growth of the disease cancer. As used herein, a "neoplasm", also referred to as a "tumor", is intended to encompass hematopoietic neoplasms as well as solid neoplasms. Examples of neoplasms include, but are not limited to melanoma, non-small cell lung, small-cell lung, lung, hepatocarcinoma, retinoblastoma, astrocytoma, glioblastoma, gum, tongue, leukemia, neuroblastoma, head, neck, breast, pancreatic, prostate, renal, bone, testicular, ovarian, mesothelioma, sarcoma, cervical, gastrointestinal, lymphoma, brain, colon, bladder, myeloma, or other malignant or benign neoplasms.

[0189] Other hyperproliferative diseases include, but are not limited to neurofibromatosis, rheumatoid arthritis, Waginer's granulomatosis, Kawasaki's disease, lupus erathematosus, midline granuloma, inflammatory bowel disease, osteoarthritis, leiomyomas, adenomas, lipomas, hemangiomas, fibromas, vascular occlusion, restenosis, atherosclerosis, pre-neoplastic lesions, carcinoma in situ, oral hairy leukoplakia, or psoriasis, and pre-leukemias, anemia with excess blasts, and myelodysplastic syndrome.

[0190] Particular neoplasms of interest in the present invention include, but are not limited to hematopoietic neoplasms. For example, a hematopoietic neoplasm may include acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, chronic myelomonocytic leukemia, juvenile myelomonocyte leukemia, multiple myeloma, chronic lymphocytic leukemia or other malignancy of hematologic origin.

[0191] In a preferred embodiment of the present invention, the peptide compositions are administered in an effective amount to decrease, reduce, inhibit or abrogate the growth of a tumor. The amount may vary from about 0.1 μ g to about 100g of the lactoferrin composition. Preferably, the lactoferrin composition is orally administered in the range of 1mg to 100g per day, more preferably about 20mg to about 10g per day with the most preferred dose being 4.5g per day. Intravenously administered lactoferrin can be in the range of 0.1 μ g to about 10g per day, more preferably about 0.1 μ g to about 1mg with the most preferred dose being 250 mg per day. Preferably, a peptide composition is intratumorally administered in the range of 0.1 μ g to 10g per day with the most preferred dose being 100 μ g per day. Topically, the amount of lactoferrin related peptides may vary from about 1 μ g to about 100g. Preferably, the topical gel, solution, capsule or tablet comprises a concentration of about 0.01% to about 20% of lactoferrin related peptides. More preferably, the topical gel, solution, capsule or tablet may comprise a concentration of about 1% to about 8.5% lactoferrin related peptides.

[0192] In certain embodiments intratumoral administration of the composition includes intratumoral injection, electroporation, or surgical or endoscopic implantation. Intratumoral injection, or injection into the tumor vasculature is specifically contemplated for discrete, solid, accessible tumors. Local, regional or systemic administration also may be appropriate.

[0193] The tumor being treated may not, at least initially, be resectable. Treatments with the lactoferrin composition may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following

treatments, resection may be possible. Additional treatments subsequent to resection will serve to eliminate microscopic residual disease at the tumor site.

[0194] Alternatively, the present invention may be used at the time of surgery, and/or thereafter, to treat residual or metastatic disease. For example, a resected tumor bed may be injected or perfused with a formulation comprising the lactoferrin composition. The perfusion may be continued post-resection, for example, by leaving a catheter implanted at the site of the surgery. Periodic post-surgical treatment is also envisioned.

[0195] Continuous administration also may be applied where appropriate, for example, where a tumor is excised and the tumor bed is treated to eliminate residual, microscopic disease. Delivery via syringe or catheterization is preferred. Such continuous perfusion may take place for a period from about 1-2 hours, to about 6-12 hours, to about 12-24 hours, to about 1-2 days, to about 1-2 weeks or longer following the initiation of treatment. Generally, the dose of the therapeutic composition via continuous perfusion will be equivalent to that given by a single or multiple injections, adjusted over a period of time during which the perfusion occurs. It was further contemplated that limb perfusion may be used to administer therapeutic compositions of the present invention, particularly in the treatment of melanomas and sarcomas.

[0196] Still yet, a further embodiment is a method of enhancing a mucosal immune response in the gastrointestinal tract in a subject comprising the step of administering orally to said subject a peptide composition. It is also envisioned that the lactoferrin related peptide stimulates interleukin-18 following oral administration, which inhibits angiogenesis and thereby has activity against tumor cells which are dependent on neovascularization.

[0197] A further embodiment of the present invention is a method of treating a hyperproliferative disease comprising the step of supplementing the systemic immune system by increasing the amount of lactoferrin related peptides in the systemic circulation. Preferably, the composition is administered intravenously. It is envisioned that the lactoferrin related peptides stimulate interleukin-18 following intravenous administration, which inhibits angiogenesis and thereby has activity against tumor cells which are dependent on neovascularization.

[0198] A further embodiment of the present invention is a method of treating a hyperproliferative disease comprising the step of supplementing a local or systemic immune system by increasing the amount of lactoferrin in the vicinity of the tumor. Vicinity of the tumor refers to the general area of the tumor, for example the lactoferrin can be administered directly into or on the tumor, or in the general area of the tumor, but not directly into the tumor. The

general area may include the margin area or near or adjacent the margin area of the tumor. Preferably, the lactoferrin composition is administered intratumorally. It is envisioned that the lactoferrin related peptides stimulate interleukin-18 following intratumoral administration, which inhibits angiogenesis and thereby has activity against tumor cells which are dependent on neovascularization.

[0199] A further embodiment of the present invention is a method of treating a hyperproliferative disease comprising the step of supplementing a local or systemic immune system by increasing the amount of a lactoferrin related peptide in the skin in the vicinity of the tumor. Preferably, the composition is administered topically. As above, administration in the vicinity of the tumor includes administration near or adjacent to the margins of the tumor or directly in the margin area of the tumor. It is envisioned that the lactoferrin related peptides stimulate interleukin-18 and GM-CSF in the local tissue (e.g., keratinocytes), which enhances immune cells. It is envisioned that the lactoferrin related peptides stimulate interleukin-18 following intratumoral administration, which inhibits angiogenesis and thereby has activity against tumor cells which are dependent on neovascularization.

[0200] In certain embodiments, it may be desirable to combine the peptide composition of the present invention with other agents effective in the treatment of hyperproliferative disease, such as anti-cancer agents, or with surgery. An "anti-cancer" agent is capable of negatively affecting cancer in a subject, for example, by killing cancer cells, inducing apoptosis in cancer cells, reducing the growth rate of cancer cells, reducing the incidence or number of metastases, reducing tumor size, inhibiting tumor growth, reducing the blood supply to tumor or cancer cells, promoting an immune response against cancer cells or a tumor, preventing or inhibiting the progression of cancer, or increasing the lifespan of a subject with cancer. Anti-cancer agents include biological agents (biotherapy), chemotherapy agents, and radiotherapy agents. More generally, these other compositions would be provided in a combined amount effective to kill or inhibit proliferation of the cell. This process may involve administering the peptide composition of the present invention and the agent(s) or multiple factor(s) at the same time. This may be achieved by administering a single composition or pharmacological formulation that includes both agents, or by administering two distinct compositions or formulations, at the same time, or at times close enough so as to result in an overlap of this effect, wherein one composition includes the peptide composition and the other includes the second agent(s).

[0201] Alternatively, the peptide composition of the present invention may precede or follow the other anti-cancer agent treatment by intervals ranging from minutes to weeks. In embodiments where the other anti-cancer agent and peptide composition are administered or applied separately to the cell, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and peptide composition would still be able to exert an advantageously combined effect on the cell. In such instances, it is contemplated that one may contact the cell with/administer both modalities within about 1-14 days of each other and, more preferably, within about 12-24 hours of each other. In some situations, it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

a) Chemotherapy

[0202] Cancer therapies also include a variety of chemical based treatments. Some examples of chemotherapeutic agents include without limitation antibiotic chemotherapeutics such as Doxorubicin, Daunorubicin, Adriamycin, Mitomycin (also known as mutamycin and/or mitomycin-C), Actinomycin D (Dactinomycin), Bleomycin, Plicomycin, plant alkaloids such as Taxol, Vincristine, Vinblastine, miscellaneous agents such as platinum based agents (e.g., Cisplatin (CDDP)), etoposide (VP16), Tumor Necrosis Factor, and alkylating agents such as, Carmustine, Melphalan (also known as alkeran, L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcosyl, (a phenylalanine derivative of nitrogen mustard), Cyclophosphamide, Chlorambucil, Busulfan (also known as myleran), taxane based agents (e.g., docetaxel) and Lomustine.

[0203] Some examples of other agents include, but are not limited to, Carboplatin, Procarbazine, Mechlorethamine, Irinotecan, Topotecan, Ifosfamide, Nitrosurea, Etoposide (VP16), Tamoxifen, Raloxifene, Toremifene, Idoxifene, Droloxifene, TAT-59, Zindoxifene, Trioxifene, ICI 182,780, EM-800, Estrogen Receptor Binding Agents, Gemcitabine, Navelbine, Farnesyl-protein transferase inhibitors, Transplatinum, 5-Fluorouracil, hydrogen peroxide, and Methotrexate, Temazolomide (an aqueous form of DTIC), Mylotarg, Dolastatin-10, Bryostatins, or any analog or derivative variant of the foregoing.

b) Radiotherapeutic Agents

[0204] Radiotherapeutic agents and factors include radiation and waves that induce DNA damage for example, γ -irradiation, X-rays, UV-irradiation, microwaves, electronic emissions, radioisotopes, and the like. Therapy may be achieved by irradiating the localized tumor site with the above described forms of radiations. It is most likely that all of these factors

effect a broad range of damage to DNA, the precursors of DNA, the replication and repair of DNA, and the assembly and maintenance of chromosomes.

[0205] Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

c) Surgery

[0206] Approximately 60% of persons with cancer will undergo surgery of some type, which includes preventative, diagnostic or staging, curative and palliative surgery. Curative surgery is a cancer treatment that may be used in conjunction with other therapies, such as the treatment of the present invention, chemotherapy, radiotherapy, hormonal therapy, gene therapy, immunotherapy and/or alternative therapies.

[0207] Curative surgery includes resection in which all or part of cancerous tissue is physically removed, excised, and/or destroyed. Tumor resection refers to physical removal of at least part of a tumor. In addition to tumor resection, treatment by surgery includes laser surgery, cryosurgery, electrosurgery, and microscopically controlled surgery (Mohs' surgery). It is further contemplated that the present invention may be used in conjunction with removal of superficial cancers, precancers, or incidental amounts of normal tissue.

[0208] Upon excision of part of all of cancerous cells, tissue, or tumor, a cavity may be formed in the body. Treatment may be accomplished by perfusion, direct injection or local application of the area with an additional anti-cancer therapy. Such treatment may be repeated, for example, every 1, 2, 3, 4, 5, 6, or 7 days, or every 1, 2, 3, 4, and 5 weeks or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. These treatments may be of varying dosages as well.

d) Other Biotherapy Agents

[0209] It is contemplated that other biological agents may be used in combination with the present invention to improve the therapeutic efficacy of treatment. These additional agents include, without limitation, agents that affect the upregulation of cell surface receptors and GAP junctions, cytostatic and differentiation agents, inhibitors of cell adhesion, agents that increase the sensitivity of the hyperproliferative cells to apoptotic inducers, or other biological agents, as well as biotherapy such as for example, hyperthermia.

[0210] Hyperthermia is a procedure in which a patient's tissue is exposed to high temperatures (up to 106°F). External or internal heating devices may be involved in the application of local, regional, or whole-body hyperthermia. Local hyperthermia involves the application of heat to a small area, such as a tumor. Heat may be generated externally with high-

frequency waves targeting a tumor from a device outside the body. Internal heat may involve a sterile probe, including thin, heated wires or hollow tubes filled with warm water, implanted microwave antennae, or radiofrequency electrodes.

[0211] A patient's organ or a limb is heated for regional therapy, which is accomplished using devices that produce high energy, such as magnets. Alternatively, some of the patient's blood may be removed and heated before being perfused into an area that will be internally heated. Whole-body heating may also be implemented in cases where cancer has spread throughout the body. Warm-water blankets, hot wax, inductive coils, and thermal chambers may be used for this purpose.

[0212] Hormonal therapy may also be used in conjunction with the present invention. The use of hormones may be employed in the treatment of certain cancers such as breast, prostate, ovarian, or cervical cancer to lower the level or block the effects of certain hormones such as testosterone or estrogen and this often reduces the risk of metastases.

[0213] Adjuvant therapy may also be used in conjunction with the present invention. The use of adjuvants or immunomodulatory agents include, but are not limited to tumor necrosis factor; interferon alpha, beta, and gamma; IL-2 and other cytokines; F42K and other cytokine analogs; or MIP-1, MIP-1beta, MCP-1, RANTES, and other chemokines.

e) Immunotherapy

[0214] Immunotherapeutics, generally, rely on the use of immune effector cells and molecules to target and destroy cancer cells. The immune effector may be, for example, an antibody specific for some marker on the surface of a tumor cell. The antibody alone may serve as an effector of therapy or it may recruit other cells to actually affect cell killing. The antibody also may be conjugated to a drug or toxin (chemotherapeutic, radionuclide, ricin A chain, cholera toxin, pertussis toxin, etc.) and serve merely as a targeting agent. Alternatively, the effector may be a lymphocyte carrying a surface molecule that interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells and NK cells.

[0215] It is contemplated that vaccines that are used to treat cancer may be used in combination with the present invention to improve the therapeutic efficacy of the treatment. Such vaccines include peptide vaccines or dendritic cell vaccines. Peptide vaccines may include any tumor-specific antigen that is recognized by cytolytic T lymphocytes. Yet further, one skilled in the art realizes that dendritic cell vaccination comprises dendritic cells that are pulsed with a peptide or antigen and the pulsed dendritic cells are administered to the patient.

[0216] Examples of tumor-specific antigens that are being used as vaccines in melanoma include, but are not limited to gp100 or MAGE-3. These antigens are being administered as peptide vaccines and/or as dendritic cell vaccines.

B. Wounds and other Integument Disorders

1. Wounds

[0217] In accordance with the present invention, a peptide composition provided in any of the above-described pharmaceutical carriers is orally, topically, or parenterally administered to a subject suspected of or having a wound.

[0218] The present invention is designed for the treatment of any type of wound, which includes, but is not limited to skin wound, internal wound, gastrointestinal wound, oral wound, bone wounds, ophthalmic wound, surgical wound, or any combination thereof. Wounds can be found on but not limited to skin, internal organs, stomach and intestines (gastrointestinal), oral mucosa, and eye (ophthalmic wounds, e.g., corneal ulcers, radiokeratotomy, corneal transplants, epikeratophakia and other surgically induced wounds in the eye). Depending on the process that causes the wounds, wounds can also be classified as but are not limited to incisional wounds, excisional wounds, diabetic ulcers, venous stasis ulcers, decubitus or pressure ulcers, chemical wounds, and burn wounds.

[0219] A further embodiment of the present invention is administering the inventive composition to treat skin wounds. Skin wounds further comprise but are not limited to full-thickness wounds and partial-thickness wounds. Full-thickness wounds involve the complete removal of epidermis and dermis to the depth of fascial planes or subcutaneous fat. In the loose-skinned species, the thin musculature of the panniculus carnosus, which firmly adheres to the base of the dermis, is usually removed as well. In partial-thickness wounds a substantial amount of dermis, mostly reticular, is left behind, and, more importantly, the bases of most epidermal appendages (sebaceous and sweat glands, hair follicles) remain intact.

[0220] Yet further, a wound can be further defined as an acute wound. Acute wounds have a relatively rapid rate of healing, especially in healthy subjects. However, in the elderly or immunocompromised healing can be prolonged. Healing is also prolonged if the wound becomes infected. Preferred acute wounds that are to be treated with the present composition include, but are not limited to partial-thickness burns, lacerations, bullet wounds or infected wounds.

[0221] A wound is also further defined as a chronic wound. Examples of chronic wounds or chronic ulcers include, but are not limited to diabetic ulcers, venous stasis ulcers, decubitus or pressure ulcers. Yet further, chronic wounds can also include infected wounds.

Chronic wounds are wounds that do not repair or do so extremely slowly, and show partial or total lack of structural organization and functional coordination with normal tissue. Chronic wounds or chronic ulcers can be broadly classified into three major types: diabetic ulcers, venous stasis ulcers, decubitus or pressure ulcers. Diabetic ulcers often occur on a foot. Chronic diabetic state and poor glucose control results in poor peripheral circulation and microcirculation due to progressive arteriosclerosis; neuropathic changes that result in an insensate extremity prone to trauma; and intrinsic defects in the wound healing process that may include reduced abundance and response to cellular growth factors. In the case of venous ulcers, venous hypertension causes disturbed microcirculation and pathological changes of the capillaries, elevated persistent levels of pro-inflammatory cytokines and proteases. Fibroblast senescence and respond less to growth factors, which distribute unfavorably. Proteolytic enzymes and their inhibitors are imbalanced. Pressure ulcers occur when skin is under pressure without movement to allow blood flow for 8-12 hours.

[0222] In a preferred embodiment of the present invention, the inventive composition is administered in an effective amount to seal, to close, to improve or to repair the wound. Also, it is envisioned that the composition of the present invention can also decrease, reduce, or inhibit, bacterial infections of the wound, which aid in the healing process of a wound. Thus, one of skill in the art realizes that depending upon the wound type, location, health of the subject, etc., the peptide composition of the present invention may be administered for any given period of time until the wound is healed at least by 5%, 10%, 20%, 30%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% or any range in between.

[0223] For topical administration, the gel formulation of the present invention may be used to coat fibers of an absorbent gauze dressing to form a wound healing bandage which may then be placed on a wound. The low viscosity formulation is preferred for this use. The wound healing bandage may be prepared by soaking a gauze dressing with an aqueous gel solution containing lactoferrin having wound healing activity. The bandage can then be applied to the wound so that the coated fibers of the gauze contacts the wound and stimulate the rate of wound healing.

[0224] In those applications where the present invention is a gel that is applied to an internal or incisional wound, it is preferred that the gel forming polymer be biodegradable. The naturally occurring polymers are generally biodegradable. Examples of these are collagen, the glycosaminoglycans, gelatin and starch. The cellulose are not biodegradable. The synthetic

polymers such as the vinyl polymers are not degradable. The biodegradability of the polymers described herein is well known to those skilled in the art.

[0225] A further embodiment of the present invention is a method of treating a wound comprising the step of supplementing the local immune system by increasing the amount of a lactoferrin related peptide in the vicinity of the wound. Preferably, the peptide is administered topically to the wound.

[0226] Yet further, the present invention also provides a method of treating a wound comprising the step of supplementing the systemic immune system by increasing the amount of a lactoferrin related peptide in the systemic circulation. Preferably, the lactoferrin is administered via a parenteral route, which includes, but is not limited to intramuscular, intravenous, intraperitoneal, intraocular, intraarticular or into a surgical field.

[0227] In further embodiments, the present invention provides a method of enhancing the immune system of a subject suffering from a wound by administering to the subject a peptide composition. Depending upon the mode of administration, different arms of the immune system are enhanced. For example, topical administration of the composition results in enhancement of the local immune system, i.e., in the vicinity of the wound. Parenteral administration of the composition results in enhancement of the systemic immune system. Yet further, oral administration of the composition results in enhancement of the mucosal immune system, which can also result in systemic effects as well. It is further contemplated that IL-18 or GM-CSF stimulate the production or activity of cells involved in wound repair, for example, but not limited to keratinocytes, endothelial cells, dendritic cells, fibroblasts, and myofibroblasts. Yet further, it is envisioned that lactoferrin related peptides inhibit the production of TNF-alpha, which may lead to excess inflammation and tissue destruction for example by stimulating the production of metalloproteinases.

[0228] It is further envisioned that supplementing the local immune system in a subject by administering topically a therapeutically effective amount of the inventive composition in the vicinity of the wound can result in the killing of bacteria infecting the wound. Still further, topical administration of a composition comprising a lactoferrin peptide related compound may stimulate the production of a cytokine or a chemokine. Cytokines, for example, interleukin-18 or granulocyte/macrophage colony-stimulating factor, can also stimulate the production or activity of cells involved in wound repair. The cells involved in wound repair include, but are not limited to keratinocytes, endothelial cells, fibroblasts, dendritic cells, and myofibroblasts. The inhibition of TNF-alpha further inhibits the migration and maturation of

dendritic cells and the production of metalloproteinases. The dendritic cells can be Langerhans cells.

[0229] In order to increase the effectiveness of the composition of the present invention, it may be desirable to combine the composition of the present invention with other agents effective in the treatment of wounds, such as growth factors, skin replacement therapy, enzymatic and surgical debridement, moist wound dressings, cleansers, antibiotics. Such wound healing agents are capable of negatively affecting a wound in a subject, for example, by enhancing the growth rate of skin cells, augmenting the blood supply to skin cells, promoting an immune response against bacteria infecting the wound, killing bacteria, cleaning ischemic tissue, promoting the closure of the wound. More generally, these other wound healing agents are provided in a combined amount effective to promote the healing of a wound. This process may involve administering the composition of the present invention and the agent(s) or multiple factor(s) at the same time. This may be achieved by administering a single composition or pharmacological formulation that includes both agents, or by administering two distinct compositions or formulations, at the same time, or at times close enough so as to result in an overlap of this effect, wherein one composition includes the lactoferrin composition and the other includes the second agent(s).

[0230] Alternatively, the composition of the present invention may precede or follow the other wound healing agent treatment by intervals ranging from minutes to weeks. In embodiments where the other wound healing agent and inventive composition are administered or applied separately to the wound, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and human lactoferrin composition would still be able to exert an advantageously combined effect on the wound. In such instances, it is contemplated that one may contact the wound with/administer both modalities within about 1-14 days of each other and, more preferably, within about 12-24 hours of each other. In some situations, it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

a) Growth Factors

[0231] Wound healing therapies include growth factor based treatments. Examples include, but are not limited to Regranex™ (Becaplermin-BB gel), AuTolo-Gel (autologous activated platelet releasate), Procuren (autologous thrombin-induced platelet releasate). Growth factors act without limitation by promoting granulation or the formation of new highly

vascularized connective tissue; stimulating proliferation, differentiation and migration of epithelial cells, vascular endothelial cells and other skin cells; enhancing the production of collagen, collagenase, and extracellular matrix.

b) Skin Replacement Therapy

[0232] Examples include but are not limited to Apligraf (bilayered living skin), Trancyte (Human fibroblast-derived temporary skin substitute), Dermagraft (permanent, one-layer skin substitute), Epicel (living one-layer artificial skin), Integra (collagen-based skin regeneration template), AlloDerm (single-layer artificial skin made from human cadavers), CCS (living, cultured, artificial skin).

c) Enzymatic and Surgical Debridement

[0233] Debridement is a process or procedure to clean ischemic or dead tissue. Enzymatic debriders include Accuzyme papain-urea debriding ointment and Collagenase Santyl. Surgical debridement refers to physical removal of at least part of the ischemic or dead tissue in a wound. Debridement may be repeated, for example, every 1, 2, 3, 4, 5, 6, or 7 days, or every 1, 2, 3, 4, and 5 weeks or every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months. Enzymatic debridement treatments may be of varying dosages as well. It is further contemplated that the present invention may be used in conjunction with enzymatic or surgical debridement.

d) Dressings

[0234] Wound healing therapies include a variety of treatments based on dressings. Dressing categories include but are not limited to amorphous hydrogels, hydrogel sheets, absorptives, alginates, biological and synthetic dressings, collagens, composites, contact layers, elastic gauzes, foams, gauzes and non-woven dressings, hydrocolloids, impregnated dressings, silicone gel sheets, silver dressings, transparent films, wound fillers

e) Cleansers

[0235] Examples include but are not limited to Biolex, Lamin, Wound Wash Saline, Techni-Care, CarraKlenz, DiaB Klenz, MicroKlenz, RadiaCare Klenz, UltraKlenz, Comfee Sea-Clens, Optipore Sponge, Saf-Clens, Shur-Clens, Dermagran, DermaKlenz, Dumex, Gene Klenz, GRX, Allclenz, Restore, Hyperion, Medi Tech, Skintegrity, MPM Antimicrobial, ClinsWound, Septicare, Lobana Saline.

f) Antimicrobials

[0236] Examples of include but are not limited to Sulfamylon Cream, Thermazene Cream (1% silver sulfadiazine), cadexomer-iodine pads or gel. Examples of intravenous antimicrobials include but are not limited to imipenem/cilastatin, β -lactam/ β -lactamase inhibitors (ampicillin/sulbactam, piperacillin/tazobactam), and broad-spectrum cephalosporins (cefoxitin, ceftizoxime, ceftazidime). Other examples include, but are not limited to Bensal HP,

Barri-Care, Care-Creme, Formula Magic, Baza, Micro-Guard, Ca-Rezz, Diabet-X products, Mitrazol Powder, PiercingCare, Triple Care products, and various antifungal creams and powders.

g) Compression

[0237] Dynamic compression examples, include pumps and sleeves such as but not limited to ArtAssist, ArterialFlow, EdemaFlow, PulStar, Circulator Boot, Flowplus, Flowpress, Flowtron. Static compression include but are not limited to leg wrappings, gloves, socks, leg wears, leg supports, arm sleeves, stasis pads, compression hosiery, non-elastic bands, high compression bandages, zinc impregnated bandages, elastic bandages.

h) Oxygen Therapy

[0238] Examples of systemic hyperbaric oxygen therapy include but are not limited to compartments for one patient to lay down, for one patient to sit up to 25 degree angle, for one patient to sit up to 90 degree angle, for more than one patient to be treated simultaneously. Examples of topical hyperbaric oxygen therapy include but are not limited to disposable topical hyperbaric oxygen systems for extremity ulcers, disposable topical hyperbaric oxygen systems for decubitis, post-op and trauma wounds.

i) Hydrotherapy, Electric Therapy

[0239] Examples include but are not limited to dry hydrotherapy machines; non-contact thermal wound care systems for use on partial- and full-thickness wounds that maintain warmth and humidity in the wound area; systems that provide non-thermal, pulsed high frequency, high peak power, electromagnetic energy to treat edema and pain in acute and chronic wounds; systems that use controlled, localized negative pressure and support for moist wound healing; pulsatile irrigators with controllable pressures below 15 psi for site-specific treatment of various wounds with variety of tips; various wound irrigation and whirlpool systems.

j) Nutritional Therapy Products

[0240] Examples include but are not limited to isotonic, high-protein, fiber-containing tube feedings to support wound healing; high-protein, cholesterol-free nutritional supplements.

k) Cohesives, Glues, Sealants, Patches

[0241] Examples include but are not limited to Dermabond, CoStasis, CoSeal, BioGlue, FibRx, FocalSeal, FloSeal, AutoSeal, Indermil, Syvek, LiquiSheild, LiquiBand, Quixil, CryoSeal, VIGuard Fibrin Sealant, and various tapes, closures, and securement products.

l) Topical Wound Healing Promoters

[0242] Examples include but are not limited to topical aerosols which stimulate the capillary bed of chronic wounds; skin protectants with zinc-nutrient formulations; topical gels to

help scars feel softer and smoother; hydrophilic ointments that cleanse degraded proteins, promote healthy granulation, control local inflammation and reduce wound odors; oil-and-water wound dressing emulsions that selectively recruit macrophages.

m) Other Biotherapy agents

[0243] Adjuvant therapy may also be used in conjunction with the present invention. The use of adjuvants or immunomodulatory agents include, but are not limited to tumor necrosis factor; interferon alpha, beta, and gamma; IL-2 and other cytokines; F42K and other cytokine analogs; or MIP-1, MIP-1beta, MCP-1, RANTES, and other chemokines.

2. Psoriasis

[0244] In accordance with the present invention, a peptide composition provided in any of the above-described pharmaceutical carriers is orally, topically, or parenterally administered to a subject suspected of or having psoriasis.

[0245] Psoriasis is a chronic inflammatory skin disorder that undergoes repeated relapse and remission and affects one to three percent of the world's population. The disease can begin at any age and has its peak appearance in the third decade. Its severity, course, and remissions are unpredictable. (See, T. P. Habif, in: *Clinical Dermatology*, Mosby, Mo. (1996) and *The Textbook of Medicine* eds: J. B. Wyngaarden and L. H. Smith, W., W. B. Saunders Company, Philadelphia (1985)).

[0246] Patients with psoriasis can be divided into two groups, those with a genetic predisposition and those that respond to epigenetic, i.e. environmental factors. The most common form is chronic plaque psoriasis and is characterized by hyperplasia of the epidermis and inflammation of the dermis and epidermis. These changes arise due to activation of a T-lymphocyte cell mediated dermal immune reaction in regional lymph nodes in response to unidentified antigenic stimuli. The activated T-cells cause keratinocyte cells to proliferate and assume a psoriasis phenotype. The inflammatory reaction is caused by proinflammatory cytokine proteins that are induced in response to the environmental stimulus and results in infiltration of the dermis and epidermis by inflammatory white blood cells.

[0247] The present invention provides a method of enhancing the immune system of a subject suffering from psoriasis by administering to the subject a peptide composition. Depending upon the mode of administration, different arms of the immune system are enhanced. For example, topical administration of the composition results in enhancement of the local immune system, i.e., in the vicinity of the wound. Parenteral administration of the composition results in enhancement of the systemic immune system. Yet further, oral administration of the

composition results in enhancement of the mucosal immune system, which can also result in systemic effects as well.

[0248] Psoriasis has been shown to be caused by inappropriate local immune responses which involve the de novo production of TNF- α by keratinocytes (Gilhar et al., 1996, Clin. Exp. Immunol. 106: 134-142). Accordingly, in one embodiment, the present invention provides compositions that directly interfere with the production of TNF- α by keratinocytes, thus preventing the inappropriate local immune response causing psoriasis. More specifically, the present invention provides novel pharmaceutical compositions comprising a lactoferrin related peptide product for the treatment of psoriasis. In a preferred embodiment, the compositions are formulated for topical application in about 0.5% to about 5% carrier. In alternative embodiments, the compositions are formulated for intradermal injections.

[0249] In order to increase the effectiveness of the composition of the present invention, it may be desirable to combine the composition of the present invention with other agents effective in the treatment of psoriasis, such as anti-inflammatory agents. This process may involve administering the composition of the present invention and the agent(s) or multiple factor(s) at the same time. This may be achieved by administering a single composition or pharmacological formulation that includes both agents, or by administering two distinct compositions or formulations, at the same time, or at times close enough so as to result in an overlap of this effect, wherein one composition includes the lactoferrin composition and the other includes the second agent(s).

[0250] Alternatively, the composition of the present invention may precede or follow the other anti-inflammatory agent treatment by intervals ranging from minutes to weeks. In embodiments where the other anti-inflammatory agent and inventive composition are administered or applied separately to the anti-inflammatory, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and the inventive composition would still be able to exert an advantageously combined effect on the psoriasis.

[0251] Typical anti-inflammatory agents are topical agents, for example, but not limited to are corticosteroids (hydrocortisone and analogs). Systemic corticosteroids, for example, can induce prompt resolution of psoriatic lesions, but suppression requires ever-increasing doses.

C. Respiratory Disorders

[0252] In accordance with the present invention, the composition provided in any of the above-described pharmaceutical carriers is orally administered to a subject suspected of or having a respiratory disorder. The respiratory disorder can be an allergic or non-allergic respiratory disorder.

[0253] According to the invention, an allergic or non-allergic respiratory disorder includes asthma, emphysema, bronchitis, chronic obstructive pulmonary disease, sinusitis and allergic rhinitis. In specific embodiments, the respiratory disorder is characterized by increased responsiveness of the trachea and bronchi to various stimuli, i.e., allergens, resulting in widespread narrowing of the airways.

[0254] The composition is administered in an effective amount to decrease, reduce, inhibit or abrogate the obstruction of the airway or the hyperresponsiveness of the respiratory system to the allergen or other stimuli. The amount of lactoferrin related peptide in the composition may vary from about 1 mg to about 100 g. Preferably, the composition that is orally administered contains the range of 1 mg to 10 g of peptide per day, more preferably, 10 mg to about 1 g. More preferably, the composition of the present invention also contains metal chelators. A preferred metal chelator is EDTA. More preferably, the composition that is orally administered contains the ratio of 1:10,000 to about 2:1 EDTA to lactoferrin related peptide.

[0255] A further embodiment is a method of enhancing a mucosal immune response in the gastrointestinal tract in a subject comprising the step of administering orally to said subject the composition of the present invention. It is envisioned that oral administration of lactoferrin related peptides stimulate IL-18 in the lungs, sinuses or systemically. Yet further, it is contemplated that an enhancement of lactoferrin related peptides can reduce the infiltration of inflammatory cells into the lung.

[0256] In order to increase the effectiveness of administration of the composition of the present invention, it is desirable to combine these compositions with an additional agent. For example, known asthma agents are used in combination with the composition of the present invention. Exemplary agents known to treat asthma include mast cell degranulation agents (i.e., Cromolyn sodium or Nedocromil sodium), leukotriene inhibitors (i.e., Montelukast sodium, Zafirlukast, or Pranlukast hydrate), corticosteroids (i.e., Beclomethasone, Budesonide, Ciclesonide, Hydrolysable glucocorticoid, Triamcinolone acetonide, Flunisolide, Mometasone furoate, or Fluticasone propionate), β -Antagonists (i.e., Albuterol, Bambuterol, Formoterol, Salbutamol, Terbutaline sulfate, or Salmeterol), IgE binding inhibitors (i.e., Omalizumab),

Adenosine A2 agonists, Anti-CD23 antibody, E-Selectin antagonists, P-Selectin antagonists, L-Selectin antagonists, interleukin inhibitors/monoclonal antibodies, pulmonary surfactants, neurokinin antagonists, NF-Kappa-B inhibitors, PDE-4 inhibitors (i.e., Cilomilast, or Roflumilast), Thromboxan A2 inhibitors (i.e., Ramatroban, or Seratrodast), tryptase inhibitors, VIP agonists or antisense agents.

[0257] Yet further, the agent is a known agent used to treat allergic rhinitis. Exemplary agents include, but are not limited to H1 antihistamines i.e., terfenadine or astemizole; alpha-adrenergic agents; and glucocorticoids, i.e., beclomethasone or flunisolide.

[0258] In addition, the agent is a known agent to treat sinusitis, more specifically, chronic sinusitis. Exemplary agents/therapies include, but are not limited to surgery (e.g., enlarging a sinus passage, remove obstructing bone or nasal polyps, mucosal stripping, removal of sinuses); corticosteroids (e.g., oral, intranasal, nebulized, or inhaled); antibiotics (e.g., oral, intranasal, nebulized, inhaled or intravenous); anti-fungal agents; salt-water nasal washes and mist sprays; anti-inflammatory agents; decongestants (oral or nasal); guaifenesin; potassium iodide; leukotriene inhibitors (e.g., montelukast); mast cell degranulating agents; topical moisturizing applications (e.g., nasal sprays or gels which may contain moisturizing agents such as propylene glycol or glycerin); hot air inhalation; mechanical devices to aid in breathing; enzymatic cleansers (e.g., papaya enzymes); and antihistamine sprays.

[0259] Still further, the agent is a known agent to treat COPD or chronic bronchitis or emphysema. Exemplary agents/interventions include, but are not limited to oxygen; bronchodilator drugs [e.g., short and long acting beta-2 stimulants, anticholinergics (e.g., ipratropium bromide, theophylline compounds or a combination), steroids (topical or oral), or mucolytic agents (e.g., ambroxol, ergosterin, carbocysteine, iodinated glycerol)]; antibiotics; anti-fungals; moisturization by nebulization; anti-tussives; respiratory stimulants (e.g., doxapram, almitrine bismesylate); surgery (e.g., bullectomy, lung volume reduction surgery, lung transplantation); and alpha 1 antitrypsin administration.

[0260] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0261] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination.

D. Infectious Diseases

[0262] In certain embodiment of the invention, the present invention is useful for the treatment and/or prevention of infectious disease. Infectious diseases include infections of viral etiology such as HIV, West Nile Virus, influenza, Herpes, viral hepatitis, Epstein Bar, polio, viral encephalitis, measles, chicken pox, Papilloma virus etc.; or infections of bacterial etiology such as bacterial meningitis, paramenigeal infections, septic thrombophlebitis, pneumonia, tuberculosis, myocarditis, bacteremia, syphilis, etc.; or infections of parasitic etiology such as malaria, trypanosomiasis, leishmaniasis, candidiasis, trichomoniasis, amoebiasis, etc.

1. Viral

[0263] The present invention can have applications therefore in the prevention and treatment of viral diseases. The following pathogenic viruses which are mentioned by way of example, influenza A, B and C, parainfluenza, paramyxoviruses, Newcastle disease virus, respiratory syncytial virus, measles, mumps, adenoviruses, adenoassociated viruses, parvoviruses, Epstein-Barr virus (EBV), rhinoviruses, coxsackieviruses, echoviruses, reoviruses, rhabdoviruses, lymphocytic choriomeningitis, coronavirus, polioviruses, herpes simplex (HSV), human immunodeficiency viruses (HIV), cytomegaloviruses, papillomaviruses, human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), varicella-zoster, poxviruses, rubella, rabies, picornaviruses, rotavirus and Kaposi associated herpes virus.

2. Bacterial

[0264] In addition to the viral diseases mentioned above, the present invention is also useful in the prevention, inhibition, or treatment of bacterial infections. The following bacteria are mention by way of example, including, but not limited to, serotypes of pneumococci, streptococci such as *S. pyogenes*, *S. agalactiae*, *S. equi*, *S. canis*, *S. bovis*, *S. equinus*, *S. anginosus*, *S. sanguis*, *S. salivarius*, *S. mitis*, *S. mutans*, other viridans streptococci, peptostreptococci, other related species of streptococci, enterococci such as *Enterococcus faecalis*, *Enterococcus faecium*, Staphylococci, such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, particularly in the nasopharynx, *Hemophilus influenzae*, *Pseudomonas* species such as *Pseudomonas aeruginosa*, *Pseudomonas pseudomallei*, *Pseudomonas mallei*, *brucellas* such as *Brucella melitensis*, *Brucella suis*, *Brucella abortus*, *Bordetella pertussis*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Moraxella catarrhalis*, *Corynebacterium*

diphtheriae, *Corynebacterium ulcerans*, *Corynebacterium pseudotuberculosis*, *Corynebacterium pseudodiphtheriticum*, *Corynebacterium urealyticum*, *Corynebacterium hemolyticum*, *Corynebacterium equi*, etc. *Listeria monocytogenes*, *Nocardia asteroides*, Bacteroides species, Actinomycetes species, *Treponema pallidum*, Leptospira species and related organisms. The invention may also be useful against gram negative bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus*, *Serratia species*, *Acinetobacter*, *Yersinia pestis*, *Francisella tularensis*, Enterobacter species, Bacteriodes and Legionella species and the like.

3. Fungal Infections

[0265] Yet further, either fungal and other mycotic pathogens or cells infected with fungal or other mycotic pathogens may be used in the present invention to prevent and/or treat diseases, ranging from mycoses involving skin, hair, or mucous membranes, such as, but not limited to, Aspergillosis, *Black piedra*, Candidiasis, Chromomycosis, Cryptococcosis, Onychomycosis, or Otitis externa (otomycosis), Phaeohyphomycosis, Phycomycosis, Pityriasis versicolor, ringworm, *Tinea barbae*, *Tinea capitis*, *Tinea corporis*, *Tinea cruris*, *Tinea favosa*, *Tinea imbricata*, *Tinea manuum*, *Tinea nigra (palmaris)*, *Tinea pedis*, *Tinea unguium*, *Torulopsosis*, *Trichomycosis axillaris*, *White piedra*. Fungal and mycotic pathogens that can be used in the present invention include, but are not limited to, *Absidia spp.*, *Actinomadura madurae*, *Actinomyces spp.*, *Allescheria boydii*, *Alternaria spp.*, *Anthopsis deltoidea*, *Apophysomyces elegans*, *Arnium leporinum*, *Aspergillus spp.*, *Aureobasidium pullulans*, *Basidiobolus ranarum*, *Bipolaris spp.*, *Blastomyces dermatitidis*, *Candida spp.*, *Cephalosporium spp.*, *Chaetoconidium spp.*, *Chaetomium spp.*, *Cladosporium spp.*, *Coccidioides immitis*, *Conidiobolus spp.*, *Corynebacterium tenuis*, *Cryptococcus spp.*, *Cunninghamella bertholletiae*, *Curvularia spp.*, *Dactylaria spp.*, *Epidermophyton spp.*, *Epidermophyton floccosum*, *Exserophilum spp.*, *Exophiala spp.*, *Fonsecaea spp.*, *Fusarium spp.*, *Geotrichum spp.*, *Helminthosporium spp.*, *Histoplasma spp.*, *Lecythophora spp.*, *Madurella spp.*, *Malassezia furfur*, *Microsporium spp.*, *Mucor spp.*, *Mycocentrospora acerina*, *Nocardia spp.*, *Paracoccidioides brasiliensis*, *Penicillium spp.*, *Phaeosclera dematioides*, *Phaeoannellomyces spp.*, *Phialemonium obovatum*, *Phialophora spp.*, *Phoma spp.*, *Piedraia hortai*, *Pneumocystis carinii*, *Pythium insidiosum*, *Rhinocladiella aquaspersa*, *Rhizomucor pusillus*, *Rhizopus spp.*, *Saksenaea vasiformis*, *Sarcinomyces phaeomuriformis*, *Sporothrix schenckii*, *Syncephalastrum racemosum*, *Taeniolella boppii*, *Torulopsosis spp.*, *Trichophyton spp.*, *Trichosporon spp.*, *Ulocladium chartarum*, *Wangiella dermatitidis*, *Xylohypha spp.*, and *Zygomycetes spp.*

[0266] In addition, the invention may prove useful in controlling protozoan or macroscopic infections by organisms such as *Cryptosporidium*, *Isospora belli*, *Toxoplasma gondii*, *Trichomonas vaginalis*, *Cyclospora* species, for example, and for *Chlamydia trachomatis* and other *Chlamydia* infections such as *Chlamydia psittaci*, or *Chlamydia pneumoniae*, for example.

4. Bacteremia and septic shock

[0267] In accordance with the present invention, the composition provided in any of the above-described pharmaceutical carriers is administered to a subject suspected of or having bacteremia, sepsis, septic shock or sequelae. These conditions could be caused by gram-negative, gram-positive bacteria or other infectious agents such as *Candida* in any foci of the body and are at a risk of developing into or have developed into a systemic inflammatory response syndrome.

[0268] Yet further, bacteremia may be caused by surgical manipulation of infected oral tissues or routine dental manipulations; catheterization of an infected lower urinary tract; incision and drainage of an abscess; and colonization of indwelling devices, especially IV and intracardiac catheters, urethral catheters, and ostomy devices and tubes. The primary site of infection is usually in the lungs, in the GU or GI tract, or in soft tissues including the skin in patients with decubitus ulcer. In chronically ill and immunocompromised subjects, gram-negative bacteremia occurs more commonly, than in a healthy subject. Additionally, these immunocompromised subjects may develop bloodstream infections caused by aerobic bacilli, anaerobes, and fungi.

[0269] Predisposing factors for septic shock include diabetes mellitus; cirrhosis; leukopenic states, especially those associated with underlying neoplasms or treatment with cytotoxic agents; antecedent infection in the urinary, biliary, or GI tracts; invasive devices, including catheters, drainage tubes, and other foreign materials; and prior treatment with antibiotics, corticosteroids, or ventilatory devices. Septic shock occurs more often in newborns, subjects > 35 yr, pregnant women, and those seriously immunocompromised by underlying diseases or iatrogenic complications of treatment.

[0270] According to the invention, the above-described method is used for the prophylaxis of bacteremia, sepsis, septic shock, related conditions or their consequences. In specific embodiments, the disorder is characterized by a risk of endotoxemia resulting from the use of antibiotic and the subsequent release of endotoxin, as well as positively identified bacteremia.

[0271] A person at risk for developing bacteremia, sepsis, septic shock and/or related conditions is a person that is considered to be immunocompromised and/or chronically ill. The immunocompromised subject, who is, at the time of bacterial exposure, has a pre-existing condition that reduces one or more mechanisms for normal defense against infection. The immunocompromised condition may be due to a defect or dysfunction of the immune system or to other factors that heighten susceptibility to infection, for example immunosuppressive agents. Thus, prophylactically, it is envisioned that the lactoferrin composition can reduce any of the following: the levels of circulating bacteria, the risk of the subject developing sepsis, septic shock, organ failure, and decrease the morbidity and mortality associated with bacteremia.

[0272] In a preferred embodiment of the present invention, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate the risk of developing bacteremia and minimizing the effects of already existing bacteremia, sepsis, septic shock or related conditions. The amount of lactoferrin related peptides in the composition may vary from about 1 mg to about 100 g.

[0273] The guiding principle in the use of lactoferrin related peptides is to administer the treatment at the earliest signs of bacteremia, sepsis or septic shock being developed to attenuate the development of bacteremia and to reduce the extent of organ damage that results from sepsis and septic shock. The improvement is any observable or measurable improvement. Thus, one of skill in the art realizes that a treatment may improve the patient or subject's condition, but may not be a complete cure of the disease. In certain aspects, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate levels of bacteria in circulation. In further aspects, an improvement can consist of any of the following, for example, decrease in the levels of circulating bacteria, attenuating the development of sepsis, attenuating the development of septic shock, attenuating the development of organ failure, decreasing morbidity associated with bacteremia and decreasing mortality (death) associated with bacteremia. Thus, after administration of lactoferrin related peptides, if any of the above conditions improve, then the amount of lactoferrin related peptides are considered to be an effective amount. Yet further, administration of lactoferrin related peptides will also attenuate the development of sepsis, septic shock and other conditions related thereto.

[0274] In certain aspects, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate the severity of sepsis or septic shock. In further aspects, an improvement can consist of any of the following, for example, decreasing mortality, decreasing

morbidity, attenuating the development organ failure, decreasing days of hospitalization, decreasing or eliminating days of intensive care such as in an intensive care unit, decreasing or eliminating the use of supportive care such as a mechanical ventilator or decreasing the incidence of sequelae such as ARDS. Survival in patients with organ failure at baseline and prevention and reversal of organ failure are also evaluated. Thus, after administration of lactoferrin related peptides, if any of the above conditions improve, then the amount of lactoferrin related peptides are considered to be an effective amount.

[0275] In certain aspects, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate the severity of ALI or ARDS. In further aspects, an improvement can consist of any of the following, for example, decrease in mortality, attenuating the development organ failure, decreasing days of hospitalization, decreasing or eliminating days of intensive care such as in an intensive care unit, or decreasing or eliminating the use of supportive care such as a mechanical ventilator or PaO₂/FiO₂ ratios. Thus, after administration of lactoferrin related peptides, if any of the above conditions improve, then the amount of are considered to be an effective amount.

[0276] In order to increase the effectiveness of the composition, it may be desirable to combine these compositions and methods of the invention with a known agent effective in the treatment or prevention of bacteremia, sepsis, septic shock and related conditions, for example known agents to treat bacterial infections, e.g., antibiotics, known agents for the treatment of sepsis, e.g., Drotrecogin alfa (activated) and agents to treat inflammation. In some embodiments, it is contemplated that a conventional therapy or agent, including but not limited to, a pharmacological therapeutic agent may be combined with the composition of the present invention.

[0277] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0278] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination. In other aspects, one or more agents

may be administered substantially simultaneously, or within about minutes to hours to days to weeks and any range derivable therein, prior to and/or after administering the composition.

[0279] Administration of the composition to a cell, tissue or organism may follow general protocols for the administration of cardiovascular therapeutics, taking into account the toxicity, if any. It is expected that the treatment cycles would be repeated as necessary. In particular embodiments, it is contemplated that various additional agents may be applied in any combination with the present invention.

[0280] Pharmacological therapeutic agents and methods of administration, dosages, etc. are well known to those of skill in the art (see for example, the “Physicians Desk Reference”, Goodman & Gilman’s “The Pharmacological Basis of Therapeutics”, “Remington’s Pharmaceutical Sciences”, and “The Merck Index, Eleventh Edition”, incorporated herein by reference in relevant parts), and may be combined with the invention in light of the disclosures herein. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject, and such individual determinations are within the skill of those of ordinary skill in the art.

[0281] Non-limiting examples of a pharmacological therapeutic agent that may be used in the present invention include an antimicrobial agent, an anti-sepsis agent, an anti-inflammatory agent, an antithrombotic/fibrinolytic agent, a blood coagulant, an antiarrhythmic agent, an antihypertensive agent, a vasopressor, or agents to treat metabolic acidosis. In certain aspects of the present invention, antimicrobial agents, e.g., antibiotics are used in combination with the composition of the present invention.

a) Anti-microbial agents

[0282] In certain embodiments, an “antimicrobial agent” can be used in combination with the lactoferrin composition. An antimicrobial agent may comprise an antibiotic, anti-fungal, and anti-viral agent.

[0283] Antibiotics inhibits the growth of microorganisms without damage to the host. For example, the antibiotic may inhibit cell wall synthesis, protein synthesis, nucleic acid synthesis, or alter cell membrane function. Classes of antibiotics that can possibly be used in conjunction with the peptide include, but are not limited to, macrolides (i.e., erythromycin), penicillins (i.e., nafcillin), cephalosporins (i.e., cefazolin), carbapenems (i.e., imipenem, aztreonam), other beta-lactam antibiotics, beta-lactam inhibitors (i.e., sulbactam), oxalines (i.e. linezolid), aminoglycosides (i.e., gentamicin), chloramphenicol, sulfonamides (i.e.,

sulfamethoxazole), glycopeptides (i.e., vancomycin), quinolones (i.e., ciprofloxacin), tetracyclines (i.e., minocycline), fusidic acid, trimethoprim, metronidazole, clindamycin, mupirocin, rifamycins (i.e., rifampin), streptogramins (i.e., quinupristin and dalbapristin), lipopeptide (i.e., daptomycin), polyenes (i.e., amphotericin B), azoles (i.e., fluconazole), and echinocandins (i.e., caspofungin acetate). Examples of specific antibiotics that can be used include, but are not limited to, erythromycin, nafcillin, cefazolin, imipenem, aztreonam, gentamicin, sulfamethoxazole, vancomycin, ciprofloxacin, trimethoprim, rifampin, metronidazole, clindamycin, teicoplanin, mupirocin, azithromycin, clarithromycin, ofloxacin, lomefloxacin, norfloxacin, nalidixic acid, sparfloxacin, pefloxacin, amifloxacin, gatifloxacin, moxifloxacin, gemifloxacin, enoxacin, fleroxacin, minocycline, linezolid, temafloxacin, tosufloxacin, clinafloxacin, sulbactam, clavulanic acid, amphotericin B, fluconazole, itraconazole, ketoconazole, and nystatin. Other examples of antibiotics, such as those listed in Sakamoto et al, U.S. Pat. No. 4,642,104 herein incorporated by reference will readily suggest themselves to those of ordinary skill in the art.

[0284] Anti-viral agents can also be used in combination the peptide composition to treat and/or prevent a viral infection or disease. Such anti-viral agents include, but are not limited to protease inhibitors (e.g., saquinavir, ritonavir, amprenavir), reverse transcriptase inhibitors (e.g., azidothymidine (AZT), lamioridine (3TC), dideoxyinosine (ddl), dideoxycytidine (ddC), zidovudine), nucleoside analogs (e.g., acyclovir, penciclovir).

[0285] In certain embodiments, anti-fungal agents can be used in combination with the peptide composition to treat and/or prevent a fungal infection. Such anti-fungal agents include, amphotericin B (Amphocin®, Fungizone®), butoconazole (Femstat®), clotrimazole (Mycelex®, Gyne-Lotrimin®, Lotrimin®, Lotrisone®), fluconazole (Diflucan®), flucytosine (Ancobon®), griseofulvin (Fulvicin P/G®, Grifulvin V®, Gris-PEG®), itraconazole (Sporanox®), ketoconazole (Nizoral®), miconazole (Femizol-M®, Monistat®), nystatin (Mycostatin®), terbinafine (Lamisil®), terconazole (Terazol®), or tioconazole (Vagistat®).

b) Other agents

[0286] Anti-sepsis agents include, but are not limited to Drotrecogin alfa (activated). Agents used for the treatment of ALI and ARDS include but are not limited to intrapulmonary instillation of surfactants, and leukotriene modifiers. Anti-inflammatory agents include, but are not limited to non-steroidal anti-inflammatory agents (e.g., naproxen, ibuprofen, celecoxib) and steroidal anti-inflammatory agents (e.g., glucocorticoids).

[0287] Non-limiting examples of non-pharmacologic interventions that may be used in the present invention include supportive care such as organ support in sepsis and septic shock and low tidal volume ventilation protocols in ALI and ARDS.

E. Pain

[0288] In accordance with the present invention, the composition provided in any of the above-described pharmaceutical carriers is administered to a subject who has experienced pain which may be acute or chronic in nature.

[0289] Causes of acute pain include, but are not limited to pain following trauma such as a blunt or sharp injury, bullet wounds, or surgery.

[0290] Causes of chronic pain include, but are not limited to pain associated with chronic diseases such as cancer, arthritis, inflammatory disease, chronic wounds, cardiovascular accidents, disorders of the spinal chord or central nervous system, and recovery from surgery.

[0291] In a preferred embodiment of the present invention, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate pain. Thus, a subject is administered a therapeutically effective amount of a lactoferrin composition so that the subject has an improvement in the parameters relating to pain including subjective measures such as pain scores and grading and objective measures including use of additional pain medications. The improvement is any observable or measurable improvement. Thus, one of skill in the art realizes that a treatment may improve the patient condition, but may not be a complete cure of the disease. The amount of lactoferrin in the composition may vary from about 1 ng to about 100 g each day.

[0292] In certain embodiments, the lactoferrin related peptide composition is administered to a subject to modulate chronic or acute pain in the subject. Modulation of pain is achieved by administering an effective amount of the composition to decrease, reduce, inhibit or abrogate pain. Specifically, it is contemplated that lactoferrin stimulates or enhances cytokine production or activity. For example, lactoferrin can enhance the production or activity of TNF- α resulting in modulation of pain, acute or chronic, in the subject.

[0293] In order to increase the effectiveness of the composition, it may be desirable to combine these compositions and methods of the invention with a known agent effective in the treatment of pain both directly and indirectly. In some embodiments, it is contemplated that a conventional therapy or agent, including but not limited to, a pharmacological therapeutic agent, a non-pharmacological pain management techniques or a combination thereof, may be combined with the composition of the present invention.

[0294] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0295] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination. In other aspects, one or more agents may be administered within of from substantially simultaneously, about minutes to hours to days to weeks and any range derivable therein, prior to and/or after administering the composition.

[0296] Administration of the composition to a cell, tissue or organism may follow general protocols for the administration of pain therapeutics, taking into account the toxicity, if any. It is expected that the treatment cycles would be repeated as necessary. In particular embodiments, it is contemplated that various additional agents may be applied in any combination with the present invention.

a) Pharmacological Therapeutic Agents

[0297] Pharmacological therapeutic agents and methods of administration, dosages, etc. are well known to those of skill in the art (see for example, the "Physicians Desk Reference", Goodman & Gilman's "The Pharmacological Basis of Therapeutics", "Remington's Pharmaceutical Sciences", and "The Merck Index, Eleventh Edition", incorporated herein by reference in relevant parts), and may be combined with the invention in light of the disclosures herein. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject, and such individual determinations are within the skill of those of ordinary skill in the art.

[0298] Non-limiting examples of a pharmacological therapeutic agent that may be used in the present invention include non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, indomethacin, ibuprofen, naproxen, acetaminophen, and ketoprofen); opioid analgesics (e.g., codeine, morphine, methadone, demerol, fentanyl, oxycodone, and levorphanol), second generation NSAIDs (e.g., COX-2 inhibitors); and anti-depressant drugs (e.g., tricyclic antidepressants, sedatives, tranquilizers, hypnotics, anti-histamines, and amphetamines).

b) Non-Pharmacological Pain Techniques

[0299] In certain aspects, a therapeutic agent may comprise a non-pharmacological pain management techniques. Non-pharmacological pain management techniques are well known to those of skill in the art, and may comprise, but are not limited to acupuncture or acupressure, local anesthesia/analgesia, regional anesthesia/analgesia (e.g., epidural or spinal analgesia/anesthesia), general anesthesia/analgesia (e.g., intravenous anesthetics or opioid pump) and chiropractic. Non-pharmacological pain-reduction agents include, but are not limited to devil's, capsaicin, menthold or L-phenylalanine.

F. Cardiovascular Diseases

[0300] In accordance with the present invention, the composition provided in any of the above-described pharmaceutical carriers is administered to a subject who has experienced or is at risk of developing cardiovascular disease. Risk factors include, but are not limited to elevated levels of cholesterol or CRP. One of skill in the art can determine the patients who would potentially benefit from a therapeutic agent that would reduce circulating levels of total cholesterol or triglycerides or cardiovascular inflammation.

[0301] Cardiovascular diseases and/or disorders include, but are not limited to, diseases and/or disorders of the pericardium, heart valves (e.g., incompetent valves, stenosed valves, Rheumatic heart disease, mitral valve prolapse, aortic regurgitation), myocardium (e.g., coronary artery disease, myocardial infarction, heart failure, ischemic heart disease, angina) blood vessels (e.g., hypertension, arteriosclerosis, aneurysm) or veins (e.g., varicose veins, hemorrhoids). In specific embodiments, the cardiovascular disease is atherosclerosis.

[0302] In specific embodiments of the present invention, the peptide composition is administered to a subject suffering from or at risk for developing atherosclerosis. Thus, it is envisioned that the peptide composition modulates or reduces the severity and/or incidence of atherosclerosis.

[0303] Prophylactic treatment can be administered to those subjects at risk for developing atherosclerosis. One risk factor is an atherogenic lipoprotein profile. For example, a ratio of serum cholesterol to high density lipoproteins of above 5:1 indicates a higher than average risk of developing atherosclerosis. Other factors indicating increased risk for atherosclerosis include a serum cholesterol level of above 240 mg/dl; a high density lipoprotein level below about 35 mg/dl; and a low density lipoprotein level above about 160 mg/dl.

[0304] Another embodiment includes treating a human subject with an elevated level of circulating total cholesterol or CRP according to the then medically established guidelines. It is contemplated that the composition of the present invention reduces or attenuates

the levels of circulating total cholesterol, low density lipoproteins or very low density lipoproteins. It is contemplated that the composition of the present invention can interfere with how cholesterol enters the circulation either via absorption from food (exogenous pathway) or synthesis by the liver (endogenous pathway).

[0305] Another embodiment includes treating a human subject having dyslipidemia. Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. These disorders may be manifested by elevation of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, and a decrease in the high-density lipoprotein (HDL) cholesterol concentration. Thus, it is envisioned that the composition of the present invention can reduce or abrogate the effects of lipoprotein metabolism, such as dyslipidemia.

[0306] In a preferred embodiment of the present invention, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate cardiovascular disease. Thus, a subject is administered a therapeutically effective amount of a lactoferrin composition so that the subject has an improvement in the parameters relating to cardiovascular disease including circulating levels of total cholesterol, HDL, LDL, VLDL, triglycerides and C-reactive protein (CRP). The amount of lactoferrin in the composition may vary from about 1 ng to about 20 g. Preferably, the composition that is orally administered contains the range of 0.5 g to 5 g of lactoferrin per day.

[0307] The improvement is any observable or measurable improvement. Thus, one of skill in the art realizes that a treatment may improve the patient condition, but may not be a complete cure of the disease. In certain aspects, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate excess amounts of cholesterol levels in circulation. A subject requires treatment for cholesterol levels based upon any of the following situations: LDL of 160 mg/ml or greater; LDL of 130-159 mg/ml and also have two or more cardiovascular risk factors; LDL of 100 mg/ml or greater in subjects with coronary heart disease (CHD); triglycerides of 200 mg/dl or higher; total cholesterol of 240 mg/dl or higher or HDL of less than 40 mg/dl. Thus, after administration of lactoferrin related compounds, if any of the above conditions improve, then the amount is considered an effective amount to decrease, reduce, inhibit or abrogate cholesterol levels in the circulation.

[0308] Another embodiment is a method of reducing vascular inflammation by administering the composition of the present invention. Vascular inflammation can be tied to a number of the underlying processes contributing to atherosclerosis which include endothelial

dysfunction, vascular proliferation and matrix alteration. Recent studies have emphasized the involvement of inflammation in mediating all stages of atherosclerosis. Vascular inflammation is thought to be a consequence of damage to the vascular endothelium and may also involve the proliferation of vascular smooth muscle cells (vsmcs). One precursor of lesion development in humans may be focal accumulation of vsmcs within the intima. In early atherosclerosis, vsmcs may contribute to the development of the atheroma through the production of pro-inflammatory mediators such as monocyte chemoattractant protein 1 and vascular cell adhesion molecule, and through the synthesis of matrix molecules required for the retention of lipoproteins. Inflammation of the vascular endothelium and proliferation of vsmcs may also impact the stability of the plaque through the formation of a firm fibrous cap. Indeed, in lipid-laden lesions in which the fibrous cap is thin and weak, there is evidence of vsmc apoptosis, especially at the "shoulder" region, associated with inflammation. In addition, the local inflammatory milieu can induce expression of collagenase and inhibit expression of proteolytic inhibitors, thus rendering the fibrous cap weak and susceptible to rupture. Lactoferrin, having known anti-inflammatory properties, may thus serve to inhibit the underlying processes associated with the development of atherosclerosis.

[0309] In further embodiments, the composition may also reduce vascular spasms or vascular hyper-reactivity. Vascular spasms are a sudden, brief tightening of a blood vessel, which can temporarily reduce blood flow to tissues supplied by that vessel.

[0310] Still further, the composition may also promote endothelial integrity or healing. Endothelia are the layer of cells lining the blood vessels. Endothelial dysfunction most commonly refers to impairment of endothelium-dependent vasodilation and widespread abnormalities in endothelial integrity and homeostasis. It is believed that HDLs help maintain endothelial integrity, facilitate vascular relaxation, inhibit blood cell adhesion to vascular endothelium, reduce platelet aggregability and coagulation, and may favor fibrinolysis. The integrity or completeness of the endothelia lining of the vessels is important to preventing/treating the development of plaques and atherosclerosis. Thus, it is envisioned that the composition of the present invention will promote or modulate endothelial integrity or healing.

[0311] Yet further, another embodiment is a method of preventing a cardiovascular disease in a subject at risk for developing a cardiovascular disease comprising the step of administering to the subject a peptide composition in an amount sufficient to result in prophylaxis of the cardiovascular disease in the subject. In preferred embodiments, the

cardiovascular disease is atherosclerosis. It is envisioned that the composition not only possess therapeutic benefits for those subjects suffering from cardiovascular diseases, but also possess prophylactic properties for those subjects at risk for developing cardiovascular disease. A subject at risk may or may not be cognizant of their disease state or potential disease state and may or may not be aware that they are need of treatment. Thus, prophylactically, it is envisioned that the composition can reduce any of the following: the levels of circulating total cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL), levels of vascular inflammation, circulating C-reactive protein (CRP), triglycerides, and the proliferation of vascular smooth muscle cells in the subject. Yet further, the composition may also increase the levels of circulating high density lipoproteins (HDL).

[0312] In order to increase the effectiveness of the composition, it may be desirable to combine these compositions and methods of the invention with a known agent effective in the treatment or prevention of cardiovascular disease or disorder, for example known agents to treat or prevent atherosclerosis. In some embodiments, it is contemplated that a conventional therapy or agent, including but not limited to, a pharmacological therapeutic agent, a surgical therapeutic agent (e.g., a surgical procedure) or a combination thereof, may be combined with the composition of the present invention.

[0313] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0314] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination. In other aspects, one or more agents may be administered substantially simultaneously, or within about minutes to hours to days to weeks and any range derivable therein, prior to and/or after administering the composition.

[0315] Administration of the composition to a cell, tissue or organism may follow general protocols for the administration of cardiovascular therapeutics, taking into account the toxicity, if any. It is expected that the treatment cycles would be repeated as necessary. In particular embodiments, it is contemplated that various additional agents may be applied in any combination with the present invention.

a) Pharmacological Therapeutic Agents

[0316] Pharmacological therapeutic agents and methods of administration, dosages, etc. are well known to those of skill in the art (see for example, the "Physicians Desk Reference", Goodman & Gilman's "The Pharmacological Basis of Therapeutics", "Remington's Pharmaceutical Sciences", and "The Merck Index, Eleventh Edition", incorporated herein by reference in relevant parts), and may be combined with the invention in light of the disclosures herein. Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject, and such individual determinations are within the skill of those of ordinary skill in the art.

[0317] Non-limiting examples of a pharmacological therapeutic agent that may be used in the present invention include an antihyperlipoproteinemic agent, an antiarteriosclerotic agent, an anti-cholesterol agent, an anti-inflammatory agent, an antithrombotic/fibrinolytic agent, a blood coagulant, an antiarrhythmic agent, an antihypertensive agent, or a vasopressor. In certain aspects of the present invention, anti-cholesterolemic agents are used in combination with the composition of the present invention. Anti-cholesterol agents include but are not limited to HMG-CoA Reductase inhibitors, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid and derivatives thereof, fibric acid and derivatives thereof. HMG-CoA Reductase inhibitors include statins, for example, but not limited to atorvastatin calcium (Lipitor®), cerivastatin sodium (Baycol®), fluvastatin sodium (Lescol®), lovastatin (Advicor®), pravastatin sodium (Pravachol®), and simvastatin (Zocor®). Agents known to reduce the absorption of ingested cholesterol include, for example, Zetia®. Bile acid sequestrants include, but are not limited to cholestyramine, cholestipol and colesevalam. Other anti-cholesterol agents include fibric acids and derivatives thereof (e.g., gemfibrozil, fenofibrate and clofibrate); nicotinic acids and derivatives thereof (e.g., nician, lovastatin) and agents that extend the release of nicotinic acid, for example niaspan. Anti-inflammatory agents include, but are not limited to non-steroidal anti-inflammatory agents (e.g., naproxen, ibuprofen, celecoxib) and steroidal anti-inflammatory agents (e.g., glucocorticoids).

b) Surgical Therapeutic Agents

[0318] In certain aspects, a therapeutic agent may comprise a surgery of some type, which includes, for example, preventative, diagnostic or staging, curative and palliative surgery. Surgery, and in particular a curative surgery, may be used in conjunction with other therapies, such as the present invention and one or more other agents.

[0319] Such surgical therapeutic agents for cardiovascular diseases and disorders are well known to those of skill in the art, and may comprise, but are not limited to, performing surgery on an organism, providing a cardiovascular mechanical prostheses, angioplasty, coronary artery reperfusion, catheter ablation, providing an implantable cardioverter defibrillator to the subject, mechanical circulatory support or a combination thereof. Non-limiting examples of a mechanical circulatory support that may be used in the present invention comprise an intra-aortic balloon counterpulsation, left ventricular assist device or combination thereof.

G. Autoimmune Disorders

[0320] According to the present invention, a subject that is suspected of an autoimmune disease or a subject suffering from an autoimmune disease is treated with the peptide composition of the present invention.

[0321] The pathogenesis of autoimmune disorders is mediated by the aberrant activation, differentiation and trafficking of leukocytes in response to tissue self-antigens. Autoimmune reactions can often have fatal consequences. They can cause the destruction of vital tissue which manifests in the development of chronic autoimmune diseases. The driving forces in the progression of these diseases are autoreactive immune cells. In most cases, these autoreactive cells are CD4 + T-cells which somehow escaped the self-tolerance control mechanisms of the immune system. In non-pathogenic situations, CD4+ T-cells act as T helper cells, which control or mediate the activation and differentiation of other immune cells such as cytotoxic CD8+ T-cells, NK cells, granulocytes, macrophages and B-cells. However, in the situation of chronic autoimmune diseases, CD4 + T- cells are no longer just mediators, but are rather key players of the autoimmune response. In particular, they are either directly or indirectly responsible for the characteristic tissue destruction that occurs in autoimmune diseases, which is triggered by the recognition of autoantigens. These autoantigens are derived from self-proteins of the attacked tissue and are presented to the autoreactive CD4+ T- cells by antigen-presenting cells (APCs), such as macrophages, dendritic cells or B-cells. In addition, aberrant T cell-dependent or T cell-independent antibody production by activated B cells plays a critical role in initiating and amplifying tissue damage in autoimmune disorders.

[0322] Such autoimmune disorders that can be treated using the composition of the present invention include, but are not limited to, the following: Alopecia Areata, Ankylosing Spondylitis, Antiphospholipid Syndrome, aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinemia, pure red cell aplasia, chronic neutropenias, amegakaryocytic thrombocytopenia, antiphospholipid syndromes, autoimmune

thrombocytopenia, autoimmune hemolytic syndromes, antiphospholipid syndromes, autoimmune gastritis, achlorhydria, Autoimmune Addison's Disease, Autoimmune Diabetes, Autoimmune Hemolytic Anemia, Autoimmune Hepatitis, Autoimmune hypophysitis, Autoimmune orchiditis, autoimmune ovarian failure, Behcet's Disease, Bullous Pemphigoid, Cardiomyopathy, Celiac Sprue-Dermatitis, Cicatrical pemphigoid, Chronic Fatigue Immune Dysfunction Syndrome (CFIDS), Chronic Inflammatory Demyelinating Polyneuropathy, Interstitial cystitis, Churg-Strauss Syndrome, Cicatricial Pemphigoid, CREST Syndrome, Cold Agglutinin Disease, Crohn's Disease, Dermatitis herpetiformis, Discoid Lupus, Drug-induced autoimmune disorders, Endometriosis, Epidermolysis bullosa acquisita, Essential Mixed Cryoglobulinemia, Fibromyalgia-Fibromyositis, Glomerulonephritis, Good Pasture Syndrome, Graft Versus Host Disease, Graves' Disease, Guillain-Barré, Hashimoto's Thyroiditis, Idiopathic Inflammatory Myopathies, Idiopathic Pulmonary Fibrosis, Idiopathic Thrombocytopenia Purpura (ITP), IgA Nephropathy, Insulin Dependent Diabetes, Juvenile Arthritis, Lichen Planus, Systemic Lupus Erythmatosus, Ménière's Disease, Metal-induced autoimmunity disorders, Mixed Connective Tissue Disease, Multiple Sclerosis, Myasthenia Gravis, Myocarditis, Myositis, Optic neuritis, Painless/postpartum thyroiditis, Peripheral nerve vasculitis, Pemphigus Foliaceus, Pemphigus Vulgaris, Pernicious Anemia, Polyarteritis Nodosa, Polychondritis, Polyglandular Syndromes, Polymyalgia Rheumatica, Polymyositis and Dermatomyositis, Postinfectious autoimmune disorders, Primary Agammaglobulinemia, Primary Biliary Cirrhosis, Psoriasis, Psoriatic Arthritis, Reactive Arthritis, Raynaud's Phenomenon, Reiter's Syndrome, Rheumatic Fever, Rheumatoid Arthritis, Sarcoidosis, Scleritis, Scleroderma, Sjögren's Syndrome, Stiff-Man Syndrome, Takayasu Arteritis, Temporal Arteritis/Giant-cell Arteritis, Ulcerative Colitis, Uveitis, Vasculitis, Vitiligo, and Wegener's Granulomatosis.

[0323] In certain embodiments, the composition of the present invention is administered to a subject suffering from graft versus host disease (GVHD), organ transplant rejection, autoimmune hepatitis, primary biliary cirrhosis, autoimmune cholangitis, primary sclerosing cholangitis, irritable bowel syndrome (IBS), multiple sclerosis (MS), chronic granulomatous disease, ankylosing spondylitis, scleroderma, polymyositis, (dermato)myositis, systemic vasculitis, systemic lupus erythematosus (SLE), Crohn's disease, insulin-dependent diabetes (type 1) or ulcerative colitis.

1. Organ Transplant Rejection and GVHD

[0324] In accordance with the present invention, the composition provided in any of the above-described pharmaceutical carriers is administered as a therapeutic drug to a subject

who has undergone organ transplant (kidney, heart, lung, liver, pancreas, bone marrow, peripheral stem cells) and/or as a prophylactic drug to organ and/or tissue transplant, for example bone marrow (BM) or peripheral stem cell donor cells, to prevent the development of GVHD in recipients and/or to prevent or attenuate transplant rejection in the recipients. One of skill in the art can determine the patients who would potentially benefit from a therapeutic agent that would reduce chronic allograft rejection and toxicity associated with standard therapy, or the development of GVHD.

[0325] A further embodiment is treating, preventing or reducing the risk of developing graft-versus-host-disease by administering a lactoferrin composition to the donor organ or donor tissue prior to transplantation into the recipient. It is envisioned that administering the composition to the donor tissue/organ will attenuate the immune cells in the donor/organ and prevent the development of the immune response that is mounted against the recipient's tissue, thus preventing or attenuating GVHD. In further embodiments, the recipient and the donor organ/tissue can be treated with the composition of the present invention.

[0326] Additional embodiments of the present invention include a method of treating, preventing or attenuating the severity of tissue or organ transplant rejection in a recipient comprising the step of administering to the donor a lactoferrin composition in an amount sufficient to attenuate the tissue or organ transplant rejection in the recipient. It is envisioned that the composition reduces allogeneic immune responses in the recipient. The composition can also be administered to both the recipient and the donor.

[0327] Another embodiment is a method of treating, preventing or attenuating the severity of xenograft tissue or xenograft organ transplant rejection in a recipient comprising the step of administering to the xenograft donor a composition in an amount sufficient to attenuate the tissue or organ transplant rejection in the recipient. The composition can also be administered to both the recipient and the xenograft donor.

[0328] In particular embodiments, progenitor cells or stem cells may be isolated from at least one organ, cell, tissue or organism. Stem cells can be isolated from embryonic or nonembryonic donors. The tissues from which the stem cells can be isolated include, for example, but are not limited to the bone marrow, the spleen, the liver, peripheral blood, umbilical cord tissue, umbilical cord blood, adipose tissue or skin. Yet further, tissue grafts may be used in the present invention. The tissue may be part or separated from an organism. In certain embodiments, a tissue may comprise, but is not limited to, adipocytes, alveolar, ameloblasts, axon, basal cells, blood (e.g., lymphocytes), blood vessel, bone, bone marrow, peripheral stem

cells, brain, breast, cartilage, cervix, colon, cornea, embryonic, endometrium, endothelial, epithelial, esophagus, facia, fibroblast, follicular, ganglion cells, glial cells, goblet cells, kidney, liver, lung, lymph node, muscle, neuron, ovaries, pancreas, peripheral blood, prostate, skin, skin, small intestine, spleen, stem cells, stomach, testes, or ascite tissue.

[0329] In specific embodiments, an organ is the graft. Organs are comprised of tissues having a special function. Exemplary organs that are used in grafts in the present invention include, but are not limited to heart, kidney, pancreas, lung, or liver.

[0330] In a preferred embodiment of the present invention, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate chronic allograft rejection and toxicity related to standard therapy. The amount of lactoferrin in the composition may vary from about 1 ng to about 100 g, more preferably, 1mg to about 20g. Preferably, the composition that is orally administered contains the range of 0.1 g to 5 g of lactoferrin per day.

[0331] The improvement is any observable or measurable improvement. Thus, one of skill in the art realizes that a treatment may improve the patient or subject's condition, but may not be a complete cure of the disease. In certain aspects, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate levels of an immune response against a graft in the recipient. In further aspects, an improvement can consist of any of the following, for example, increased function of the graft, for example, increased urine output for kidney grafts or decreased jaundice for liver grafts; reduction in inflammation; reduction in general discomfort of the recipient; an overall increased tolerance for the graft. Thus, after administration of lactoferrin related peptides, if any of the above conditions improve, then the amount is considered to be an effective amount.

[0332] An improvement in GHVD is also any observable or measurable improvement. Thus, one of skill in the art realizes that a treatment may improve the patient or subject's condition, but may not be a complete cure of the disease. In certain aspects, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate levels of immune response from the donor's cells, tissue and/or organ against the host's tissues. GVHD can be acute or chronic or mild or severe. Improvements in acute symptoms include any of the following, for example, decrease skin rash, decrease diarrhea, increase in liver function, a decrease in susceptibility to infection. Improvements in chronic symptoms include, but are not limited to decrease skin rash, decrease dermatitis, decrease hair loss, a decrease liver damage, decrease dry eyes and mouth, a decrease susceptibility to infections and decrease lung and/or

gastrointestinal disorders. Thus, after administration of lactoferrin related peptides, if any of the above conditions improve, then the amount is considered to be an effective amount.

[0333] Still yet, a further embodiment is a method of regulating a mucosal immune response in the gastrointestinal tract or a systemic immune response in a subject comprising the step of administering a lactoferrin related peptide composition to said subject the composition of the present invention. It is envisioned that composition stimulates MIP-3 α and interleukin-18 in the gastrointestinal tract, which regulates immune responses. For example, interleukin-18 modulates both Th1/Th2 responses. It is known by those of skill in the art that IL-18 plays an important role in allogeneic stem cell transplantation. Pre-treatment of allogeneic donors with IL-18 significantly improves survival and reduces clinical and pathological indices of acute GVHD in BMT recipients. Other cytokines may also be enhanced or repressed for example, but not limited to IL-1, IL-2, IL-6, IL10, IL-12 and GM-CSF. It is also envisioned that lactoferrin stimulates Th1/Th2 type-responses through the induction and/or repression of Th1 and Th2 cytokines.

[0334] In order to increase the effectiveness of administration of the composition of the present invention, it is desirable to combine these compositions with standard therapy. For example, known immunosuppressant agents are used in combination with the composition of the present invention. Exemplary agents known to prevent organ rejection are T cell modifiers such as cyclosporine (Neoral®, Sandimmune®), prednisone (Novo Prednisone®, Apo Prednisone®), azathioprine (Imuran®), tacrolimus or FK506 (Prograf®), mycophenolate mofetil (CellCept®), OKT3 (Muromonab CO3®, Orthoclone®), ATGAM® & Thymoglobulin® or serine-threonine phosphatase calcineurin (CN) inhibitors. In specific embodiments, the standard or approved treatment of GVHD, which is high doses corticosteroids, primarily high-dose methylprednisolone, is used in combination with the lactoferrin composition of the present invention.

[0335] In addition to immunosuppressant other anti-rejection and/or anti-GVHD therapies can be used in combination with the lactoferrin composition of the present invention. For example, therapies for preconditioning and prophylaxis of GVHD include, but are not limited to total body irradiation, cytosine arabinoside, L-phenylalanine mustard, cyclophosphamide, etoposide, triethylene thiophosphoramide, antithymocyte globulin, bisulfan, tacrolimus, methylprednisolone, cyclosporin, or methotrexate. Experimental therapies for treatment of GVHD include, but are not limited to cytokine inhibitors/antagonists (e.g., anti-TNF α antibody); IL-1 receptor antagonist; recombinant IL-1 receptor; inhibitors of T-cell

activation (e.g., tacrolimus); antimetabolites (e.g., mycophenolate mofetil); anti-CD3 antibody (muromonab, OKT3); anti-CD25 antibody; anti-IL2 receptor monoclonal antibody daclizumab; extracorporeal photopheresis using ex vivo 8-methoxypsoralen; anti-thymocyte globulins (Thymoglobulin® or ATGAM®); ABX-CBL or CBL-1; or Visilizumab (Nuvion®).

[0336] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0337] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination.

H. Endocrine/Metabolism Disorders

1. Diabetes mellitus

[0338] In accordance with the present invention, the composition provided in any of the above-described pharmaceutical carriers is administered to a subject who has experienced or is at high risk of having diabetes mellitus. Thus, it is envisioned that the composition of the present invention may be administered to a subject to regulate diabetes mellitus. The composition modulates at least one symptom of diabetes mellitus, for example, decrease blood glucose or modulate blood insulin levels.

[0339] Risk factors for type I diabetes include islet-cell antibodies and those of type 2 or gestational diabetes include inactivity, obesity, siblings with diabetes, and history of diabetes during pregnancy. One of skill in the art can determine the patients who would potentially benefit from a therapeutic agent that would reduce circulating levels of glucose.

[0340] In a preferred embodiment of the present invention, the composition is administered in an effective amount to decrease, reduce, inhibit or abrogate high glucose, or to reduce total body weight, glycosylated hemoglobin (HbA1c), or blood pressure or to modulate blood insulin levels. In the case of a diabetic condition, successful reduction of hyperglycemia by the lactoferrin composition may be manifested by the fasting plasma glucose level falling below 126 mg/dL, the 2-hour plasma glucose level during an oral glucose tolerance test (OGTT) falling below 200 mg/dL, or if a random plasma glucose determination reading below 200 mg/dL in a symptomatic individual. In the case of a pre-diabetic condition, a successful reduction of hyperglycemia by the lactoferrin composition may be manifested by the fasting

plasma glucose falling below 110 mg/dL and/or the 2-hour plasma glucose on the OGTT falling below between 140 mg/dL. The amount of lactoferrin related peptides in the composition may vary from about 0.1 µg to about 100 g, more preferably, from about 1 µg to about 20 g, or any range therebetween. In specific embodiments, the composition that is administered contains the range of 0.1 g to 5 g of lactoferrin per day.

[0341] Glycohemoglobin (or glycosylated hemoglobin) is measured to monitor or accurately record blood glucose levels, and it is not influenced by acute changes in blood glucose or by the interval since the last meal. Glycohemoglobin is formed when glucose reacts non-enzymatically with the hemoglobin A molecule and is composed of several fractions, the major one being Hb A1c. Total glycohemoglobin (Hb A1) and Hb A1c (expressed as the percentage of total hemoglobin) vary in proportion to the average level of glucose over the lifespan of the red blood cell (RBC), thereby providing an index of glycemic control.

[0342] Further aspects of the invention include reducing blood glucose in a patient suffering from diabetes mellitus by administering to a subject an effective amount of the composition such that the amount of the lactoferrin related peptides modulates blood glucose. The blood glucose is monitored by the level of glycosylated hemoglobin (HbA1c).

[0343] Another aspect is a method of modulating blood insulin in a patient suffering from diabetes mellitus by administering to a subject an effective amount of the composition such that the amount modulates blood insulin. Modulating blood insulin includes reducing or maintaining blood insulin levels or increasing blood insulin levels. Modulating blood insulin levels in the present invention includes increasing blood insulin levels in insulin-dependent diabetes (Type I) or decreasing or maintaining insulin levels in non-insulin-dependent diabetes (Type II).

[0344] In order to increase the effectiveness of administration of the composition of the present invention, it is desirable to combine the compositions with an additional agent. For example, known diabetes agents are used in combination with the composition of the present invention. Exemplary agents known to treat high glucose or insulin sulfonylureas, biguanides, alpha-glucosidase, thiazolidinedione, meglitinide, and amino acid D-phenylalanine derivative. Other antidiabetic agents may also include, a weight loss regimen and/or a diet alteration.

[0345] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not

expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0346] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination.

2. Treatment of Fragile Bone Diseases

[0347] In accordance with the present invention, the peptide composition provided in any of the above-described pharmaceutical carriers is administered to a subject suspected of or having a fragile bone condition.

[0348] The present invention is designed for the treatment of any type of fragile bone condition or any disorder relating to bone loss including but not limited to osteoporosis, age-associated osteoporosis, postmenopausal osteoporosis, osteitis deformans (Paget's disease), osteogenesis imperfecta (brittle bones), and osteopetrosis.

[0349] Bone loss disorders arise from an imbalance in the formation of new healthy bone and the resorption of old bone, skewed toward a net loss of bone tissue. This bone loss includes a decrease in both mineral content and protein matrix components of the bone, and leads to an increased fracture rate of, predominantly, femoral bones and bones in the forearm and vertebrae. These fractures, in turn, lead to an increase in general morbidity, a marked loss of stature and mobility, and, in many cases, an increase in mortality resulting from complications.

[0350] Bone loss occurs in a wide range of subjects, including postmenopausal women, patients who have undergone hysterectomy, patients who are undergoing or have undergone long-term administration of corticosteroids, patients suffering from Cushing's syndrome, and patients having gonadal dysgenesis.

[0351] Unchecked, bone loss can lead to osteoporosis, a major debilitating disease whose prominent feature is the loss of bone mass (decreased density and enlargement of bone spaces) without a reduction in bone volume, producing porosity and fragility.

[0352] Osteoporosis is common in the elderly of both sexes but is more pronounced in postmenopausal women. Osteoporosis may occur as a primary disorder or as a secondary complication of several diseases. It is proposed that genetic factors determine the size of the bone mass achieved in young adulthood. With aging, the increased osteoclastic function and the slowing of osteoblastic activity induced by endocrine influences, particularly decreased estrogen levels, result in a net negative balance in the continued turnover of bone. Osteoporosis causes bone pain owing to microfractures; results in loss in height and stability of the vertebral

column; and predisposes to fractures of femoral necks, wrists, and vertebrae. The condition remains asymptomatic until skeletal fragility is well advanced.

[0353] Paget's disease is currently considered to be a slow paramyxoviral infection of osteoblasts and then osteoclasts. The condition is divided into an initial osteolytic stage, followed by a mixed osteolytic-osteoblastic stage, evolving ultimately into burn-out quiescent osteosclerotic stage. Because new bone formation in active disease is disordered and poorly mineralized, it is soft and porous, lacks structural stability, and is vulnerable to fracture or deformation under stress. Patients may demonstrate fractures, nerve compression, osteoarthritis, and skeletal deformities.

[0354] Osteogenesis imperfecta or brittle bones refers to a group of closely related genetic disorders caused by qualitative or quantitative abnormal synthesis of type I collagen, constituting about 90% of the matrix of bone. Syndromes range from one variant (type II) that is uniformly fatal in the perinatal period (from multiple bone fractures) to other variants marked by increased predisposition to fracture but compatible with survival. Morphologically the basic change in all is osteopenia or too little bone, with marked thinning of the cortices and rarefaction of the trabeculae.

[0355] Osteopetrosis refers to a group of rare hereditary diseases characterized by overgrowth and sclerosis of bone, with marked thickening of the cortex and narrowing or filling of the medullary cavity impairing hematopoiesis. Despite too much bone, it is brittle and fractures easily. The autosomal recessive form is evident from birth, with anemia, neutropenia, infections and eventual death. The autosomal dominant form is benign but predisposes to fractures. Common to all forms is a hereditary defect in osteoclast function resulting in reduced bone resorption and enhanced net bone overgrowth.

[0356] In a preferred embodiment of the present invention, lactoferrin related peptides are administered in an effective amount to stabilize or reduce bone fragility, to strengthen the bone, inducing the growth of healthy bone, modulate calcium levels, and modulate mineral accumulation in the skeleton. The amount may vary from about 1 μ g to about 100 g of lactoferrin related peptides. Preferably, the amount that is administered is in the range of 10 mg to 25 g. Most preferably, the amount that is administered is in the range of 10 μ g to 5g.

[0357] It is often desirable to deliver the composition of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms may be utilized. For example, a dosage form may contain a pharmaceutically acceptable non-toxic salt

of the compounds which has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt such as those just described, may be formulated in a gel, for example, an aluminum monostearate gel with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulation in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above may also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow release, depot or implant formulations, e.g. liposomes, are well known in the literature. See, for example, "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978.

[0358] Still yet, a further embodiment is a method of promoting the stimulation or inhibition of cytokines, growth factors or mediators of bone growth or resorption. Such growth factors include, but not limited to insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF- β), and growth hormone releasing factor (GRF). Mediators of bone growth or resorption include, but are not limited to parathyroid hormone (PTH), calcitonin or 1,25-dihydroxycholecalciferol (1,25(OH) $_2$ D $_3$).

[0359] Still yet, a further embodiment is a method of activating or inhibiting cells involved in bone remodeling including but not limited to osteoblasts, osteoclasts, chondrocytes, endothelial cells, and fibroblasts.

[0360] In order to increase the effectiveness of the composition of the present invention, it may be desirable to combine the composition of the present invention with other agents effective in the treatment of fragile bone diseases including but not limited to calcium and cholecalciferol (vitamin D) supplements, estrogen replacement therapy (ERT), raloxifene, calcitonin, bisphosphonates such as alendronate and cyclical etidronate, statins, recombinant human parathyroid hormone (rhPTH), insulin-like growth factor-1 (IGF-1), and transforming

growth factor-beta (TGF-1). This process may involve administering the lactoferrin composition of the present invention and the agent(s) or multiple factor(s) at the same time. This may be achieved by administering a single composition or pharmacological formulation that includes both agents, or by administering two distinct compositions or formulations, at the same time, or at times close enough so as to result in an overlap of this effect, wherein one composition includes the human lactoferrin composition and the other includes the second agent(s).

[0361] Alternatively, the composition of the present invention may precede or follow the other bone healing agent treatment by intervals ranging from minutes to weeks. In embodiments where the other bone healing agent and the inventive composition are administered or applied separately, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and the composition would still be able to exert an advantageously combined effect on the condition.

I. Immunosuppressed Subjects

[0362] In order to carry out methods of the present invention, the composition of the present invention is administered to an immunosuppressed individual or an individual whose immune system is expected to be suppressed.

[0363] As noted above, the subject method is suited for preventing infection and/or inflammation in immunosuppressed individuals or individuals whose immune systems are expected to be repressed. In one aspect, the immunosuppressed subject exhibits neutropenia, or suffers from AIDS or any form of cancer including lymphoma and myeloma. In yet another aspect, the subject undergoes or is expected to undergo a therapy selected from the group consisting of chemotherapy, radiotherapy, and autologous peripheral stem cell transplant.

[0364] An effective amount of the lactoferrin composition depends on the severity and/or course of immunosuppression, the patient's clinical history and response, and the discretion of the attending physician. The composition is suitably administered to the patient at one time or over a series of treatments. The initial candidate dosage may be administered to a patient. The proper dosage and treatment regimen can be established by monitoring the progress of therapy using conventional techniques known to the people skilled of the art.

[0365] The amount of active ingredients that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors, including the activity of the specific composition employed, the age, body weight, general health, sex, diet, time of administration,

route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy, and can be determined by those skilled in the art.

[0366] In order to achieve effective prophylaxis, preferably, the lactoferrin composition is administered prior to the inception neutropenia, more specifically Grade 3 or higher neutropenia and continued on the same schedule daily for the entire period during which the patient is at a high risk of neutropenic fever, infection or mucositis.

[0367] It is envisioned that the immune response is enhanced by lactoferrin stimulating cytokines and/or chemokines. Exemplary cytokines include interleukin-18 and GM-CSF in the gastrointestinal tract, which are known to enhance immune cells or stimulate production of immune cells.

[0368] Certain treatment regimens include administering the composition in which the concentration of lactoferrin related peptides that is provided is in the range of 1 g to about 100 g/ml and the composition is a solution that is swished in the mouths of the subjects for a few minutes (e.g., about 4 minutes) and then swallowed. This process can be repeated multiple times a day, for example twice or more each day, for a total of three doses per 24 hour period. The doses are taken immediately after meals (one each after breakfast, lunch and dinner), or at similarly spaced intervals throughout the day. Subjects are asked not to eat or drink anything for a least one hour after swallowing the dose. The treatment may be terminated in the event of significant drug related adverse effects observed during one of the interim safety analyses.

[0369] The multiple administration of lactoferrin related peptides each day can maximize the exposure of the oral cavity and gut to the drug. Preferably, patients an effective amount of the composition prophylactically for 21-28 days starting from the commencement of chemotherapy. Daily dosing continues through the neutropenic phase until the earliest of the following: a) Absolute Neutrophil Count (ANC) is ≥ 600 cells/ μL for three consecutive days, and mucositis (if present) has improved to Grade 2 or better for three consecutive days; or b) patient is discharged from the hospital or outpatient transplant setting. A last-day-of-therapy evaluation is performed within 24 hours after the last dose. The patients are also required to return for an end-of-treatment evaluation, to be performed 3-7 days after the last dose.

[0370] The treatment regimen in the present invention can prevent or attenuate infections in immunosuppressed patients, for example, patients undergoing aggressive chemotherapy or radiotherapy. The treatment reduces incidence, duration, and severity, and prolongs the infection-free interval of neutropenic infection (neutropenic fever). For the purpose of this invention, fever is considered as an oral temperature of at least 38.0°C on at least two

occasions within 24 hours, or a single oral temperature of at least 38.3°C. Neutropenic fever is defined as fever that begins when the patient is neutropenic (ANC < 500). The end of neutropenic fever is defined as the point at which the patient begins a period of 48 hours without fever (as defined above), whether or not the patient is still neutropenic. Incidence of neutropenic fever is calculated as the number of patients experiencing one or more episodes of neutropenic fever. Onset of neutropenic fever is determined in two ways: (1) days between the transfusion and the first episode of neutropenic fever and (2) days between a neutrophil count < 1000/ μ L and the first episode of neutropenic fever. Duration of neutropenic fever is defined as the number of days between the onset and the end of neutropenic fever. Severity of neutropenic fever is determined by the average temperature of the patient during the period of neutropenic fever. Infection-free interval is the period between the end of an infective fever and the onset of the next infective fever.

[0371] The present treatment also reduces the incidence, severity, and duration of oral and GI mucositis by improving all clinical criteria used for mucositis evaluation (pain, salivation, appetite, and oral inflammation). The incidence, duration, and severity of oral mucositis are assessed for each patient. Oral mucositis is graded using the Oral Mucositis Assessment Scale (OMAS).

[0372] Prophylactic and concomitant use of antibiotics may be used during the treatment according to patient's conditions and usual standard of care in the medical profession. Use of hematopoietic growth factors is not recommended routinely, but G-CSF may be used as part of the standard of clinical care at the discretion of the doctors. All medications necessary for the patient's well being may also be administered.

[0373] The responses of the patients in the course of treatment are closely monitored by evaluating various response parameters. The treatment protocol may be adjusted accordingly depending on the improvement of the patient's physical conditions.

J. Gastrointestinal Disorders

[0374] In accordance with the present invention, the peptide composition provided in any of the above-described pharmaceutical carriers is administered to a subject suspected of or having a gastrointestinal disorder.

[0375] Gastrointestinal disorders include, but are not limited to, heartburn, bloating, postoperative ileus, abdominal pain and discomfort, early satiety, epigastric pain, nausea, vomiting, burbulence, regurgitation, intestinal pseudoobstruction, anal incontinence, gastroesophageal reflux disease, irritable bowel syndrome, ulcerative colitis, Crohn's disease,

menstrual cramps, pancreatitis, spastic and interstitial cystitis and ulcers and the visceral pain associated therewith.

[0376] In certain embodiments, the peptide composition is administered to a subject suffering from Crohn's disease, colitis, necrotizing enterocolitis, endometriosis, irritable bowel syndrome, pancreatitis, periodontal disease, and ulcerative colitis.

K. Neurological Conditions

[0377] In accordance with the present invention, the peptide composition provided in any of the above-described pharmaceutical carriers is administered to a subject suspected of or having a neurological disorder.

[0378] It is envisioned that the composition of the present invention when administered to a subject suffering from a neurological disorder, stimulates the immune system thereby alleviating the neurological conditions. Thus, the composition of the present invention can be useful with regard to the prevention, treatment, or amelioration of neurological, psychiatric, psychological, conscious state, behavioral, mood, and thought activity (unless otherwise indicated these will be collectively referred to herein as "neurological activity" which includes "psychological activity" or "psychiatric activity"). When referring to a pathological or undesirable condition associated with the activity, reference may be made to a neurological disorder which includes "psychiatric disorder" or "psychological disorder" instead of neurological activity or psychiatric or psychological activity. Although the activity to be modulated usually manifests itself in the form of a disorder such as a attention or cognitive disorders (e.g., Autistic Spectrum Disorders); mood disorder (e.g., major depressive disorder, bipolar disorder, and dysthymic disorder) or an anxiety disorder (e.g., panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder and phobic disorder); neurodegenerative diseases (e.g., multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Huntington's Disease, Guillain-Barre syndrome, myasthenia gravis, sleep disorders, and chronic idiopathic demyelinating disease (CID)), one skilled in the art appreciates that the invention may also find application in conjunction with enhancing or diminishing any neurological or psychiatric function, not just an abnormality or disorder.

[0379] In certain embodiments, the lactoferrin related peptide composition is administered to a subject suffering from multiple sclerosis, Alzheimer's disease, Parkinson's disease, muscular dystrophy, sleep or depression.

[0380] Neurological are diagnosed based upon the accumulation of physical, chemical, and historical behavioral data on each patient. One of skill in the art is able to perform the appropriate examinations to accumulate such data. One type of examination can include neurological examinations, which can include mental status evaluations, which can further include a psychiatric assessment. Other types of examinations can include, but are not limited to, motor examination, cranial nerve examination, and neuropsychological tests (e.g., Minnesota Multiphasic Personality Inventory, Beck Depression Inventory, or Hamilton Rating Scale for Depression). Thus, any improvement is based upon an improvement in any of the examinations that are used to diagnose a neurological disorder.

[0381] In addition to the above examinations, imaging techniques can be used to determine normal and abnormal brain function that can result in disorders. Functional brain imaging allows for localization of specific normal and abnormal functioning of the nervous system. This includes electrical methods such as electroencephalography (EEG), magnetoencephalography (MEG), single photon emission computed tomography (SPECT), (SPECT), as well as metabolic and blood flow studies such as functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) which can be utilized to localize brain function and dysfunction.

[0382] In order to increase the effectiveness of administration of the composition of the present invention, it is desirable to combine the compositions with an additional agent. For example, known agents that are known to be stimulatory or inhibitory are used in combination with the composition of the present invention to treat a variety of neurological conditions.

[0383] Herein, stimulating drugs comprise medications, anesthetic agents, synthetic or natural peptides or hormones, neurotransmitters, cytokines and other intracellular and intercellular chemical signals and messengers, and the like. In addition, certain neurotransmitters, hormones, and other drugs are excitatory for some tissues, yet are inhibitory to other tissues. Therefore, where, herein, a drug is referred to as an "excitatory" drug, this means that the drug is acting in an excitatory manner, although it may act in an inhibitory manner in other circumstances and/or locations. Similarly, where an "inhibitory" drug is mentioned, this drug is acting in an inhibitory manner, although in other circumstances and/or locations, it may be an "excitatory" drug.

[0384] Similarly, excitatory neurotransmitter agonists (e.g., norepinephrine, epinephrine, glutamate, acetylcholine, serotonin, dopamine), agonists thereof, and agents that act

to increase levels of an excitatory neurotransmitter(s) (e.g., edrophonium; Mestinox; trazodone; SSRIs (e.g., fluoxetine, paroxetine, sertraline, citalopram and fluvoxamine); tricyclic antidepressants (e.g., imipramine, amitriptyline, doxepin, desipramine, trimipramine and nortriptyline), monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine, isocarboxasid)), generally have an excitatory effect on neural tissue, while inhibitory neurotransmitters (e.g., dopamine, glycine, and gamma-aminobutyric acid (GABA)), agonists thereof, and agents that act to increase levels of an inhibitory neurotransmitter(s) generally have an inhibitory effect. (Dopamine acts as an excitatory neurotransmitter in some locations and circumstances, and as an inhibitory neurotransmitter in other locations and circumstances.) However, antagonists of inhibitory neurotransmitters (e.g., bicuculline) and agents that act to decrease levels of an inhibitory neurotransmitter(s) have been demonstrated to excite neural tissue, leading to increased neural activity. Similarly, excitatory neurotransmitter antagonists (e.g., prazosin, and metoprolol) and agents that decrease levels of excitatory neurotransmitters may inhibit neural activity. Yet further, lithium salts and anesthetics (e.g., lidocaine) may also be used in combination with the present invention.

[0385] In specific embodiments, antidepressants are administered in combination with the present invention to treat an affective disorder, such as depression. Such antidepressants include, but are not limited to monoamine oxidase inhibitors, 5-HT_{1A} agonists, selective 5-HT uptake inhibitors, imipramine or clomipramine.

[0386] The composition of the present invention may precede, be co-current with and/or follow the other agent(s) by intervals ranging from minutes to weeks. In embodiments where the composition of the present invention, and other agent(s) are applied separately to a cell, tissue or organism, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the composition and agent(s) would still be able to exert an advantageously combined effect on the cell, tissue or organism.

[0387] Various combination regimens of the composition and one or more agents are employed. One of skill in the art is aware that the composition of the present invention and agents can be administered in any order or combination.

L. Hematological Disorders

[0388] In accordance with the present invention, the peptide composition provided in any of the above-described pharmaceutical carriers is administered to a subject suspected of or having a hematological disorder. Such disorders can include, but are not limited to anaemia, sickle cell anemia or cachexia.

M. Ocular Disorders

[0389] In accordance with the present invention, the peptide composition provided in any of the above-described pharmaceutical carriers is administered to a subject suspected of or having an ocular disorder. Such disorders include, but are not limited to conjunctivitis, dry eye disease, glaucoma, allergic eye disease, uveitis or ocular infection.

[0390] Dry eye disease or keratoconjunctivitis sicca affects about 4 million people in the U.S. of which about 1.5 million have moderate to severe disease. Globally, 60 million people use artificial tears (Damato et al. 1984, Hikichi et al. 1995, Bjerrum et al. 1997, Schein et al. 1997). Despite the high levels of incidence, there is currently no highly effective treatment. Development of therapeutic treatments has been hampered by the lack of knowledge regarding the etiology of the condition to its complexity. However, it has now been suggested that inflammation affecting the lacrimal gland and ocular surface underlies the pathophysiological process (Pflugfelder et al. 1986, Raphael et al. 1988, Pepose et al. 1990, Kroemer et al. 1991, Jones et al. 1994, Pflugfelder et al. 1999, Turner et al. 2000). Thus, it is contemplated that the peptide composition of the present invention can be used to decrease the inflammatory response thereby treating the ocular disease or disorder.

[0391] In certain embodiments, the lactoferrin compositions are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 4 to 8. The establishment of a specific dosage regimen for each individual is left to the discretion of the clinicians. The amount of lactoferrin will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.05% to 2% and most preferably in an amount 0.1 to 1.0% by weight. The dosage form may be a solution, suspension microemulsion. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled clinician.

V. Examples

[0392] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Anti -Microbial Effects of Said Peptides

[0393] The novel peptides described in this application have shown substantial anti-microbial activity. Peptide MICs were determined by the broth microdilution method recommended by the NCCLS (M7-A5). In each medium, the concentrations of peptide were serial two-fold dilutions ranging from 8192 to 8 µg/mL. Mueller-Hinton broth and Peptone broth were used throughout, using the following media: 1) 5rCAMHB, 2) CAMHB supplemented with 3% lysed horse blood, 3) Haemophilus test medium, 4) peptone broth at pH 7, 5) peptone broth at pH 7.5, 6) peptone broth supplemented with 25 µg/mL calcium and 12.5 µg/mL magnesium, 7) peptone broth supplemented with 1.5 g/L soluble starch. On each day of testing, colony counts were performed on the broth from the growth control well immediately after inoculation from two randomly selected isolates to assure appropriate inoculum density. A total of 742 clinical bacterial isolates representing 35 species were tested.

Table 2. MIC Geomeans for Said Novel Peptides

Peptide	Sequence Position																																		MIC GeoMean			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34				
LPF-21	R	R	R	R	R	S	V	Q	W	C	A	V	S	Q	P	E	A	T	K	C	F	Q	W	Q	R	N	M	R	K	R	R	R	R					84
LPF-22	R	R	R	R	R	S	V	Q	W	C	A	V	S	Q	P	E	A	T	K	C	F	Q	W	Q	R	N	M	R	K	R	R	R	R					91
LPF-23	R	R	R	R	R	S	V	Q	W	C	A	V	S	Q	P	E	A	T	K	C	F	Q	W	Q	R	N	M	R	K	R	R	R	R	R			84	
LPF-24	R	R	R	R	R	S	V	Q	W	Q	A	V	S	Q	P	I	A	T	E	Q	F	Q	W	Q	R	N	M	R	K	R	R	R					43/61	
LPF-26	R	R	R	R	R	S	V	Q	W	A	A	V	S	Q	P	I	A	T	E	A	F	Q	W	Q	R	N	M	R	K	R	R	R					65	
LPF-31	R	R	R	R	R	S	V	Q	W	Q	A	V	S	Q	P	E	A	T	K	Q	F	Q	W	Q	R	N	M	R	K	R	R	R					41	
LPF-32	R	R	R	R	R	S	V	Q	W	Q	A	V	S	Q	P	G	A	T	K	Q	F	Q	W	Q	R	N	M	R	K	R	R	R					25	
LPF-33	R	R	R	R	R	S	V	Q	W	Q	A	V	S	Q	P	I	A	T	K	Q	F	Q	W	Q	R	N	M	R	K	R	R	R					28	
LPF-34	R	R	R	R	R	S	V	Q	W	Q	A	V	S	Q	P	Q	A	T	G	Q	F	Q	W	Q	R	N	M	R	K	R	R	R					32	
LPF-35	R	R	R	R	R	S	V	Q	W	Q	A	V	S	Q	P	I	A	T	I	Q	F	Q	W	Q	R	N	M	R	K	R	R	R					15	
LPF-36	R	R	R	R	R	S	V	Q	W	A	A	V	S	Q	P	I	A	T	K	A	F	Q	W	Q	R	N	M	R	K	R	R	R					24	

Example 2

Stimulation of Immune Response by LPF-35

[0394] Balb/c naïve mice were treated orally with LPF-35 (5 mg/kg) or placebo once a day for 3 days. One day later (day 4), mice were sacrificed and spleens & whole blood (PBMC) were collected. Spleen: NK cells were separated and counted. Cells were tested in vitro for NK-activity (Figure 1) against YAC targets using an LDH-releasing test. PBMC: cells were analyzed by FACS for the expression of the following T-cell markers: CD3/CD4, CD3/CD8, CD4/CD69 and CD8/CD69. T-cell activity is shown in Figure 2.

Example 3

LPF-35 in a Mouse Paw Edema Model of Inflammation

[0395] Using the following experimental arrangement it was determined that LPF-35 acts as a systemic anti-inflammatory agent after oral administration. Test substance LPF-35 at 5 mg/kg and reference agent Aspirin at 100 mg/kg were administered orally once daily for 5 consecutive days to groups of 8 ICR (4 male and 4 female) derived mice weighing 22 ± 2 gms. One hour after 5th dose, right hind paw was injected with carrageenan (0.05 ml of 1%

suspension intraplantar). The hind paw edema was measured 4 hours later. Convention: reduction of hind paw edema by 30 percent or more indicates significant acute anti-inflammatory activity. Each animal was fasted overnight before Carrageenan challenge.

[0396] The Table 3 below shows the average (n = 8) paw swelling volume (mL/100).

Table 3

Treatment	Route	Dose	Paw Volume (x 0.01 ml)			
			RP	LP	Diff.	% Inhibition.
Vehicle (PBS Buffer)	PO	5 ml/kg x 5	19.63	12.25	7.38	--
LPF-35	PO	5 mg/kg x 5	18.75	12.63	6.13	17
Aspirin	PO	100 mg/kg x 5	17.38	12.38	5.00	32

LPF35 vs vehicle, unpaired t test, one-tailed p = 0.0101

LPF35 vs. Aspirin, unpaired t test, one-tailed p = 0.0233

Example 4

Effect of LPF-35 in Lipopolysaccharide-induced Septic Shock in Mice

[0397] An LPS-induced model of endotoxemia was used to demonstrate that LPF-35 is effective in reducing mortality in a mouse model of sepsis. Groups of 8-10 C57BL/6J mice 18 ± 1g were used. Animals received 20 ng/mouse doses of E. coli Lipopolysaccharide (LPS) (IV) immediately after pre-treatment with D(+)-Galactosamine (20 mg/mouse IV). Animals were treated by an oral administration of LPF-35 at 1, 6 and 12 hours after challenge with LPS. Mortality was recorded every 12 hours over a 3-day period. In this model, reduction of mortality by 50 % or more relative to the vehicle-treated group indicates significant protection. In this experiment doses of LPF-35 ranging between 5-100 µg were tested.

Table 4

Treatment	Route & dose	N of animals used	% Survival
LPF-35	5 µg x 3, p.o.	8	25
LPF-35	25 µg x 3, p.o.	8	25
LPF-35	100 µg x 3, p.o.	8	50
vehicle	0 µg x 3, p.o.	8	0

Example 5

Effect of LPF-35 in a Mouse Model of Septic Shock

[0398] In a second experiment with LPF-35 in a mouse model of sepsis the highest effective dose of LPF-35 was shown to be more effective than a positive control, recombinant

human lactoferrin (rhLF). Groups of 8-16 C57BL/6J mice 18 ± 1 g were used. Animals received 20 ng/mouse doses of E. coli Lipopolysaccharide (LPS) (IV) immediately after pre-treatment with D(+)-Galactosamine (20 mg/mouse IV). Animals were treated by an oral administration of LPF-35, rhLF or vehicle control at 1, 6 and 12 hours after challenge with LPS. Mortality was recorded every 12 hours over a 3-day period. Results of Experiments with LPF-35 and rhLF in a Model of Sepsis are shown in figure 3.

Example 6

LPF-35 in a Rabbit Model of Dry Eye Disease

[0399] Experimental evidence suggests that peptide LPF-35 is effective in an animal model of dry eye disease. Rabbits were dosed in the eyes with 50 uL of isotonic saline (Vehicle n=6) or LPF-35 peptide (n=3) and the eyes were held open for 2 hr except for the Background (untreated) group (n=3). After sacrifice, the corneas were stained with methylene blue, the stain extracted with acetone and sodium sulfate and analyzed with a spectrophotometer at absorbance 660 nm (Abs 660nm) as a measure of eye damage. Results of experiments with LPF-35 in a Model of Dry Eye Disease are shown in figure 4.

Example 7

LPF-32 and LPF-35 in a Sheep Model of Allergic Asthma

[0400] Peptides LPF-32 and LPF-35 were both tested in an established sheep model of allergic asthma. In both cases these peptides demonstrated the ability to substantially inhibit late phase inflammation and airway hyperresponsiveness. Allergic sheep previously characterized as dual responders (displaying early and late phases of bronchoconstriction), were administered peptide followed by inhalation challenge with *Ascaris suum* antigen.

[0401] Baseline dose response curves to aerosolized carbachol were obtained in all sheep 1-3 days before the start of dosing. Sheep were dosed with peptide or placebo by nebulization or oral gavage in the inhaled and oral experiments respectively. The sensitized sheep were then challenged with *Ascaris suum* antigen to produce early and late airway responses, as measured by mean lung resistance (pulmonary flow resistance, RL). Mean lung resistance was measured using tracheal and pleural pressure catheters connected to a differential pressure transducer. On the challenge day measurements of RL were obtained before the antigen challenge and then repeated 30 min after rhLF treatment, after which the sheep were challenged with *Ascaris suum* antigen. Measurements of RL were obtained immediately after challenge, and hourly from 1-6 h after challenge and on the half-hour from 6 1/2-8 h after challenge. Measurements of RL were obtained 24 h after challenge followed by the 24 h post challenge dose response curve.

[0402] To assess airway responsiveness, cumulative dose response curves to carbachol were obtained, as measured by specific lung resistance, or SRL (SRL=RL * thoracic gas volume). The sheep inhaled a saline solution, then 10 consecutive breaths of increasing carbachol concentrations up to 4% wt/vol. The provocation test was discontinued when SRL increased 400% from the post saline value, or after the highest carbachol concentration had been administered. Airway hypersensitivity (AH) was determined by calculating the cumulative carbachol dose that increased SRL by 400% over the post-saline value by interpolation from the dose response curve. Actively dosed animals were compared to placebo treated animals or their own historical controls. Results of Experiments with Inhaled LPF-32/35 in a Sheep Model of Asthma are shown in figure 5. Results of Experiments with Oral LPF-35 in a Sheep Model of Asthma are shown in figure 6.

Example 8
LPF-35 in Wound Healing

[0403] Experiments have shown that LPF-35 is effective in accelerating the rate and incidence of wound healing. Groups of 7 ICR male mice were anesthetized, the shoulder and back region of each animal was shaved, and a sharp punch (ID 12 mm) was used to remove the skin including panniculus carnosus and adherent tissues. The wound area, traced onto clear plastic sheets on days 3, 5, 7, 9 and 11 or 12, was quantitated with an Image Analyzer. An LPF-35 solution and placebo (PBS) were applied topically at 0.02ml per wound immediately following injury and once daily thereafter for a total of 11 consecutive days. The unpaired Student's t test was applied for comparison between treated and vehicle group. Differences were considered statistical significant at $P < 0.05$. In addition, the incidence of animals reaching 75% wound closure was assessed and differences compared using Fisher's exact test. Differences were considered of statistical significance at $p < 0.05$ levels. Results of experiments with Oral LPF-35 in a Mouse Model of Wound Healing are shown in figure 7.

Example 9
LPF-35 in a Mouse Model of Diabetes

[0404] In this experiment LPF-35 was tested in a mouse model of diabetes. C57BL mice (n=4) were used to test serum glucose and insulin levels in treated mice versus controls. Mice were administered oral LPF-3 once daily for 3 days. Baseline glucose and insulin levels were determined and compared to levels 90 minutes after the last dose. The percentage change was recorded. LPF-35 produced significant declines in both serum glucose and insulin relative to placebo. Results of Experiments with Oral LPF-35 in a Mouse Model of Diabetes are shown in figure 8.

Example 10**LPF-35 Stimulates MIP3- α In vitro**

[0405] In this experiment it was demonstrated, in vitro, that LPF-35 stimulates the expression of MIP3- α in Hepatocytes. MIP3- α has been associated with the stimulation of innate immune responses. Using a 96-well format, we exposed tissue samples to various concentrations of placebo or test compound (LPF-35 at 0.04 and 0.2 mg/mL). Supernatant was collected (in 75 microL aliquots) from cells at 2 h and 4 h after the administration of test compounds and was tested for concentration of MIP3- α by ELISA. LPF-35 Stimulates MIP3-a In vitro as shown in figure 9.

Example 11**LPF-35 in a Phenylquinone (PQ) Writhing Model of Pain in Mice**

[0406] In this experiment, vehicle (LPF-35 diluent buffer, pH 7.0, 10 mL/kg) and LPF-35 (1000 mg/kg) are administered orally to 2 groups of 3 ICR mice weighing 22+/-2 g one hour before PQ is injected intraperitoneally at 2 mg/kg. The number of writhings observed over the subsequent 5-10 minute period is recorded. Similarly, mice are pre-treated with vehicle or LPF-35 at the same doses as above twice daily for 3 days. Two groups of 3 ICR mice weighing 22+/-2 g are used. Sixty minutes following the last dose, PQ is injected intraperitoneally at 2 mg/kg. The number of writhings is recorded over the following 5-10 minutes. Reduction in the number of writhing indicates analgesic activity. Morphine is used as a positive control.

Example 12**LPF-35 in a Paw Flinch Model of Pain in Rats**

[0407] In this experiment the formalin paw flinch rat model is used to test the potential analgesic effect and dose response of oral LPF-35. The formalin test is widely used as a peripheral inflammatory nociceptive test. Briefly, rats are given a subplantar injection of 2% formalin into the right hind paw in a volume of 50 microliters. The animals are then transferred to a Perspex observation chamber where pain behavior is quantified by counting the incidents of spontaneous flinching of the injected paw during two distinct periods of flinching activity; (0-10 min after injection) and (10-30 min after injection). Reduction in the number of paw flinches indicates analgesic activity. To define the best experimental conditions for LPF-35, several doses are tested. In addition, LPF-35 is administered orally at several time points before the nociceptive test. Morphine is used as a positive control.

Example 13**LPF-35 in a Tail Flick Model of Pain in Rats**

[0408] In this model the tail-flick test was used to assess the analgesic properties of LPF-35. Rats were restrained with a cloth restrainer. The middle dorsal surface of tail was heated

with a focused beam of radiant heat. To measure analgesic effect, the time required to elicit a flick of the tail was recorded. An increase in the time required to elicit a tail flick indicates analgesic activity. Various doses of LPF-35 were administered at different time points prior to the test. Morphine was used as a positive control. A single oral dose of LPF-35 increased the tail-flick response time to heat by 16% compared to control.

Example 14

LPF-35 in an Acetic Acid Writhing Model of Pain in Rats

[0409] Another model that was used to test the analgesic efficacy of LPF-35 was the acetic acid writhing test in rats. Rats were administered an i.p. injection of acetic acid (0.5%, 20 mL/kg). The number of writhes exhibited for each animal during the 10 minutes following administration of acetic acid was recorded. Reduction in the number of writhing indicates analgesic activity. Various doses of LPF-35 were administered at different time points prior to the test. Morphine was used as a positive control. Immediately after the test, the rats were sacrificed and ascites were collected for measurement of PGE2 contents. PGE2 is believed to be an important mediator of inflammatory nociception. A single oral dose of LPF-35 administered 60 minutes prior to the test reduced the number of writhings by 18% compared to control.

Example 15

Tolerance Development with LPF-35 versus Morphine

[0410] Chronic administration of morphine is known to result in the development of tolerance and a loss of analgesic effect in the rat. To test whether rats can become tolerant to LPF-35, use the tail-flick model of pain in rats. This test is the most widely used nociceptive assay to measure the development of opioid tolerance in the rat spinal cord. Intrathecal catheters are implanted under anesthesia. Rats are shaved and sterilized. The posterior superficial neck muscles are separated and a catheter inserted through the occipital membrane, gently advancing it caudally to the subarachnoid space. The external end of the catheter is capped until the day of the experiment. Animals showing normal motor function 5 days after surgery are used. Under light anesthesia, the test compound is injected at a volume of 5 microliters and flushed with 10 microliters saline 15 minutes before the test. Osmotic minipumps, implanted subcutaneously on the back under anesthesia, are used to continuously infuse the test compound. Various doses of LPF-35 are administered over a period of days to assess the development of tolerance. Morphine is used as a positive control.

Example 16

Enhancement of Morphine Analgesia with LPF-35

[0411] Co-administration of LPF-35 may result in a synergistic response that could allow the reduction in the dose of morphine used. To examine whether morphine and LPF-35 act

synergistically, the rat tail flick model is used to test various doses of morphine with and without LPF-35 co-administration. Briefly, rats are restrained with a cloth restrainer. The middle dorsal surface of tail is heated with a focused beam of radiant heat. To measure analgesic effect, the time required to elicit a flick of the tail is recorded. Various doses of LPF-35, with and without co-administration of a sub-effective dose of morphine, are used to test whether LPF-35 can potentiate the effects of Morphine.

Example 17

LPF-35 Effects on the μ -opioid Receptor

[0412] This experiment examines whether LPF-35's analgesic effect is mediated via the μ -opioid receptor. In this experiment the paw flinch model in rats is used to determine whether co-administration of naloxone (NLX) and D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Nh₂ (CTOP), 2 specific μ -opioid receptor antagonists, abrogate the analgesic effect of LPF-35.

Example 18

LPF-35 Effects on West Nile Virus in Hamsters

[0413] In this experiment one group of hamsters receives oral placebo (rhLF vehicle: PBS solution) and 4 additional groups receive 4 doses of oral LPF-35 (10, 50, 200 or 500 mg/kg) once per day via oral gavage. Three different regimens are tested: 3 days before virus inoculation, the same day of infection (day 0), and 3 days after infection for a total of 3 experiments. 14 days after injection of the virus, the two groups of hamsters are inoculated intraperitoneally with 10⁴ TCID₅₀ of WNV strain NY385-99. After virus inoculation (day 0), the animals are bled daily for 6–7 days to measure their level of viremia and immune response. The hamsters are observed for 20 additional days for signs of illness or death.

Example 19

LPF-35 Effects in a Mouse Model of Squamous Cell Cancer

[0414] The effect of orally administered LPF-35 on the development of O12 subcutaneous tumors are examined and compared to the effect of LPF-35 administered by an intravenous (i.v.) route. Human squamous cell carcinoma (O12) is used, employing 5 x 10⁶ cell in 200 mL injected to the right flank of athymic nude mice. Eleven days post tumor injection, when tumor volumes measure ~ 20 mm³, mice are divided in three groups (1 placebo control and two LPF-35-treated) at 8 animals per group. One group is treated with 5 mg/kg LPF-35 i.v. (50 mL injections) once a day for five days; a second group is treated with 25 mg/kg LPF-35 orally by gavage (0.2 mL per dose) twice a day for eight days; the placebo group is treated following the oral schedule. Tumors are measured twice a week for the duration of the experiment and the body weights are determined at the time of tumor measurements.

Example 20

LPF-35 Effects in an Animal Model of Obesity

[0415] LPF-35 is tested in a mouse model of obesity. Four-week-old-male mice are fed D12492i 60% kcal fat diet from Research Diets Inc. until they reach 8 weeks of age (total time on diet is 4 weeks). Control mice are fed D12450Bi 10% kcal diet from Research Diets, Inc. Mice are individually ear-notched and housed 4 per cage. All 24 mice are weighed at the start of the protocol and weekly thereafter. Serum is collected and stored at -80°C from all 24 mice at the start and the end of the feeding protocol. Diet is weighed twice daily to determine food intake. The 16 DIO mice are divided into groups of eight. Group 1 receives a placebo by oral gavage daily starting on day 15 for 15 days. Group 2 receives LPF-35 by oral gavage daily starting on day 15 for 15 days. Following the 4 week feeding protocol for each group, mice are weighed and serum is analyzed for changes relative to control.

Example 21**LPF-35 Effects in an Animal Model of Hypercholesterolemia**

[0416] The effects of LPF-35 on cholesterol are tested in a mouse model of diet-induced hypercholesterolemia. Mice ($n=5$) are fed a high cholesterol diet until serum lipid levels stabilize. Oral LPF-35 or placebo is then administered daily for 5 consecutive days. At the end of that period serum lipids are again measured and changes from baseline recorded.

Example 22**LPF-35 Effects in an in vitro Model of Osteoporosis**

[0417] The effect of LPF-35 in osteoporosis is determined by testing osteoclast motility in vitro. Osteoclasts are taken from new-born rats ($n=3-6$). The osteoclast suspension is then applied to culture dish (20 min). Unattached cells are washed away and incubated for 2 hours. At time 0, cells are viewed by inverted phase-contrast microscope. LPF-35 is administered to incubation medium at time 30 min. Every 5 min cell images are taken using time-lapse video (90 min). Change in position and spread area of osteoclasts is measured to calculate an index of osteoclast motility.

Example 23**LPF-35 Effects in Organ Transplant and Graft-versus-Host Disease**

[0418] FK506 and cyclosporine are principal treatments for organ transplant and have also been shown to inhibit GVHD. The activity of LPF-35 in combination with FK506 was compared with FK506 alone in a heart allograft survival model in rats. Wistar Furh (WF;RT1) recipients of heart allograft from Buffalo donors (BUF;RT1b) were administered oral LPF-35 (5 mg/kg) plus FK506 (0.8mg/kg), FK506 alone or placebo. The results are presented as a mean \pm standard deviation (MST \pm SD). Significance between groups was calculated using Student T-test with $p<0.05$ considered as significant. In group # 1 control WF recipients of BUF heart

allografts (n=5) were untreated and heart allografts were rejected in an acute fashion within 6.4 ± 0.5 days. In group # 2 WF recipients of BUF heart allografts (n=10) were treated daily once (days 0 to +14) with 0.8 mg/kg FK506 delivered by oral gavage. This protocol was effective in prolonging the survival of heart allografts to a MST of 22.3 ± 6.7 days ($p=0.0002$). These results suggest that FK506 alone in this therapeutic protocol is very effective in protecting allografts from rejection. In group # 3 WF recipients of BUF heart allografts (n=6) were treated daily once (days 0 to +14) with 0.8 mg/kg FK506 delivered by oral gavage in combination with LPF-35 daily for 14 days. This protocol was effective in prolonging the survival of heart allografts to a MST of 49.5 ± 28 days ($p=0.0077$). The results showed that LPF-35 was effective in improving the results produced by FK506 alone. An effect of reducing organ transplant rejection is indicative of beneficial effects in GVHD.

Example 24

LPF-35 Effects in an Rat Model of Alzheimer's

[0419] The effects of LPF-35 in Alzheimer's is tested using the Fimbria Fornix Lesion Model in rats. Axotomy of the fimbria fornix, a cholinergic pathway that goes from the septum to the hippocampus, leads to a decrease in hippocampal ChAT content, memory impairment and hippocampal reorganization (sprouting). This procedure induces a degenerative process both at the hippocampal terminals and at the septal cellular bodies. This model mimics some of the changes observed in Alzheimer's patients and thus has been proposed to be a useful test in search of a therapy that could prevent or slow down the cholinergic neuron degeneration occurring in Alzheimer's disease.

[0420] Male Sprague-Dawley rats are anesthetized with pentobarbital. Electrolytic lesion (1 mA, 40 sec) of the fimbria-fornix is then done unilaterally. Animals are left to recover for 10 days. Oral LPF-35 is administered for 10 days, first administration starting 1 hour before lesion. ChAT activity is then measured in the hippocampus. Additionally, the number of ChAT immunoreactive positive neurons is counted in the septum.

Example 25

LPF-35 Effects in a Mouse Model of Multiple Sclerosis

[0421] To test whether LPF-35 is potentially effective in Multiple Sclerosis, the experimental autoimmune encephalomyelitis model in mice is used. In this experiment it will also be investigated whether anterior uveitis (AU), which often accompanies central nervous system (CNS) and systemic inflammatory diseases including multiple sclerosis (MS), also develops in this murine relapsing model of MS.

[0422] Experimental autoimmune encephalomyelitis (EAE) closely resembling

relapsing-remitting MS, is induced in the mice by immunization with myelin basic protein (MBP). F1 female mice are immunized with MBP in Complete Freund's Adjuvant (CFA) using Pertussis toxin as co-adjuvant. LPF-35 or placebo is then administered orally for five days. Following the treatment period, EAE is scored clinically on a scale of 0-5 based on the degree of paralysis observed in the mice. Uveitis is assessed by slit-lamp biomicroscopy. Histological analysis of the CNS and eye is also performed.

Example 26

LPF-35 Effects in a Rat Model of Irritable Bowel Syndrome

[0423] The effects of LPF-35 on symptoms of Irritable Bowel Syndrome are tested using a rat model of post-inflammatory visceral hyperalgesia. Administering an inflammatory compound to the gastro-intestinal tract is known to produce symptoms similar to IBS including reduced G.I. motility and colonic compliance. After stimulating G.I inflammation, Oral LPF-35 or placebo is administered once a day for 5 days. G.I. motility and compliance is measured and compared to baseline. Afterwards, animals are sacrificed and histopathology of the gut performed.

Example 27

LPF-35 Effects in an Animal Model of Crohn's Disease

[0424] This experiment the effects of LPF-35 are tested in an immunologic mouse model of Crohn's Disease. Immunologically mediated models are defined as models of adoptively transferred T cells or bone marrow precursors, which are introduced into immunodeficient mice. TH1 polarization may play a key role in the pathogenesis of Crohn's. This model is used to induce a TH1 immune response in mice that is then assessed with and without treatment with orally administered LPF-35. T cell response are measured along with serum cytokines to determine whether LPF-35 can alter the immunologic pathogenesis associated with Crohn's disease.

Example 28

LPF-35 Effects in a Rat Model of Endometriosis

[0425] This experiment LPF-35 is tested in a rat model of endometriosis. The primary method used for induction of endometriosis in rats has been autotransplantation of uterine squares (implants) into the peritoneal cavity. Beyond mere growth of endometrium in ectopic locations, rats with endometriosis display similar symptoms, including a reduction in fertility and fecundity, and the endometriotic implants react similarly to therapeutics as those of humans with the disease. Using this technique it is determined whether the administration of oral LPF-35 has an effect on the development of lesions in the endometrium and reduces the other symptoms of endometriosis.

Example 29

LPF-35 Effects in a Mouse Model of Parkinson's disease

[0426] LPF-35 is tested in a mouse model of Parkinson's Disease by using MPTP to test for changes in Parkinson's associated neurochemicals. MPTP is known to cause an irreversible destruction of the dopaminergic nigrostriatal pathway and symptoms of parkinsonism in humans and in monkeys. When MPTP is administered to mice, a decrease in concentrations of striatal dopamine (DA) and its metabolites DOPAC and HVA and a disappearance of nerve cells in the zona compacta of the substantia nigra are observed. Thus, MPTP administration causes biochemical and histological changes in mice similar to those seen in Parkinson's disease. This model allows the determination of the potential neuroprotective properties of a test compound on dopaminergic neurons after MPTP damage.

[0427] On day 1 MPTP (15 mg/kg, s.c.) is injected into male C57/BL6 mice once daily for 7 days. Oral LPF-35 is then administered daily for 14 days. On day 28 striata are removed, homogenized in perchloric acid, and centrifuged. The supernatant is removed and stored at -80 °C. Dopamine, DOPAC, HVA, NA, 5-HT, 5-HIAA are determined by reverse-phase HPLC and electrochemical detection.

Example 30

LPF-35 Effects in an Animal Model of Periodontal Disease

[0428] To test the effects of LPF-35 in periodontal disease, P/E-selectin adhesion molecule deficient mice that mimic the human syndrome leukocyte adhesion deficiency are used. In comparison to wild type animals, P/E-/- mice exhibit a 10-fold elevation in bacterial colonization of their oral cavities and elevated gingival tissue levels of the bone resorptive cytokine IL-1 α . Mice are administered oral LPF-35 or placebo for 14 days. Subsequently, bacterial colonization of the oral cavities and extent of gingival tissue are measured and compared to control groups.

Example 31

LPF-35 Effects in a Mouse Model of Depression

[0429] This test creates a condition in which exposure to inescapable foot shocks, an uncontrolled aversive stimulus, leads to a decreased ability to escape future aversive situations. Antidepressants such as monoamine oxidase inhibitors, 5-HT_{1A} agonists, selective 5-HT uptake inhibitors, imipramine or clomipramine have been shown to restore, at least partially, the ability of animals to escape these aversive situations.

[0430] Male Wistar rats are used in the following paradigm. For Phase 1: Helplessness induction: Inescapable electric foot shocks (0.8 mA, 10 sec duration every 20 sec for 60 min) are administered. For Phase 2. Conditioned avoidance training: Avoidance training

is performed in a 2-way shuttle box on days 3, 4 and 5; 5 min habituation followed by 30 avoidance trials; At 3 seconds light signal, animal can escape to safe side of box; 0.55 mA shock is delivered if animals fail to escape; Failure - animal fails to escape during second shock. Oral LPF-35 is administered for 5 days followed by the helplessness induction test.

Example 32

LPF-35 Effects in an Animal Model of Sleep Disorder

[0431] Hexobarbital potentiation in mice (n=3) is used to determine the effects of LPF-35 on sleep time in mice. Oral LPF-35 is administered once per day for five days prior to the test. On the test day hexobarbital sodium (90 mg/kg i.p.) is administered to induce sleep. Sleep time is then recorded. Sleep time is measured in each animal as time (maximum 180 min) from loss to recovery of righting reflex.

Example 33

LPF-35 Effects in a Rat Model of Conjunctivitis

[0432] The aim of this study is to determine whether the presence of lymphocytic infiltrates observed in the histology of ocular allergic conditions in humans or in the late phase of ocular anaphylactic reactions in experimental animals is a non-specific event dependent only on the degranulation of mast cells, or is conditioned by a specific response to antigen. With this in mind, responses to antigen and to LPF-35 are compared in an experimental model of allergic conjunctivitis. Rats are sensitised to ovalbumin and challenged topically in the left conjunctival sac either with ovalbumin or LPF-35. The presence of T cells and activated T cells in the infiltrate is studied by immunohistochemical staining on conjunctival tissue obtained at 4, 24, and 48 hours after challenge. Numbers of T cells in the conjunctival infiltrate are compared with LPF-35 challenged rats at 48 hours and with controls at 4, 24, and 48 hours.

Example 34

LPF-35 Effects in a Mouse Model of *Candida Albicans*

[0433] Specific-pathogen-free inbred CBA/N female mice 8 weeks old are intraperitoneally challenged with 5×10^8 or 1×10^9 blastoconidia. From the day of the challenge, LPF-35 or saline is injected intravenously for 5 days. Survival at day ten is measured as the primary endpoint. Five mice are used in each treatment.

Example 35

LPF-35 Effects in an Animal Model of Lupus

[0434] An active chromatin-induced systemic lupus erythematosus (SLE)-like mouse model shown to be similar to idiopathic SLE in humans, is used.

[0435] Female BALB/c mice 6-week-old are immunized with 100 μ g active or resting chromatin, isolated from ConA-activated syngeneic spleno-lymphocytes, in 200 μ L Freund's complete adjuvant (containing BCG 10 g/L) on d 0 and then boosted in Freund's

incomplete adjuvant on d 14 and chromatin suspension on d 28. Mice are treated with LPF-35 peptide by oral gavage, once-a-day at a dose range from 5 to 20 mg/kg, from day 30 until the end of experiment. Mice are sacrificed on d 45 or d 60.

[0436] Plasma samples of mice are tested by enzyme-linked immunosorbent assays (ELISA) for the presence of IgG anti-dsDNA, -ssDNA, and anti-histone antibodies. Sera are tested by ELISA for tumor necrosis factor- α (TNF- α). Spleno-lymphocyte proliferation assays is carried out and the levels of interferon- γ (IFN- γ) in supernatants are measured. Proteinuria is measured. Kidneys are examined by direct immunohistochemical method and light microscopy.

[0437] It is shown that the peptide attenuates the indicators of active chromatin-induced SLE-like disease in this mouse model of idiopathic human SLE.

Example 36

LPF-35 Effects in an Animal Model of Rheumatoid Arthritis

[0438] A rat model of arthritis is used in which paw swelling is induced by injecting Complete Freund's Adjuvant (CFA) (0.3 mg of killed *M. tuberculosis* in 0.1 mL of light mineral oil). The paw swelling is measured on days 1 and 5 (acute phase) and also on days 14 and 18 (delayed phase). Additionally, changes in animal weight are also recorded over the 18 days of the experiment.

[0439] Typically, groups of 5 rats are used per each dosing condition. LPF-35 peptide is administered orally once-a-day for 5 consecutive days beginning 1 h before CFA administration.

[0440] Administration of the peptide is expected to reduce the hind paw swelling compared to a vehicle-treated control animals.

Example 37

LPF-35 Effects in an Animal Model of Osteo Arthritis

[0441] The effects of peptides are examined using articular cartilage slices treated with hyaluronan hexasaccharides (HA6). Full-thickness slices of the human articular cartilage (~10×10×1 mm) are cultured directly in 1.0 mL of medium containing 10% FBS. Following 2 days of culture for recovery, the tissue slices are treated in the presence of HA6 (250 μ g/mL) with or without the peptide (LPF-35) in the presence of 5% of fetal bovine serum (FBS). The concentration of LPF-35 peptide is in the range from 0.1 mg/mL to 1.0 mg/mL. The culture medium containing HA6 with or without LPF-35 is changed every 4 days. Following 14 days of incubation the slices are removed and embedded in O.C.T. embedding compound (Tissue-TekR, Electron Microscopy Sciences, Washington, PA). Cryostat sections (8.0 μ m) are prepared and stained for Safranin-O and HA. Cartilage proteoglycan biosynthesis is examined by a (35)S-

sulfate incorporation assay. Cartilage slices are also examined for accumulation of proteoglycan by Safranin-O, and hyaluronan by a specific biotinylated probe.

[0442] It is shown that treatment with the peptide results in an increased synthesis of cartilage proteoglycan especially retained in the cell-associated matrix. Co-treatment with the peptide inhibits the HA6-induced depletion of cell-associated matrices as well as HA6-induced depletion of hyaluronan and proteoglycan within cartilage tissue slices.

[0443] These results demonstrate that treatment with the peptide can abrogate the catabolic events associated with a HA6-induced matrix depletion model of osteoarthritis.

Example 38

Protective Role of Lactoferrin derived Peptides in a Mouse Model of Colitis

[0444] A WT strain of *C. rodentium* is used. Before infection, *C. rodentium* are grown in Luria broth overnight, washed, and re-suspended in PBS. Bacteria concentration is determined by OD and confirmed by serial dilution and culture. WT and iNOS^{-/-} C57BL/6 eight-week-old mice are gavaged with *C. rodentium* in 100 μ l of PBS or PBS vehicle alone, at the inoculum concentration of 5×10^8 bacteria/mouse to produce consistent induction of colitis. Mice are treated with peptides starting day 1 postinfection, at pH 7 in the drinking water. Daily weights are obtained for each mouse. Water consumption is measured to determine the peptide intake for individual animals. Mice are sacrificed after 14 days or when moribund. Blood samples are obtained by intracardiac puncture, and colons are collected, weighed, and divided. Tissues fixed in 10% buffered formalin are used for histology.

[0445] Sections (6 μ m) are cut from paraffin sections and stained with H&E. Tissues are examined in a blinded manner by a pathologist (C.B.D.). Acute (neutrophilic) and chronic (lymphocytic) inflammation, and epithelial regenerative changes are each scored on a 0–4 scale, and the sum is used as an index of histologic injury.

[0446] Serum is deproteinized with an equal volume of 6% 5-sulfosalicylic acid. Concentrations of total reactive nitrogen metabolites are determined in the serum, by HPLC analysis and chemiluminescence with an NO analyzer.

[0447] Histology and serum analysis suggest a protective effect of peptides in this model of colitis.

REFERENCES CITED

[0448] All patents and publications mentioned in the specifications are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

U.S. Patent No. 5,571,691

U.S. Patent No. 5,571,697

U.S. Patent No. 5,571,896

U.S. Patent No. 5,629,001

U.S. Patent No. 6,080,559

U.S. Patent No. 5,919,913

U.S. Patent No. 6,228,614

U.S. Patent No. 6,455,687

U.S. Patent No. 6,277,817

U.S. Patent No. 6,066,469

U.S. Patent No. 6,100,054

U.S. Patent No. 6,333,311

[0449] Although the present invention and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the invention as defined by the appended claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, machine, manufacture, composition of matter, means, methods and steps described in the specification. As one will readily appreciate from the disclosure, processes, machines, manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized. Accordingly, the appended claims are intended to include within their scope such processes, machines, manufacture, compositions of matter, means, methods, or steps.

CLAIMS

[0450] What is claimed is:

1. A pharmaceutical composition that induces modulation of the immune system whereby the composition stimulates production of MIP-3alpha from hepatocytes.
2. The pharmaceutical composition of claim 1, wherein said composition inhibits bacterial growth as measured by minimum inhibitory concentration (MIC).
3. The pharmaceutical composition of claim 1, wherein said composition comprises at least four consecutive positively charged residues at the N-terminus.
4. The pharmaceutical composition of claim 1, wherein said composition comprises at least four positively charged residues at the C-terminus.
5. The pharmaceutical composition of claim 1, wherein said composition comprises at least four positively charged residues at each of the N- and C-termini.
6. The pharmaceutical composition of claim 1, wherein said composition comprises at least 25% positively charged residues.
7. The pharmaceutical composition of claim 1, wherein said composition comprises at least 33% positively charged residues.
8. The pharmaceutical composition of claim 6, wherein the positively charged residues are arginine, lysine or derivatives thereof.
9. The pharmaceutical composition of claim 7, wherein the positively charged residues are arginine, lysine or derivatives thereof.
10. The pharmaceutical composition of claim 1, further comprising a metal chelator.
11. The pharmaceutical composition of claim 10, wherein the metal chelator is selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), [ethylenebis(oxyethylenenitrilo)] tetraacetic acid (EGTA), 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA), and hydroxyethylene triamine diacetic acid (HEDTA).
12. The pharmaceutical composition of claim 1, wherein said composition comprises an amino acid sequence of SEQ.ID.NO.1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5,

SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, or SEQ.ID.NO.11.

13. An isolated polypeptide having an amino acid sequence as defined in SEQ.ID.NO. 1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, or SEQ.ID.NO.11.
14. The isolated polypeptide of claim 13, wherein said polypeptide is admixed with a pharmaceutically acceptable carrier.
15. An expression vector comprising a nucleic acid sequence encoding an amino acid sequence of SEQ.ID.NO. 1, SEQ.ID.NO.2, SEQ.ID.NO.3, SEQ.ID.NO.4, SEQ.ID.NO.5, SEQ.ID.NO.6, SEQ.ID.NO.7, SEQ.ID.NO.8, SEQ.ID.NO.9, SEQ.ID.NO.10, or SEQ.ID.NO.11.
16. The expression vector of claim 15, wherein the expression vector is further defined as a viral or plasmid vector.
17. The expression vector of claim 16, wherein the viral vector is an adenoviral vector, an adeno-associated viral vector, a retroviral vector, a lentiviral vector, a herpes viral vector, polyoma viral vector, pox vector, or hepatitis B viral vector.
18. A method of treating a pathological condition comprising the step of administering the pharmaceutical composition defined according to claim 1.
19. A method of treating a pathological condition comprising the step of administering the polypeptide defined according to claim 13.
20. A method of treating a pathological condition comprising the step of administering the expression vector defined according to claim 15.
21. The method of claim 18, wherein said polypeptide is in combination with a standard therapy to treat the pathological condition.
22. The method of claim 18, wherein the pathological condition is selected from the group consisting of hyperproliferative disease, respiratory disorder, cardiovascular disease, neurological condition, autoimmune disorder, infectious disease, gastrointestinal disorder,

endocrine and/or metabolism disorder, hematological disorder, ocular disorder, integument disorder, pain, a wound, and a combination thereof.

23. The method of claim 22, wherein hyperproliferative disease is further defined as cancer.
24. The method of claim 23, wherein the cancer is melanoma, non-small cell lung cancer, small-cell lung cancer, lung cancer, leukemia, hepatocarcinoma, retinoblastoma, astrocytoma, glioblastoma, gum cancer, tongue cancer, neuroblastoma, head cancer, neck cancer, breast cancer, pancreatic cancer, prostate cancer, renal cancer, bone cancer, testicular cancer, ovarian cancer, mesothelioma, cervical cancer, gastrointestinal cancer, lymphoma, myeloma, brain cancer, colon cancer, sarcoma or bladder cancer.
25. The method of claim 24 further comprising administering a second anti-cancer agent selected from the group consisting of chemotherapy, surgery, radiotherapy, an immunostimulant, anti-cancer biologic agent or a cancer vaccine
26. The method of claim 23, wherein hyperproliferative disease is rheumatoid arthritis, infectious arthritis, inflammatory bowel disease, osteoarthritis, leiomyomas, adenomas, lipomas, hemangiomas, fibromas, vascular occlusion, restenosis, atherosclerosis, pre-neoplastic lesions, carcinoma in situ, oral hairy leukoplakia, or psoriasis.
27. The method of claim 22, wherein the neurological condition is multiple sclerosis, Alzheimer's disease, Parkinson's disease, muscular dystrophy, sleep or depression.
28. The method of claim 22, wherein the gastrointestinal disorder is Crohn's disease, colitis, necrotizing enterocolitis, endometriosis, irritable bowel syndrome, pancreatitis, periodontal disease, or ulcerative colitis.
29. The method of claim 22, wherein the autoimmune disorder is graft versus host disease (GVHD), organ transplant rejection, autoimmune hepatitis, primary biliary cirrhosis, autoimmune cholangitis, primary sclerosing cholangitis, irritable bowel syndrome (IBS), multiple sclerosis (MS), chronic granulomatous disease, ankylosing spondylitis, scleroderma, polymyositis, (dermato)myositis, systemic vasculitis, systemic lupus erythematosus (SLE), Crohn's disease, insulin-dependent diabetes (type 1) or ulcerative colitis.

30. The method of claim 22, wherein endocrine and/or metabolism disorder is diabetes mellitus, thyroid disorder, or osteoporosis.
31. The method of claim 22, wherein the hematological disorder is anaemia, sickle cell anemia or cachexia.
32. The method of claim 22, wherein the infectious disease is caused by a virus, bacterium or a fungus.
33. The method of claim 32, wherein the virus is herpes simplex, labilis zoster, HIV, hepatitis A, hepatitis, B, or hepatitis C.
34. The method of claim 32, wherein the infectious disease is HIV, hepatitis, West Nile Virus bacterial meningitis, paramenigeal infections, septic thrombophlebitis, candidiasis, myocarditis, bacteremia, sepsis, or septic shock.
35. The method of claim 22, wherein the ocular disorder is conjunctivitis, dry eye disease, glaucoma, allergic eye disease, uveitis or ocular infection.
36. The method of claim 22, wherein the cardiovascular disease is congestive heart failure, hypertension, cardiomyopathy, myocarditis, atherosclerosis, chronic venous disease, or heart arrhythmia.
37. The method of claim 18, wherein the pathological condition is elevated cholesterol or dyslipidemia.
38. The method of claim 22, wherein the wound is a skin wound, internal wound, gastrointestinal wound, oral wound, ophthalmic wound, surgical wound or a fracture.
39. The method of claim 22, wherein the respiratory disorder is atopic asthma, non-atopic asthma, emphysema, bronchitis, chronic obstructive pulmonary disease, sinusitis, allergic rhinitis, fibrotic lung disease, ARDS, pulmonary vascular disease/pulmonary hypertension, Cor Pulmonale, or cystic fibrosis.
40. The method of claim 22, wherein the composition stimulates the production of IL-18.
41. The method of claim 22, wherein the composition stimulates the production of IL-12, GM-CSF, or IFN- γ .

42. The method of claim 22, wherein the composition stimulates or supplements immune cells.
43. The method of claim 42, wherein the immune cells are T lymphocytes, B-lymphocytes, dendritic cells (DCs), other antigen presenting cells (APCs), natural killer (NK) cells, macrophages or monocytes.
44. The method of claim 43, wherein the T lymphocytes are of CD4+, CD8+, CD3+ or CD40+ cells
45. The method of claim 43, wherein the B-lymphocytes are CD40+ cells.
46. The method of claim 22, wherein the composition is administered orally, inhalation, nasally, topically or parenterally.
47. The method of claim 46, wherein parenterally is subcutaneously, intramuscularly, intraperitoneally, intravenously, intraarterially, intramyocardially, transendocardially, transepically, intrathecally or intra-tumorally.

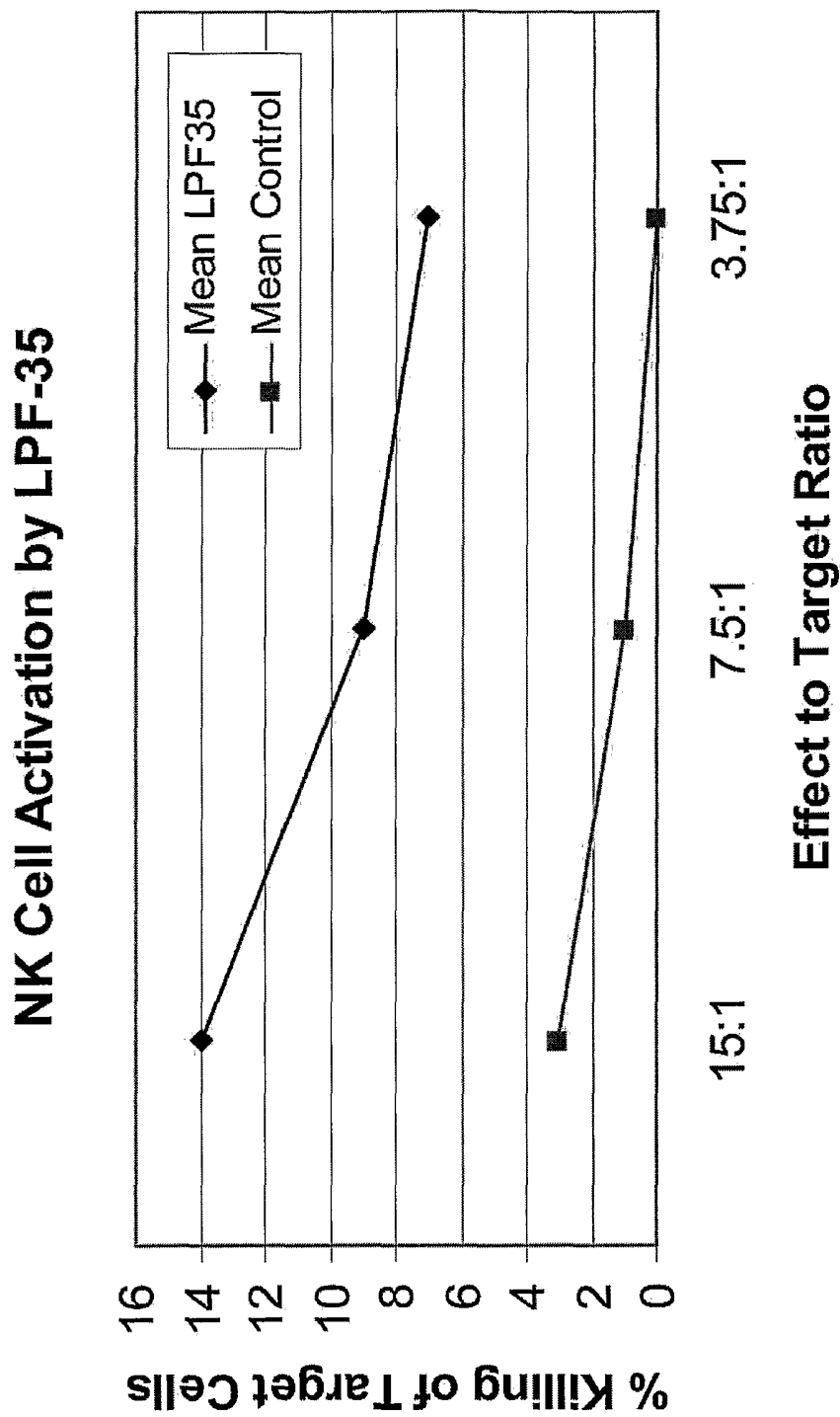


FIG. 1

LPF-35 stimulates the levels of T cells in circulation

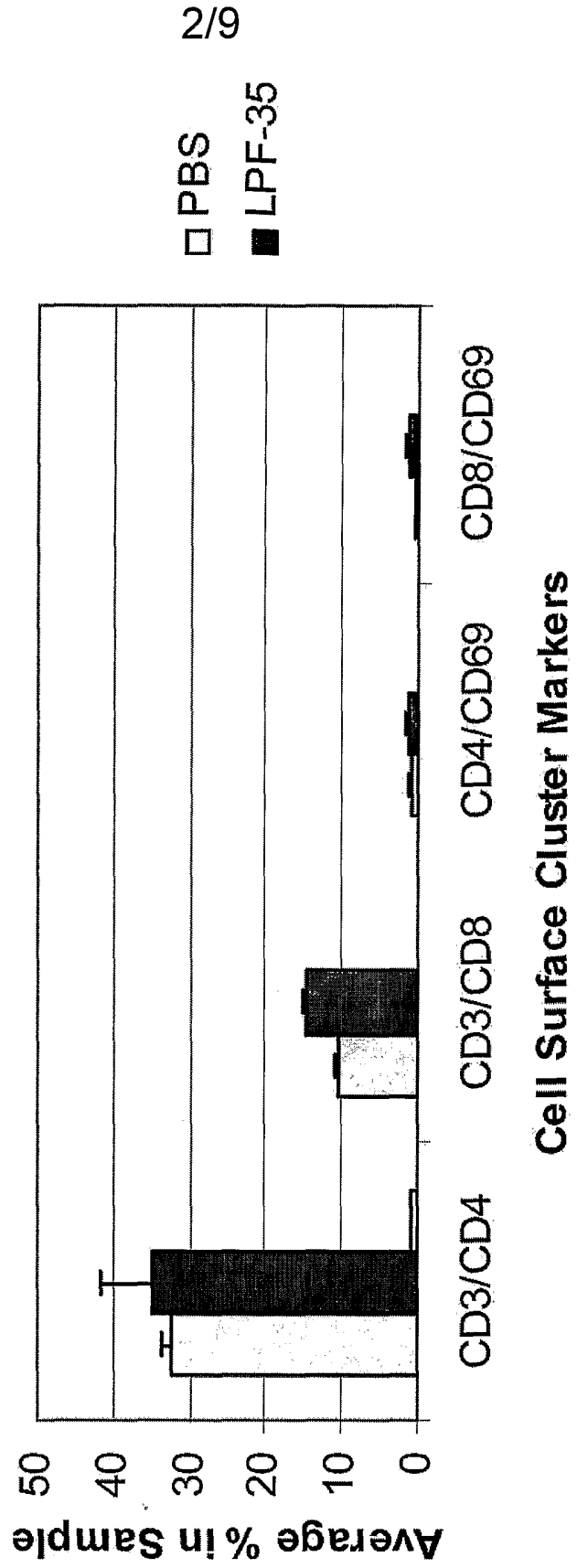


FIG. 2

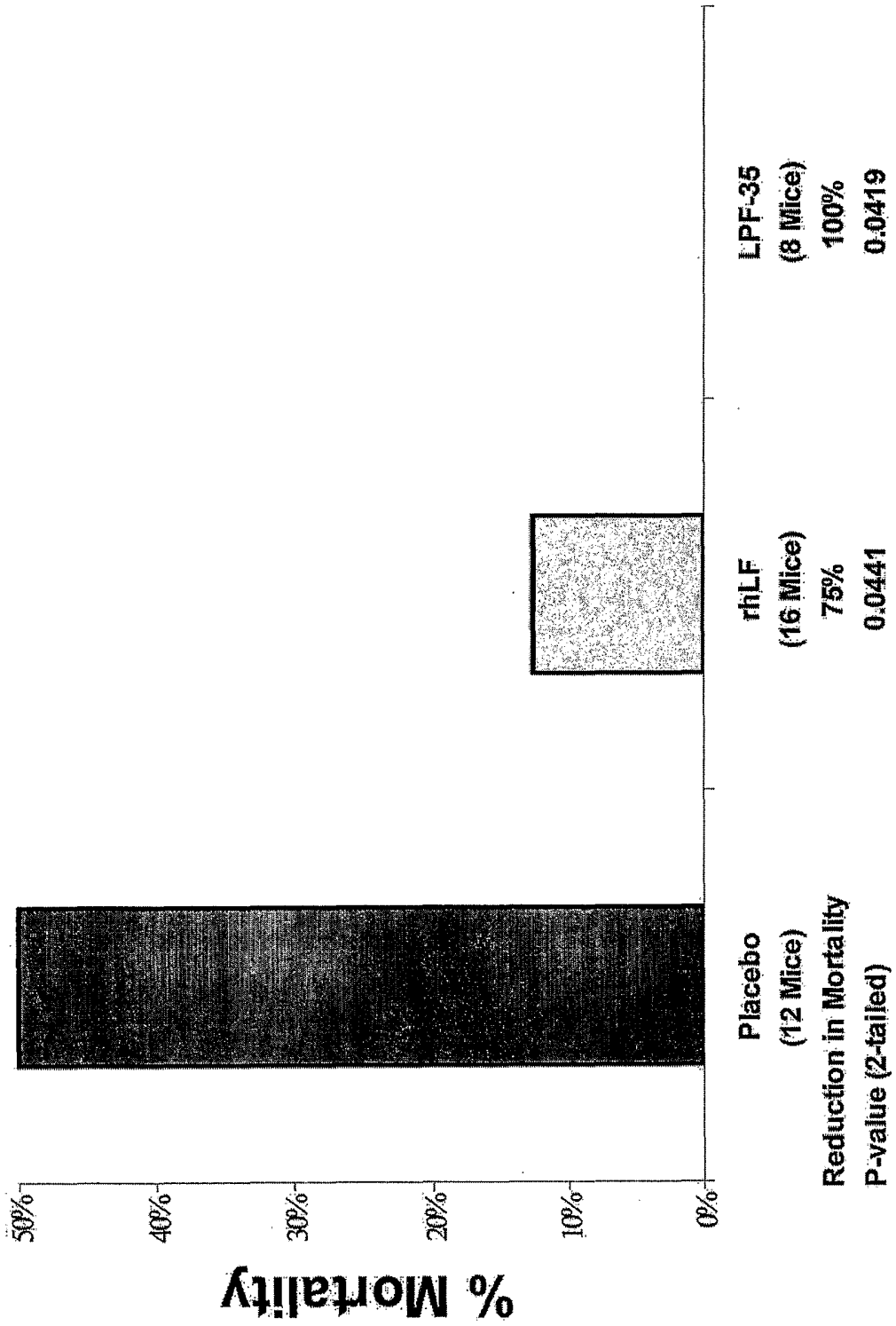


FIG. 3

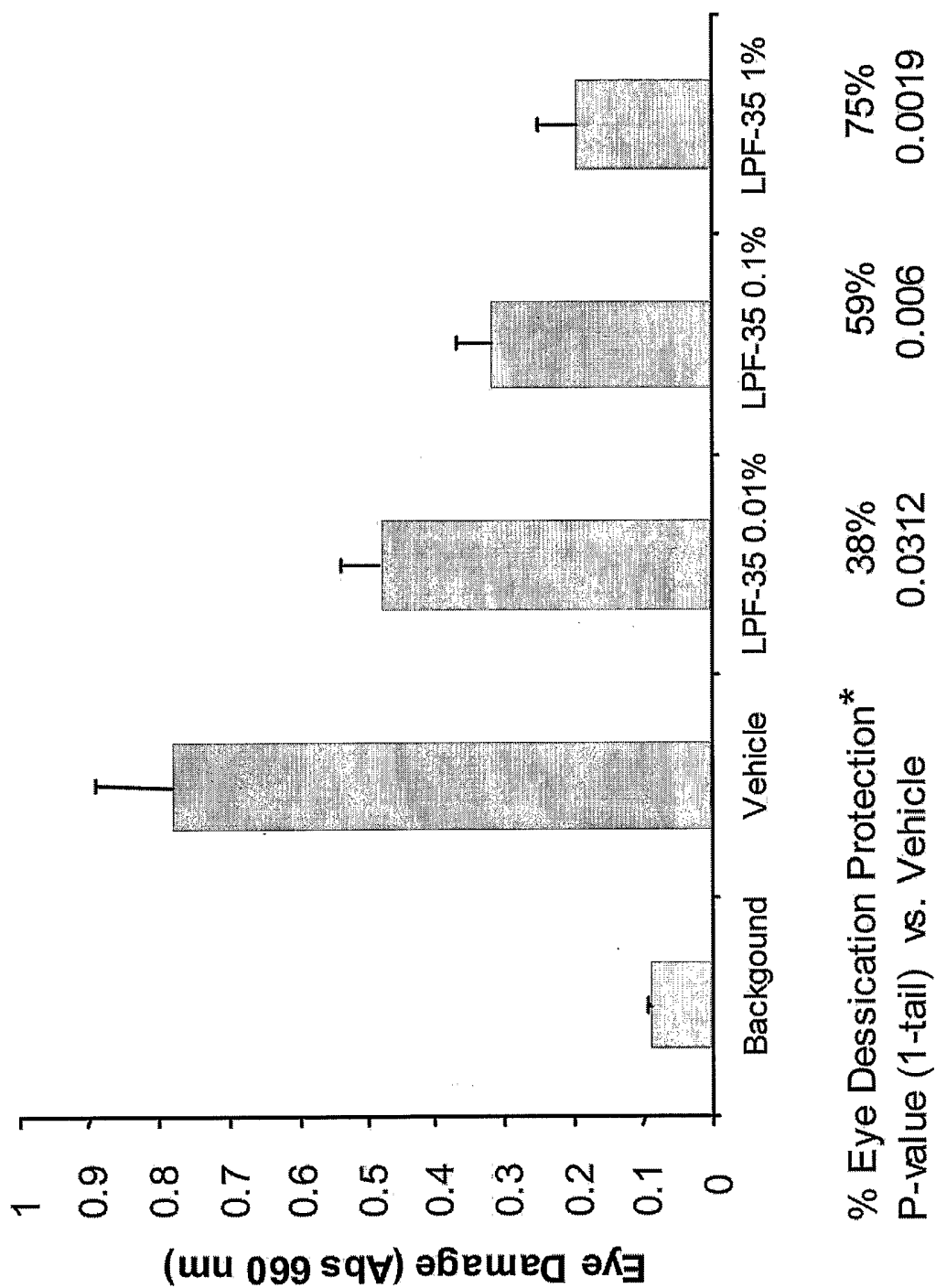


FIG. 4

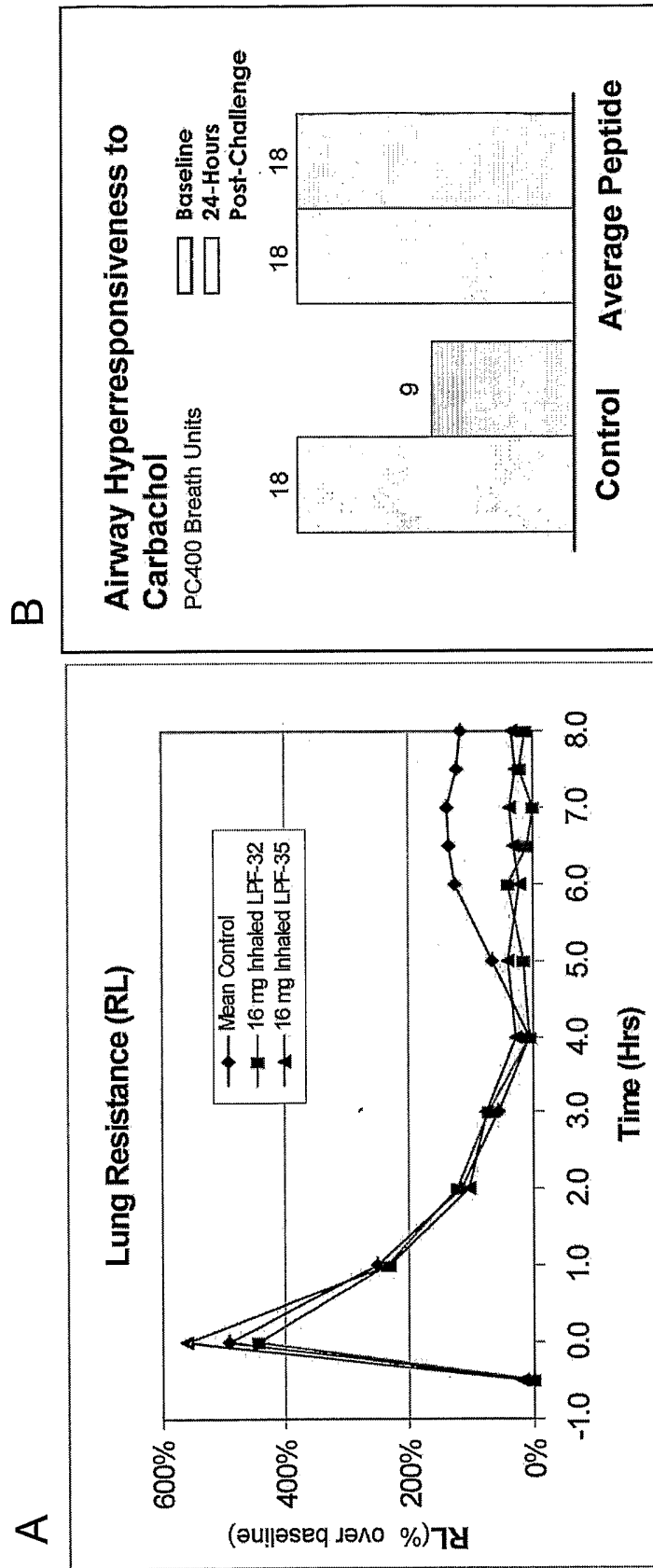


FIG. 5

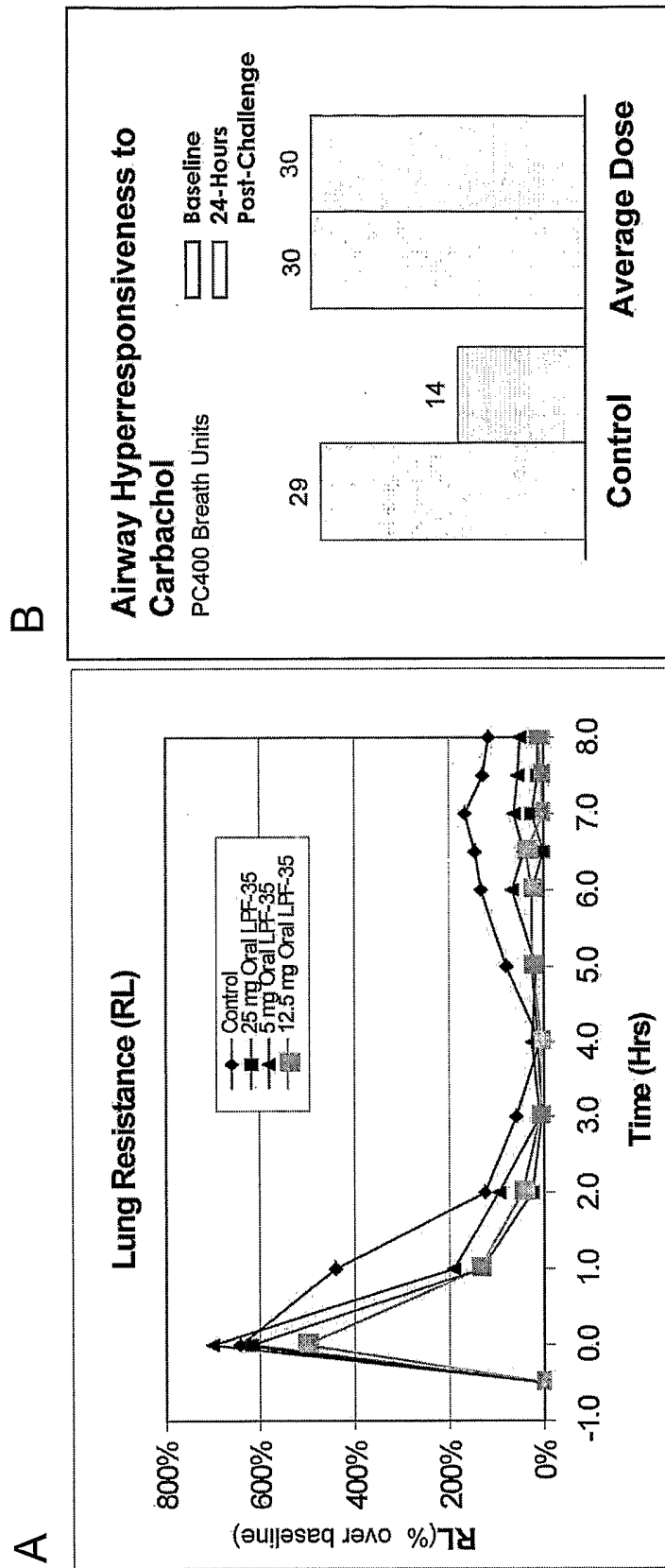


FIG. 6

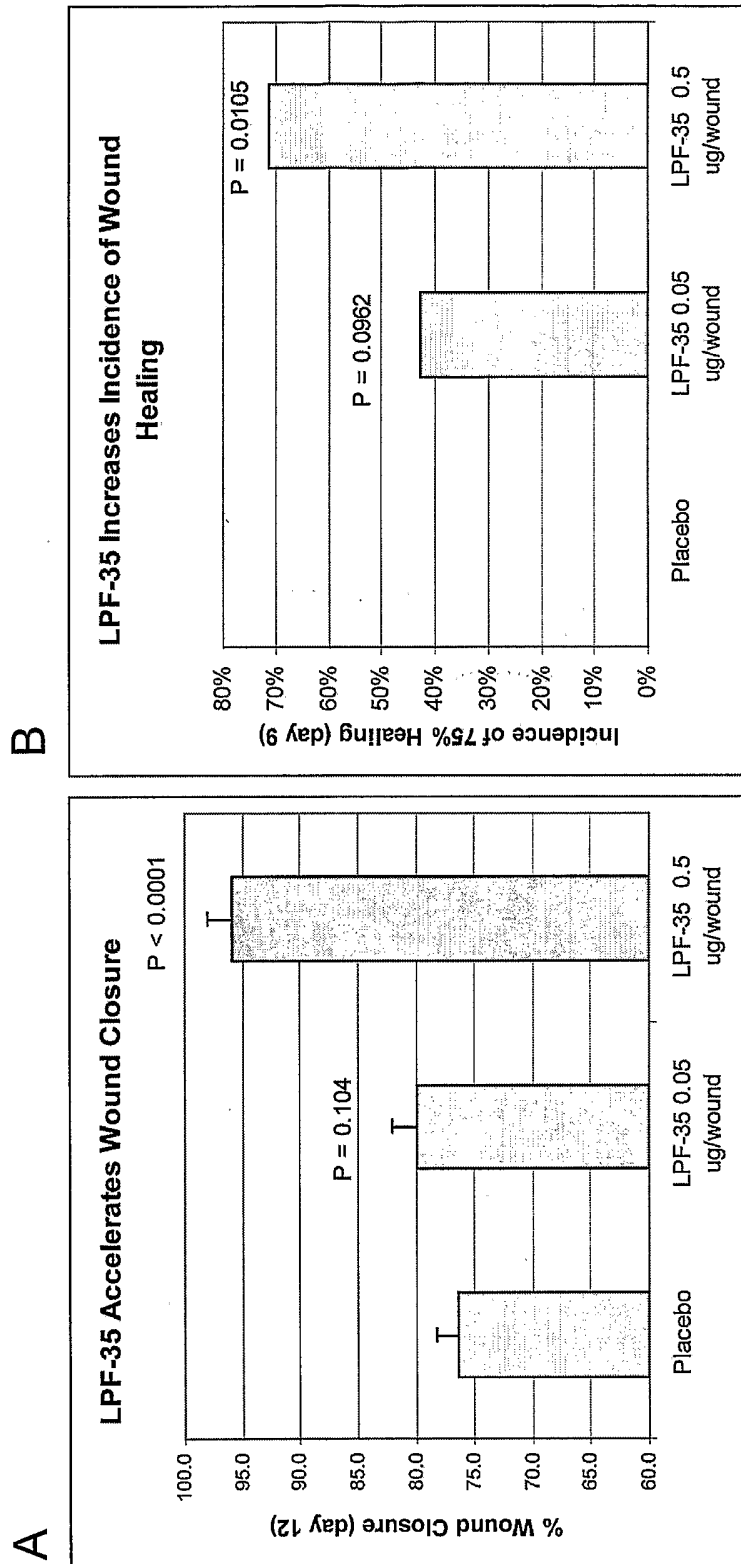


FIG. 7

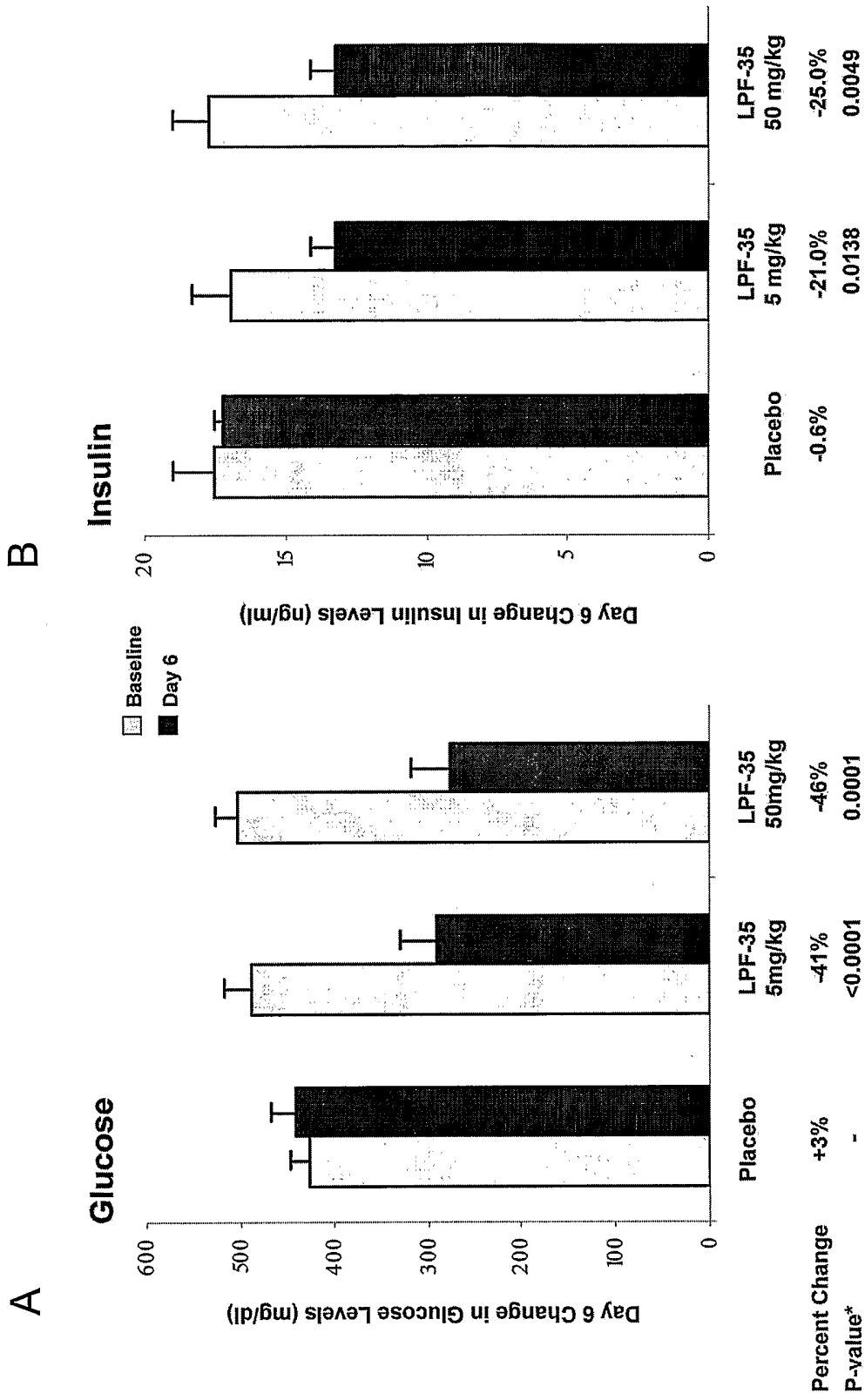


FIG. 8

Sample	0.2 mg/ml		2.0 mg/ml	
	2 hours	4 hours	2 hours	4 hours
Medium	0.1556	0.7686	-	-
LPF-21	4.53	3.08	5.92	4.73
LPF-22	4.47	9.2	3.95	8.39
LPF-23	6.48	5.42	4.54	-
LPF-24	5.01	8.71	3.6	7.63
LPF-25	4.22	7.13	4.25	-
LPF-32	5.5	8.22	5.57	7.71
LPF-33	4.11	8.33	0.82	7.47
LPF-34	0.02	-	3.94	-
LPF-35	7.95	9.57	1.86	2.17
LPF-36	5	9.79	4.1	9.03

FIG. 9

SEQUENCE LISTING

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 Glynn, Peter
 Petrak, Karel
 Engelmayer, Jose

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<400> 7

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

Gly Ala Thr Lys Gln Phe Gln Trp Gln Arg Asn Met Arg Lys Arg Arg
 20 25 30

Arg

<210> 8
 <211> 33
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Peptide

<400> 8

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

Ile Ala Thr Lys Gln Phe Gln Trp Gln Arg Asn Met Arg Lys Arg Arg
 20 25 30

Arg

<210> 9
 <211> 33
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Peptide

<400> 9

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

Gln Ala Thr Gly Gln Phe Gln Trp Gln Arg Asn Met Arg Lys Arg Arg
 20 25 30

Arg

<210> 10
 <211> 33
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic Peptide

<400> 10

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

Ile Ala Thr Ile Gln Phe Gln Trp Gln Arg Asn Met Arg Lys Arg Arg
 20 25 30

Arg

<210> 11
 <211> 33
 <212> PRT
 <213> Artificial Sequence

<220>

<223> Synthetic Peptide

<400> 11

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

Ile Ala Thr Lys Ala Phe Gln Trp Gln Arg Asn Met Arg Lys Arg Arg
 20 25 30

Arg

<210> 12

<211> 711

<212> PRT

<213> HUMAN

<400> 12

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

Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Thr Val Ser
 20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Arg
 35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60

Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
 65 70 75 80

Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
 85 90 95

Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
 100 105 110

Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
 115 120 125

Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
 130 135 140

Trp Asn Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
 145 150 155 160

Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
 165 170 175

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

Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
 195 200 205
 Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
 210 215 220
 Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
 225 230 235 240
 Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
 245 250 255
 Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
 260 265 270
 His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
 275 280 285
 Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
 290 295 300
 Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
 305 310 315 320
 Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
 325 330 335
 Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
 340 345 350
 Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
 355 360 365
 Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
 370 375 380
 Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
 385 390 395 400
 Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
 405 410 415
 Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala
 420 425 430
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
 435 440 445
 Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
 450 455 460
 Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
 465 470 475 480
 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
 485 490 495

Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
 500 505 510

Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
 515 520 525

Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
 530 535 540

Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
 545 550 555 560

Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 565 570 575

Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
 580 585 590

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

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
 610 615 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
 625 630 635 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
 645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
 660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 13
 <211> 681
 <212> PRT
 <213> COW

<400> 13

Cys Thr Ile Ser Gln Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp
 1 5 10 15

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

Phe Ala Leu Glu Cys Ile Arg Ala Ile Ala Glu Lys Lys Ala Asp Ala

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

340 345 350
 Trp Ser Gln Gln Ser Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr
 355 360 365
 Thr Asp Asp Cys Ile Val Leu Val Leu Lys Gly Glu Ala Asp Ala Leu
 370 375 380
 Asn Leu Asp Gly Gly Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val
 385 390 395 400
 Pro Val Leu Ala Glu Asn Arg Lys Ser Ser Lys His Ser Ser Leu Asp
 405 410 415
 Cys Val Leu Arg Pro Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys
 420 425 430
 Lys Ala Asn Glu Gly Leu Thr Trp Asn Ser Leu Lys Asp Lys Lys Ser
 435 440 445
 Cys His Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly
 450 455 460
 Leu Ile Val Asn Gln Thr Gly Ser Cys Ala Phe Asp Glu Phe Phe Ser
 465 470 475 480
 Gln Ser Cys Ala Pro Gly Ala Asp Pro Lys Ser Arg Leu Cys Ala Leu
 485 490 495
 Cys Ala Gly Asp Asp Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys
 500 505 510
 Glu Lys Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp
 515 520 525
 Val Gly Asp Val Ala Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr
 530 535 540
 Asn Gly Glu Ser Thr Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp
 545 550 555 560
 Phe Arg Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala
 565 570 575
 Gln Ser Cys His Leu Ala Val Ala Pro Asn His Ala Val Val Ser Arg
 580 585 590
 Ser Asp Arg Ala Ala His Val Lys Gln Val Leu Leu His Gln Gln Ala
 595 600 605
 Leu Phe Gly Lys Asn Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe
 610 615 620
 Lys Ser Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu
 625 630 635 640
 Ala Lys Leu Gly Gly Arg Pro Thr Tyr Glu Glu Tyr Leu Gly Thr Glu

645 650 655

Tyr Val Thr Ala Ile Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu
 660 665 670

Leu Glu Ala Cys Ala Phe Leu Thr Arg
 675 680

<210> 14
 <211> 707
 <212> PRT
 <213> MOUSE

<400> 14

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

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

Glu Glu Glu Lys Cys Leu Arg Trp Gln Asn Glu Met Arg Lys Val Gly
 35 40 45

Gly Pro Pro Leu Ser Cys Val Lys Lys Ser Ser Thr Arg Gln Cys Ile
 50 55 60

Gln Ala Ile Val Thr Asn Arg Ala Asp Ala Met Thr Leu Asp Gly Gly
 65 70 75 80

Thr Met Phe Asp Ala Gly Lys Pro Pro Tyr Lys Leu Arg Pro Val Ala
 85 90 95

Ala Glu Val Tyr Gly Thr Lys Glu Gln Pro Arg Thr His Tyr Tyr Ala
 100 105 110

Val Ala Val Val Lys Asn Ser Ser Asn Phe His Leu Asn Gln Leu Gln
 115 120 125

Gly Leu Arg Ser Cys His Thr Gly Ile Gly Arg Ser Ala Gly Trp Lys
 130 135 140

Ile Pro Ile Gly Thr Leu Arg Pro Tyr Leu Asn Trp Asn Gly Pro Pro
 145 150 155 160

Ala Ser Leu Glu Glu Ala Val Ser Lys Phe Phe Ser Lys Ser Cys Val
 165 170 175

Pro Gly Ala Gln Lys Asp Arg Phe Pro Asn Leu Cys Ser Ser Cys Ala
 180 185 190

Gly Thr Gly Ala Asn Lys Cys Ala Ser Ser Pro Glu Glu Pro Tyr Ser
 195 200 205

Gly Tyr Ala Gly Ala Leu Arg Cys Leu Arg Asp Asn Ala Gly Asp Val
 210 215 220

Ala Phe Thr Arg Gly Ser Thr Val Phe Glu Glu Leu Pro Asn Lys Ala
 225 230 235 240
 Glu Arg Asp Gln Tyr Lys Leu Leu Cys Pro Asp Asn Thr Trp Lys Pro
 245 250 255
 Val Thr Glu Tyr Lys Glu Cys His Leu Ala Gln Val Pro Ser His Ala
 260 265 270
 Val Val Ser Arg Ser Thr Asn Asp Lys Glu Glu Ala Ile Trp Glu Leu
 275 280 285
 Leu Arg Gln Ser Gln Glu Lys Phe Gly Lys Lys Gln Ala Ser Gly Phe
 290 295 300
 Gln Leu Phe Ala Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe Lys Glu
 305 310 315 320
 Ser Ala Ile Gly Phe Val Arg Val Pro Gln Lys Val Asp Val Gly Leu
 325 330 335
 Tyr Leu Thr Phe Ser Tyr Thr Thr Ser Ile Gln Asn Leu Asn Lys Lys
 340 345 350
 Gln Gln Asp Val Ile Ala Ser Lys Ala Arg Val Thr Trp Cys Ala Val
 355 360 365
 Gly Ser Glu Glu Lys Arg Lys Cys Asp Gln Trp Asn Arg Ala Ser Arg
 370 375 380
 Gly Arg Val Thr Cys Ile Ser Phe Pro Thr Thr Glu Asp Cys Ile Val
 385 390 395 400
 Ala Ile Met Lys Gly Asp Ala Asp Ala Met Ser Leu Asp Gly Gly Tyr
 405 410 415
 Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn
 420 425 430
 Gln Lys Ser Ser Lys Ser Asn Gly Leu Asp Cys Val Asn Arg Pro Val
 435 440 445
 Glu Gly Tyr Leu Ala Val Ala Ala Val Arg Arg Glu Asp Ala Gly Phe
 450 455 460
 Thr Trp Ser Ser Leu Arg Gly Lys Lys Ser Cys His Thr Ala Val Asp
 465 470 475 480
 Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu Ala Asn Gln Thr
 485 490 495
 Arg Ser Cys Lys Phe Asn Glu Phe Phe Ser Gln Ser Cys Ala Pro Gly
 500 505 510
 Ala Asp Pro Lys Ser Asn Leu Cys Ala Leu Cys Ile Gly Asp Glu Lys
 515 520 525

Gly Glu Asn Lys Cys Ala Pro Asn Ser Lys Glu Arg Tyr Gln Gly Tyr
 530 535 540

Thr Gly Ala Leu Arg Cys Leu Ala Glu Lys Ala Gly Asn Val Ala Phe
 545 550 555 560

Leu Lys Asp Ser Thr Val Leu Gln Asn Thr Asp Gly Lys Asn Thr Glu
 565 570 575

Glu Trp Ala Arg Asn Leu Lys Leu Lys Asp Phe Glu Leu Leu Cys Leu
 580 585 590

Asp Asp Thr Arg Lys Pro Val Thr Glu Ala Lys Asn Cys His Leu Ala
 595 600 605

Ile Ala Pro Asn His Ala Val Val Ser Arg Thr Asp Lys Val Glu Val
 610 615 620

Leu Gln Gln Val Leu Leu Asp Gln Gln Val Gln Phe Gly Arg Asn Gly
 625 630 635 640

Gln Arg Cys Pro Gly Glu Phe Cys Leu Phe Gln Ser Lys Thr Lys Asn
 645 650 655

Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Ile Pro Gly Lys
 660 665 670

Thr Thr Ser Glu Lys Tyr Leu Gly Lys Glu Tyr Val Ile Ala Thr Glu
 675 680 685

Arg Leu Lys Gln Cys Ser Ser Ser Pro Leu Leu Glu Ala Cys Ala Phe
 690 695 700

Leu Thr Gln
 705

<210> 15
 <211> 711
 <212> PRT
 <213> HUMAN

<400> 15

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

Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Ala Val Ser
 20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys
 35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60

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

Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
370 375 380

Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
385 390 395 400

Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
405 410 415

Gly Tyr Val Tyr Thr Ala Cys Lys Cys Gly Leu Val Pro Val Leu Ala
420 425 430

Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
435 440 445

Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
450 455 460

Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
465 470 475 480

Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
485 490 495

Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
500 505 510

Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
515 520 525

Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
530 535 540

Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
545 550 555 560

Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
565 570 575

Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
580 585 590

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

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
610 615 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
625 630 635 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 16
 <211> 708
 <212> PRT
 <213> COW

<400> 16

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

Cys Leu Ala Ala Pro Arg Lys Asn Val Arg Trp Cys Thr Ile Ser Gln
 20 25 30

Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu
 35 40 45

Gly Ala Pro Ser Ile Thr Cys Val Arg Arg Ala Phe Ala Leu Glu Cys
 50 55 60

Ile Arg Ala Ile Ala Glu Lys Lys Ala Asp Ala Val Thr Leu Asp Gly
 65 70 75 80

Gly Met Val Phe Glu Ala Gly Arg Asp Pro Tyr Lys Leu Arg Pro Val
 85 90 95

Ala Ala Glu Ile Tyr Gly Thr Lys Glu Ser Pro Gln Thr His Tyr Tyr
 100 105 110

Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Gln Leu Asp Gln Leu
 115 120 125

Gln Gly Arg Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
 130 135 140

Ile Ile Pro Met Gly Ile Leu Arg Pro Tyr Leu Ser Trp Thr Glu Ser
 145 150 155 160

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

Val Pro Cys Ile Asp Arg Gln Ala Tyr Pro Asn Leu Cys Gln Leu Cys
 180 185 190

Lys Gly Glu Gly Glu Asn Gln Cys Ala Cys Ser Ser Arg Glu Pro Tyr
 195 200 205

Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp

210		215		220
Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys				
225		230		235 240
Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Ser Arg Ala				
		245		250 255
Pro Val Asp Ala Phe Lys Glu Cys His Leu Ala Gln Val Pro Ser His				
		260		265 270
Ala Val Val Ala Arg Ser Val Asp Gly Lys Glu Asp Leu Ile Trp Lys				
		275		280 285
Leu Leu Ser Lys Ala Gln Glu Lys Phe Gly Lys Asn Lys Ser Arg Ser				
		290		295 300
Phe Gln Leu Phe Gly Ser Pro Pro Gly Gln Arg Asp Leu Leu Phe Lys				
305		310		315 320
Asp Ser Ala Leu Gly Phe Leu Arg Ile Pro Ser Lys Val Asp Ser Ala				
		325		330 335
Leu Tyr Leu Gly Ser Arg Tyr Leu Thr Thr Leu Lys Asn Leu Arg Glu				
		340		345 350
Thr Ala Glu Glu Val Lys Ala Arg Tyr Thr Arg Val Val Trp Cys Ala				
		355		360 365
Val Gly Pro Glu Glu Gln Lys Lys Cys Gln Gln Trp Ser Gln Gln Ser				
		370		375 380
Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile				
385		390		395 400
Val Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Asn Leu Asp Gly Gly				
		405		410 415
Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu				
		420		425 430
Asn Arg Lys Ser Ser Lys His Ser Ser Leu Asp Cys Val Leu Arg Pro				
		435		440 445
Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly				
		450		455 460
Leu Thr Trp Asn Ser Leu Lys Asp Lys Lys Ser Cys His Thr Ala Val				
465		470		475 480
Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Val Asn Gln				
		485		490 495
Thr Gly Ser Cys Ala Phe Asp Glu Phe Phe Ser Gln Ser Cys Ala Pro				
		500		505 510
Gly Ala Asp Pro Lys Ser Arg Leu Cys Ala Leu Cys Ala Gly Asp Asp				

515 520 525

Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540

Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560

Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Thr
 565 570 575

Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590

Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala Gln Ser Cys His Leu
 595 600 605

Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ser Asp Arg Ala Ala
 610 615 620

His Val Lys Gln Val Leu Leu His Gln Gln Ala Leu Phe Gly Lys Asn
 625 630 635 640

Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe Lys Ser Glu Thr Lys
 645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
 660 665 670

Arg Pro Thr Tyr Glu Glu Tyr Leu Gly Thr Glu Tyr Val Thr Ala Ile
 675 680 685

Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700

Phe Leu Thr Arg
 705

<210> 17
 <211> 711
 <212> PRT
 <213> HUMAN

<400> 17

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

Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Thr Val Ser
 20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Arg
 35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60

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

Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
370 375 380

Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
385 390 395 400

Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
405 410 415

Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala
420 425 430

Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
435 440 445

Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
450 455 460

Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
465 470 475 480

Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
485 490 495

Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
500 505 510

Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
515 520 525

Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
530 535 540

Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
545 550 555 560

Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
565 570 575

Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
580 585 590

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

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
610 615 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
625 630 635 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 18
 <211> 711
 <212> PRT
 <213> HUMAN

<400> 18

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

Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Thr Val Ser
 20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Arg
 35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60

Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
 65 70 75 80

Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
 85 90 95

Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
 100 105 110

Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
 115 120 125

Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
 130 135 140

Trp Asn Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
 145 150 155 160

Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
 165 170 175

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

Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
 195 200 205

Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
 210 215 220
 Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
 225 230 235 240
 Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
 245 250 255
 Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
 260 265 270
 His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
 275 280 285
 Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
 290 295 300
 Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
 305 310 315 320
 Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
 325 330 335
 Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
 340 345 350
 Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
 355 360 365
 Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
 370 375 380
 Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
 385 390 395 400
 Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
 405 410 415
 Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala
 420 425 430
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
 435 440 445
 Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
 450 455 460
 Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
 465 470 475 480
 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
 485 490 495
 Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
 500 505 510

Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
 515 520 525

Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
 530 535 540

Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
 545 550 555 560

Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 565 570 575

Asn Asn Asn Asp Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
 580 585 590

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

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
 610 615 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
 625 630 635 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
 645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
 660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 19
 <211> 708
 <212> PRT
 <213> WATER BUFFALO

<400> 19

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

Cys Leu Ala Ala Pro Arg Lys Asn Val Arg Trp Cys Thr Ile Ser Gln
 20 25 30

Pro Glu Trp Leu Lys Cys His Arg Trp Gln Trp Arg Met Lys Lys Leu
 35 40 45

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

Thr Ala Glu Glu Val Gln Ala Arg Arg Ala Arg Val Val Trp Cys Ala
 355 360 365

Val Gly Pro Glu Glu Gln Lys Lys Cys Gln Gln Trp Ser Gln Gln Ser
 370 375 380

Gly Gln Ile Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile
 385 390 395 400

Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Ser Leu Asp Gly Gly
 405 410 415

Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu
 420 425 430

Asn Arg Lys Ser Ser Lys His Ser Ser Leu Asp Cys Val Leu Arg Pro
 435 440 445

Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly
 450 455 460

Leu Thr Trp Asn Ser Leu Lys Gly Lys Lys Ser Cys His Thr Ala Val
 465 470 475 480

Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Ala Asn Gln
 485 490 495

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

Gly Ala Asp Pro Lys Ser Arg Leu Cys Ala Leu Cys Ala Gly Asp Asp
 515 520 525

Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540

Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560

Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Thr
 565 570 575

Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590

Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala Gln Ser Cys His Leu
 595 600 605

Ala Val Ala Pro Asn His Ala Val Val Ser Leu Ser Glu Arg Ala Ala
 610 615 620

His Val Glu Gln Val Leu Leu His Gln Gln Ala Leu Phe Gly Glu Asn
 625 630 635 640

Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe Lys Ser Glu Thr Lys
 645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
 660 665 670

Arg Pro Thr Tyr Glu Glu Tyr Leu Gly Thr Glu Tyr Val Thr Ala Ile
 675 680 685

Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700

Phe Leu Thr Arg
 705

<210> 20
 <211> 707
 <212> PRT
 <213> MOUSE

<400> 20

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

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

Glu Glu Glu Lys Cys Leu Arg Trp Gln Asn Glu Met Arg Lys Val Gly
 35 40 45

Gly Pro Pro Leu Ser Cys Val Lys Lys Ser Ser Thr Arg Gln Cys Ile
 50 55 60

Gln Ala Ile Val Thr Asn Arg Ala Asp Ala Met Thr Leu Asp Gly Gly
 65 70 75 80

Thr Leu Phe Asp Ala Gly Lys Pro Pro Tyr Lys Leu Arg Pro Val Ala
 85 90 95

Ala Glu Val Tyr Gly Thr Lys Glu Gln Pro Arg Thr His Tyr Tyr Ala
 100 105 110

Val Ala Val Val Lys Asn Ser Ser Asn Phe His Leu Asn Gln Leu Gln
 115 120 125

Gly Leu Arg Ser Cys His Thr Gly Ile Gly Arg Ser Ala Gly Trp Lys
 130 135 140

Ile Pro Ile Gly Thr Leu Arg Pro Tyr Leu Asn Trp Asn Gly Pro Pro
 145 150 155 160

Ala Ser Leu Glu Glu Ala Val Ser Lys Phe Phe Ser Lys Ser Cys Val
 165 170 175

Pro Gly Ala Gln Lys Asp Arg Phe Pro Asn Leu Cys Ser Ser Cys Ala
 180 185 190

Gly Thr Gly Ala Asn Lys Cys Ala Ser Ser Pro Glu Glu Pro Tyr Ser

	195		200		205														
Gly	Tyr	Ala	Gly	Ala	Leu	Arg	Cys	Leu	Arg	Asp	Asn	Ala	Gly	Asp	Val				
	210					215					220								
Ala	Phe	Thr	Arg	Gly	Ser	Thr	Val	Phe	Glu	Glu	Leu	Pro	Asn	Lys	Ala				
225					230				235						240				
Glu	Arg	Asp	Gln	Tyr	Lys	Leu	Leu	Cys	Pro	Asp	Asn	Thr	Trp	Lys	Pro				
				245					250					255					
Val	Thr	Glu	Tyr	Lys	Glu	Cys	His	Leu	Ala	Gln	Val	Pro	Ser	His	Ala				
			260					265					270						
Val	Val	Ser	Arg	Ser	Thr	Asn	Asp	Lys	Glu	Glu	Ala	Ile	Trp	Glu	Leu				
		275					280					285							
Leu	Arg	Gln	Ser	Gln	Glu	Lys	Phe	Gly	Lys	Lys	Gln	Ala	Ser	Gly	Phe				
	290					295					300								
Gln	Leu	Phe	Ala	Ser	Pro	Ser	Gly	Gln	Lys	Asp	Leu	Leu	Phe	Lys	Glu				
305					310					315					320				
Ser	Ala	Ile	Gly	Phe	Val	Arg	Val	Pro	Gln	Lys	Val	Asp	Val	Gly	Leu				
				325					330					335					
Tyr	Leu	Thr	Phe	Ser	Tyr	Thr	Thr	Ser	Ile	Gln	Asn	Leu	Asn	Lys	Lys				
			340					345					350						
Gln	Gln	Asp	Val	Ile	Ala	Thr	Lys	Ala	Arg	Val	Thr	Trp	Cys	Ala	Val				
		355					360					365							
Gly	Ser	Glu	Glu	Lys	Arg	Lys	Cys	Asp	Gln	Trp	Asn	Arg	Ala	Ser	Arg				
	370					375					380								
Gly	Arg	Val	Thr	Cys	Ile	Ser	Phe	Pro	Thr	Thr	Glu	Asp	Cys	Ile	Val				
385					390					395					400				
Ala	Ile	Met	Lys	Gly	Asp	Ala	Asp	Ala	Met	Ser	Leu	Asp	Gly	Gly	Tyr				
				405					410					415					
Ile	Tyr	Thr	Ala	Gly	Lys	Cys	Gly	Leu	Val	Pro	Val	Leu	Ala	Glu	Asn				
			420					425					430						
Gln	Lys	Ser	Ser	Lys	Ser	Asn	Gly	Leu	Asp	Cys	Val	Asn	Arg	Pro	Val				
		435					440					445							
Gly	Gly	Tyr	Leu	Ala	Val	Ala	Ala	Val	Arg	Arg	Glu	Asp	Ala	Gly	Phe				
	450					455					460								
Thr	Trp	Ser	Ser	Leu	Arg	Gly	Lys	Lys	Ser	Cys	His	Thr	Ala	Val	Asp				
465					470					475					480				
Arg	Thr	Ala	Gly	Trp	Asn	Ile	Pro	Met	Gly	Leu	Leu	Ala	Asn	Gln	Thr				
				485					490					495					
Arg	Ser	Cys	Lys	Phe	Asn	Glu	Phe	Phe	Ser	Gln	Ser	Cys	Ala	Pro	Gly				

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60

Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
 65 70 75 80

Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
 85 90 95

Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
 100 105 110

Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
 115 120 125

Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
 130 135 140

Trp Asn Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
 145 150 155 160

Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
 165 170 175

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

Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
 195 200 205

Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
 210 215 220

Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
 225 230 235 240

Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
 245 250 255

Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
 260 265 270

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

Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
 290 295 300

Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
 305 310 315 320

Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
 325 330 335

Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
 340 345 350

Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
 355 360 365
 Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
 370 375 380
 Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
 385 390 395 400
 Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
 405 410 415
 Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala
 420 425 430
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
 435 440 445
 Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
 450 455 460
 Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
 465 470 475 480
 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
 485 490 495
 Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
 500 505 510
 Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
 515 520 525
 Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
 530 535 540
 Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
 545 550 555 560
 Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 565 570 575
 Asn Asn Asn Asp Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
 580 585 590
 Leu Leu Cys Leu Asp Gly Lys Arg Lys Pro Val Thr Glu Ala Arg Ser
 595 600 605
 Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
 610 615 620
 Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
 625 630 635 640
 Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
 645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
 660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 22
 <211> 708
 <212> PRT
 <213> COW

<400> 22
 Met Lys Leu Phe Val Pro Ala Leu Leu Ser Leu Gly Ala Leu Gly Leu
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Cys Leu Ala Ala Pro Arg Lys Asn Val Arg Trp Cys Thr Ile Ser Gln
 20 25 30

Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu
 35 40 45

Gly Ala Pro Ser Ile Thr Cys Val Arg Arg Ala Phe Ala Leu Glu Cys
 50 55 60

Ile Arg Ala Ile Ala Glu Lys Lys Ala Asp Ala Val Thr Leu Asp Gly
 65 70 75 80

Gly Met Val Phe Glu Ala Gly Arg Asp Pro Tyr Lys Leu Arg Pro Val
 85 90 95

Ala Ala Glu Ile Tyr Gly Thr Lys Glu Ser Pro Gln Thr His Tyr Tyr
 100 105 110

Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Gln Leu Asp Gln Leu
 115 120 125

Gln Gly Arg Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
 130 135 140

Ile Ile Pro Met Gly Ile Leu Arg Pro Tyr Leu Ser Trp Thr Glu Ser
 145 150 155 160

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

Val Pro Cys Ile Asp Arg Gln Ala Tyr Pro Asn Leu Cys Gln Leu Cys
 180 185 190

Lys Gly Glu Gly Glu Asn Gln Cys Ala Cys Ser Ser Arg Glu Pro Tyr
 195 200 205

Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
 210 215 220

Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys
 225 230 235 240

Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Ser Arg Ala
 245 250 255

Pro Val Asp Ala Phe Lys Glu Cys His Leu Ala Gln Val Pro Ser His
 260 265 270

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

Leu Leu Ser Lys Ala Gln Glu Lys Phe Gly Lys Asn Lys Ser Arg Ser
 290 295 300

Phe Gln Leu Phe Gly Ser Pro Pro Gly Gln Arg Asp Leu Leu Phe Lys
 305 310 315 320

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

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

Thr Ala Glu Glu Val Lys Ala Arg Tyr Thr Arg Val Val Trp Cys Ala
 355 360 365

Val Gly Pro Glu Glu Gln Lys Lys Cys Gln Gln Trp Ser Gln Gln Ser
 370 375 380

Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile
 385 390 395 400

Val Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Asn Leu Asp Gly Gly
 405 410 415

Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu
 420 425 430

Asn Arg Lys Ser Ser Lys His Ser Ser Leu Asp Cys Val Leu Arg Pro
 435 440 445

Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly
 450 455 460

Leu Thr Trp Asn Ser Leu Lys Asp Lys Lys Ser Cys His Thr Ala Val
 465 470 475 480

Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Val Asn Gln
 485 490 495

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

Gly Ala Asp Pro Lys Ser Arg Leu Cys Ala Leu Cys Ala Gly Asp Asp
 515 520 525

Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540

Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560

Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Thr
 565 570 575

Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590

Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala Gln Ser Cys His Leu
 595 600 605

Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ser Asp Arg Ala Ala
 610 615 620

His Val Lys Gln Val Leu Leu Arg Gln Gln Ala Leu Phe Gly Lys Asn
 625 630 635 640

Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe Lys Ser Glu Thr Lys
 645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
 660 665 670

Arg Pro Thr Tyr Glu Glu Tyr Leu Gly Thr Glu Tyr Val Thr Ala Ile
 675 680 685

Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700

Phe Leu Thr Arg
 705

<210> 23
 <211> 708
 <212> PRT
 <213> CAMEL

<400> 23
 Met Lys Leu Phe Phe Pro Ala Leu Leu Ser Leu Gly Ala Leu Gly Leu
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Cys Leu Ala Ala Ser Lys Lys Ser Val Arg Trp Cys Thr Thr Ser Pro
 20 25 30

Ala Glu Ser Ser Lys Cys Ala Gln Trp Gln Arg Arg Met Lys Lys Val
 35 40 45

Arg Gly Pro Ser Val Thr Cys Val Lys Lys Thr Ser Arg Phe Glu Cys

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

Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
 210 215 220
 Val Ala Phe Val Lys Asp Ser Thr Val Phe Glu Ser Leu Pro Ala Lys
 225 230 235 240
 Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Pro Asn Asn Thr Arg Lys
 245 250 255
 Pro Val Asp Ala Phe Gln Glu Cys His Leu Ala Arg Val Pro Ser His
 260 265 270
 Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Leu Ile Trp Lys
 275 280 285
 Leu Leu Val Lys Ala Gln Glu Lys Phe Gly Arg Gly Lys Pro Ser Gly
 290 295 300
 Phe Gln Leu Phe Gly Ser Pro Ala Gly Gln Lys Asp Leu Leu Phe Lys
 305 310 315 320
 Asp Ser Ala Leu Gly Leu Leu Arg Ile Ser Ser Lys Ile Asp Ser Gly
 325 330 335
 Leu Tyr Leu Gly Ser Asn Tyr Ile Thr Ala Ile Arg Gly Leu Arg Glu
 340 345 350
 Thr Ala Ala Glu Val Glu Leu Arg Arg Ala Gln Val Val Trp Cys Ala
 355 360 365
 Val Gly Ser Asp Glu Gln Leu Lys Cys Gln Glu Trp Ser Arg Gln Ser
 370 375 380
 Asn Gln Ser Val Val Cys Ala Thr Ala Ser Thr Thr Glu Asp Cys Ile
 385 390 395 400
 Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Ser Leu Asp Gly Gly
 405 410 415
 Tyr Ile Tyr Ile Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu
 420 425 430
 Ser Gln Gln Ser Pro Glu Ser Ser Gly Leu Asp Cys Val His Arg Pro
 435 440 445
 Val Lys Gly Tyr Leu Ala Val Ala Val Val Arg Lys Ala Asn Asp Lys
 450 455 460
 Ile Thr Trp Asn Ser Leu Arg Gly Lys Lys Ser Cys His Thr Ala Val
 465 470 475 480
 Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu Ser Lys Asn
 485 490 495
 Thr Asp Ser Cys Arg Phe Asp Glu Phe Leu Ser Gln Ser Cys Ala Pro
 500 505 510

Gly Ser Asp Pro Arg Ser Lys Leu Cys Ala Leu Cys Ala Gly Asn Glu
 515 520 525

Glu Gly Gln Asn Lys Cys Val Pro Asn Ser Ser Glu Arg Tyr Tyr Gly
 530 535 540

Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Val Gly Asp Val Ala
 545 550 555 560

Phe Val Lys Asp Val Thr Val Leu Asp Asn Thr Asp Gly Lys Asn Thr
 565 570 575

Glu Gln Trp Ala Lys Asp Leu Lys Leu Gly Asp Phe Glu Leu Leu Cys
 580 585 590

Leu Asn Gly Thr Arg Lys Pro Val Thr Glu Ala Glu Ser Cys His Leu
 595 600 605

Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ile Asp Lys Val Ala
 610 615 620

His Leu Glu Gln Val Leu Leu Arg Gln Gln Ala His Phe Gly Arg Asn
 625 630 635 640

Gly Arg Asp Cys Pro Gly Lys Phe Cys Leu Phe Gln Ser Lys Thr Lys
 645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gln Gly
 660 665 670

Lys Thr Thr Tyr Glu Glu Tyr Leu Gly Pro Gln Tyr Val Thr Ala Ile
 675 680 685

Ala Lys Leu Arg Arg Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700

Phe Leu Met Arg
 705

<210> 25
 <211> 698
 <212> PRT
 <213> RAT

<400> 25
 Met Arg Phe Ala Val Gly Ala Leu Leu Ala Cys Ala Ala Leu Gly Leu
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Cys Leu Ala Val Pro Asp Lys Thr Val Lys Trp Cys Ala Val Ser Glu
 20 25 30

His Glu Asn Thr Lys Cys Ile Ser Phe Arg Asp His Met Lys Thr Val
 35 40 45

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

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

Glu Arg Ala Lys Cys Asp Glu Trp Ser Val Thr Ser Asn Gly Gln Ile
 370 375 380
 Glu Cys Glu Ser Ala Glu Ser Thr Glu Asp Cys Ile Asp Lys Ile Val
 385 390 395 400
 Asn Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly His Ala Tyr Ile
 405 410 415
 Ala Gly Gln Cys Gly Leu Val Pro Val Met Ala Glu Asn Tyr Asp Ile
 420 425 430
 Ser Ser Cys Thr Asn Pro Gln Ser Asp Val Phe Pro Lys Gly Tyr Tyr
 435 440 445
 Ala Val Ala Val Val Lys Ala Ser Asp Ser Ser Ile Asn Trp Asn Asn
 450 455 460
 Leu Lys Gly Lys Lys Ser Cys His Thr Gly Val Asp Arg Thr Ala Gly
 465 470 475 480
 Trp Asn Ile Pro Met Gly Leu Leu Phe Ser Arg Ile Asn His Cys Lys
 485 490 495
 Phe Asp Glu Phe Phe Ser Gln Gly Cys Ala Pro Gly Tyr Lys Lys Asn
 500 505 510
 Ser Thr Leu Cys Asp Leu Cys Ile Gly Pro Ala Lys Cys Ala Pro Asn
 515 520 525
 Asn Arg Glu Gly Tyr Asn Gly Tyr Thr Gly Ala Phe Gln Cys Leu Val
 530 535 540
 Glu Lys Gly Asp Val Ala Phe Val Lys His Gln Thr Val Leu Glu Asn
 545 550 555 560
 Thr Asn Gly Lys Asn Thr Ala Ala Trp Ala Lys Asp Leu Lys Gln Glu
 565 570 575
 Asp Phe Gln Leu Leu Cys Pro Asp Gly Thr Lys Lys Pro Val Thr Glu
 580 585 590
 Phe Ala Thr Cys His Leu Ala Gln Ala Pro Asn His Val Val Val Ser
 595 600 605
 Arg Lys Glu Lys Ala Ala Arg Val Ser Thr Val Leu Thr Ala Gln Lys
 610 615 620
 Asp Leu Phe Trp Lys Gly Asp Lys Asp Cys Thr Gly Asn Phe Cys Leu
 625 630 635 640
 Phe Arg Ser Ser Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Lys Cys
 645 650 655
 Leu Thr Lys Leu Pro Glu Gly Thr Thr Tyr Glu Glu Tyr Leu Gly Ala
 660 665 670

Glu Tyr Leu Gln Ala Val Gly Asn Ile Arg Lys Cys Ser Thr Ser Arg
 675 680 685

Leu Leu Glu Ala Cys Thr Phe His Lys Ser
 690 695

<210> 26
 <211> 695
 <212> PRT
 <213> HORSE

<400> 26
 Leu Gly Leu Cys Leu Ala Ala Pro Arg Lys Ser Val Arg Trp Cys Thr
 1 5 10 15
 Ile Ser Pro Ala Glu Ala Ala Lys Cys Ala Lys Phe Gln Arg Asn Met
 20 25 30
 Lys Lys Val Arg Gly Pro Ser Val Ser Cys Ile Arg Lys Thr Ser Ser
 35 40 45
 Phe Glu Cys Ile Gln Ala Ile Ala Ala Asn Lys Ala Asp Ala Val Thr
 50 55 60
 Leu Asp Gly Gly Leu Val Tyr Glu Ala Gly Leu His Pro Tyr Lys Leu
 65 70 75 80
 Arg Pro Val Ala Ala Glu Val Tyr Gln Thr Arg Gly Lys Pro Gln Thr
 85 90 95
 Arg Tyr Tyr Ala Val Ala Val Val Lys Lys Gly Ser Gly Phe Gln Leu
 100 105 110
 Asn Gln Leu Gln Gly Val Lys Ser Cys His Thr Gly Leu Gly Arg Ser
 115 120 125
 Ala Gly Trp Asn Ile Pro Ile Gly Thr Leu Arg Pro Tyr Leu Asn Trp
 130 135 140
 Thr Gly Pro Pro Glu Pro Leu Gln Lys Ala Val Ala Asn Phe Phe Ser
 145 150 155 160
 Ala Ser Cys Val Pro Cys Ala Asp Gly Lys Gln Tyr Pro Asn Leu Cys
 165 170 175
 Arg Leu Cys Ala Gly Thr Glu Ala Asp Lys Cys Ala Cys Ser Ser Gln
 180 185 190
 Glu Pro Tyr Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Glu Asn Gly
 195 200 205
 Ala Gly Asp Val Ala Phe Val Lys Asp Ser Thr Val Phe Glu Asn Leu
 210 215 220
 Pro Asp Glu Ala Asp Arg Asp Lys Tyr Glu Leu Leu Cys Pro Asp Asn

530 535 540

Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 545 550 555 560

Lys Asn Ser Glu Pro Trp Ala Lys Asp Leu Lys Gln Glu Asp Phe Glu
 565 570 575

Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Ala Glu Ala Glu Ser
 580 585 590

Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val Ser Gln Ser Asp
 595 600 605

Arg Ala Gln His Leu Lys Lys Val Leu Phe Leu Gln Gln Asp Gln Phe
 610 615 620

Gly Gly Asn Gly Pro Asp Cys Pro Gly Lys Phe Cys Leu Phe Lys Ser
 625 630 635 640

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Glu
 645 650 655

Leu Gln Gly Lys Thr Thr Tyr Glu Gln Tyr Leu Gly Ser Glu Tyr Val
 660 665 670

Thr Ser Ile Thr Asn Leu Arg Arg Cys Ser Ser Ser Pro Leu Leu Glu
 675 680 685

Ala Cys Ala Phe Leu Arg Ala
 690 695

<210> 27
 <211> 711
 <212> PRT

<213> HUMAN

<400> 27

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

Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Ala Val Ser
 20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys
 35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60

Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
 65 70 75 80

Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
 85 90 95

Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
 100 105 110
 Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
 115 120 125
 Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
 130 135 140
 Trp Asn Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
 145 150 155 160
 Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
 165 170 175
 Cys Val Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu Cys Arg Leu
 180 185 190
 Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
 195 200 205
 Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
 210 215 220
 Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
 225 230 235 240
 Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
 245 250 255
 Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
 260 265 270
 His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
 275 280 285
 Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
 290 295 300
 Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
 305 310 315 320
 Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
 325 330 335
 Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
 340 345 350
 Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
 355 360 365
 Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
 370 375 380
 Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
 385 390 395 400

Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly
 405 410 415
 Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala
 420 425 430
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
 435 440 445
 Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
 450 455 460
 Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
 465 470 475 480
 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
 485 490 495
 Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
 500 505 510
 Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
 515 520 525
 Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
 530 535 540
 Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
 545 550 555 560
 Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 565 570 575
 Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
 580 585 590
 Leu Leu Cys Leu Asp Gly Lys Arg Lys Pro Val Thr Glu Ala Arg Ser
 595 600 605
 Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
 610 615 620
 Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
 625 630 635 640
 Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
 645 650 655
 Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
 660 665 670
 Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685
 Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
705 710

<210> 28
<211> 708
<212> PRT
<213> GOAT

<400> 28

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

Cys Leu Ala Ala Pro Arg Lys Asn Val Arg Trp Cys Ala Ile Ser Leu
20 25 30

Pro Glu Trp Ser Lys Cys Tyr Gln Trp Gln Arg Arg Met Arg Lys Leu
35 40 45

Gly Ala Pro Ser Ile Thr Cys Val Arg Arg Thr Ser Ala Leu Glu Cys
50 55 60

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

Gly Met Val Phe Glu Ala Gly Arg Asp Pro Tyr Lys Leu Arg Pro Val
85 90 95

Ala Ala Glu Ile Tyr Gly Thr Glu Lys Ser Pro Gln Thr His Tyr Tyr
100 105 110

Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Lys Leu Asp Gln Leu
115 120 125

Gln Gly Gln Lys Ser Cys His Met Gly Leu Gly Arg Ser Ala Gly Trp
130 135 140

Asn Ile Pro Val Gly Ile Leu Arg Pro Pro Leu Ser Trp Thr Glu Ser
145 150 155 160

Ala Glu Pro Leu Gln Gly Ala Val Ala Arg Phe Phe Ser Ala Ser Cys
165 170 175

Val Pro Cys Val Asp Gly Lys Ala Tyr Pro Asn Leu Cys Gln Leu Cys
180 185 190

Lys Gly Val Gly Glu Asn Lys Cys Ala Cys Ser Ser Gln Glu Pro Tyr
195 200 205

Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
210 215 220

Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys
225 230 235 240

Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Thr Arg Ala

					245					250					255
Pro	Val	Asp	Ala	Phe	Lys	Glu	Cys	His	Leu	Ala	Gln	Val	Pro	Ser	His
			260					265					270		
Ala	Val	Val	Ala	Arg	Ser	Val	Asp	Gly	Lys	Glu	Asn	Leu	Ile	Trp	Glu
		275					280					285			
Leu	Leu	Arg	Lys	Ala	Gln	Glu	Lys	Phe	Gly	Lys	Asn	Lys	Ser	Gln	Arg
	290					295					300				
Phe	Gln	Leu	Phe	Gly	Ser	Pro	Glu	Gly	Arg	Arg	Asp	Leu	Leu	Phe	Lys
305					310					315					320
Asp	Ser	Ala	Leu	Gly	Phe	Val	Arg	Ile	Pro	Ser	Lys	Val	Asp	Ser	Ala
				325					330					335	
Leu	Tyr	Leu	Gly	Ser	Arg	Tyr	Leu	Thr	Ala	Leu	Lys	Asn	Leu	Arg	Glu
			340					345					350		
Thr	Ala	Glu	Glu	Leu	Lys	Ala	Arg	Cys	Thr	Arg	Val	Val	Trp	Cys	Ala
		355					360					365			
Val	Gly	Pro	Glu	Glu	Gln	Ser	Lys	Cys	Gln	Gln	Trp	Ser	Glu	Gln	Ser
	370					375					380				
Gly	Gln	Asn	Val	Thr	Cys	Ala	Thr	Ala	Ser	Thr	Thr	Asp	Asp	Cys	Ile
385					390					395					400
Ala	Leu	Val	Leu	Lys	Gly	Glu	Ala	Asp	Ala	Leu	Ser	Leu	Gly	Gly	Gly
				405					410					415	
Tyr	Ile	Tyr	Thr	Ala	Gly	Lys	Cys	Gly	Leu	Val	Pro	Val	Met	Ala	Glu
			420					425					430		
Asn	Arg	Lys	Ser	Ser	Lys	Tyr	Ser	Ser	Leu	Asp	Cys	Val	Leu	Arg	Pro
		435					440					445			
Thr	Glu	Gly	Tyr	Leu	Ala	Val	Ala	Val	Val	Lys	Lys	Ala	Asn	Glu	Gly
	450					455					460				
Leu	Thr	Trp	Asn	Ser	Leu	Lys	Gly	Lys	Lys	Ser	Cys	His	Thr	Ala	Val
465					470					475					480
Asp	Arg	Thr	Ala	Gly	Trp	Asn	Ile	Pro	Met	Gly	Leu	Ile	Ala	Asn	Gln
				485				490						495	
Thr	Gly	Ser	Cys	Ala	Phe	Asp	Glu	Phe	Phe	Ser	Gln	Ser	Cys	Ala	Pro
			500					505					510		
Gly	Ala	Asp	Pro	Lys	Ser	Ser	Leu	Cys	Ala	Leu	Cys	Ala	Gly	Asp	Asp
		515					520					525			
Gln	Gly	Leu	Asp	Lys	Cys	Val	Pro	Asn	Ser	Lys	Glu	Lys	Tyr	Tyr	Gly
	530					535					540				
Tyr	Thr	Gly	Ala	Phe	Arg	Cys	Leu	Ala	Glu	Asp	Val	Gly	Asp	Val	Ala

Ala Ala Glu Ile Tyr Gly Thr Lys Glu Ser Pro Gln Thr His Tyr Tyr
100 105 110

Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Gln Leu Asp Gln Leu
115 120 125

Gln Gly Arg Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
130 135 140

Val Ile Pro Met Gly Ile Leu Arg Pro Tyr Leu Ser Trp Thr Glu Ser
145 150 155 160

Leu Glu Pro Pro Pro Gly Ala Val Ala Lys Phe Phe Ser Ala Ser Cys
165 170 175

Val Pro Cys Ile Asp Arg Gln Ala Tyr Pro Asn Leu Cys Gln Leu Cys
180 185 190

Lys Gly Glu Gly Glu Asn Gln Cys Ala Cys Ser Ser Arg Glu Pro Tyr
195 200 205

Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
210 215 220

Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys
225 230 235 240

Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Ser Arg Ala
245 250 255

Pro Val Asp Ala Phe Lys Glu Cys His Leu Ala Gln Val Pro Ser His
260 265 270

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

Leu Leu Ser Lys Ala Gln Glu Lys Phe Gly Lys Asn Lys Ser Arg Ser
290 295 300

Phe Gln Leu Phe Gly Ser Pro Pro Gly Gln Arg Asp Leu Leu Phe Lys
305 310 315 320

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

Leu Tyr Leu Ala Ser Arg Tyr Leu Thr Thr Leu Lys Asn Leu Arg Glu
340 345 350

Thr Ala Glu Glu Val Lys Ala Arg Tyr Thr Arg Val Val Trp Cys Ala
355 360 365

Val Gly Pro Glu Glu Gln Lys Lys Cys Gln Gln Trp Ser Gln Gln Ser
370 375 380

Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile
385 390 395 400

Val Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Asn Leu Asp Gly Gly
 405 410 415

Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu
 420 425 430

Asn Arg Lys Ser Ser Lys Tyr Ser Ser Leu Asp Cys Val Leu Arg Pro
 435 440 445

Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly
 450 455 460

Leu Thr Trp Asn Ser Leu Lys Asp Lys Lys Ser Cys His Thr Ala Val
 465 470 475 480

Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Val Asn Gln
 485 490 495

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

Gly Arg Asp Pro Lys Ser Arg Leu Cys Ala Leu Cys Ala Gly Asp Asp
 515 520 525

Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540

Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560

Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Thr
 565 570 575

Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590

Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala Gln Ser Cys His Leu
 595 600 605

Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ser Asp Arg Ala Ala
 610 615 620

His Val Lys Gln Val Leu Leu His Gln Gln Ala Leu Phe Gly Lys Asn
 625 630 635 640

Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe Lys Ser Glu Thr Lys
 645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
 660 665 670

Arg Pro Thr Tyr Glu Glu Tyr Leu Gly Thr Glu Tyr Val Thr Ala Ile
 675 680 685

Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700

Phe Leu Thr Arg
705

<210> 30
<211> 711
<212> PRT
<213> HUMAN

<400> 30

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

Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Ala Val Ser
20 25 30

Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys
35 40 45

Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
50 55 60

Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
65 70 75 80

Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
85 90 95

Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
100 105 110

Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
115 120 125

Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
130 135 140

Trp Asn Val Pro Thr Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
145 150 155 160

Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
165 170 175

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

Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
195 200 205

Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
210 215 220

Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
225 230 235 240

Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg

245				250				255							
Lys	Pro	Val	Asp 260	Lys	Phe	Lys	Asp 265	Cys	His	Leu	Ala	Arg	Val 270	Pro	Ser
His	Ala	Val 275	Val	Ala	Arg	Ser	Val 280	Asn	Gly	Lys	Glu	Asp 285	Ala	Ile	Trp
Asn	Leu 290	Leu	Arg	Gln	Ala	Gln 295	Glu	Lys	Phe	Gly	Lys 300	Asp	Lys	Ser	Pro
Lys	Phe	Gln	Leu	Phe	Gly 310	Ser	Pro	Ser	Gly	Gln	Lys	Asp	Leu	Leu	Phe 320
Lys	Asp	Ser	Ala	Ile	Gly 325	Phe	Ser	Arg	Val 330	Pro	Pro	Arg	Ile	Asp	Ser 335
Gly	Leu	Tyr	Leu	Gly	Ser	Gly	Tyr	Phe	Thr 345	Ala	Ile	Gln	Asn 350	Leu	Arg
Lys	Ser	Glu 355	Glu	Glu	Val	Ala	Ala	Arg	Arg	Ala	Arg	Val 365	Val	Trp	Cys
Ala	Val 370	Gly	Glu	Gln	Glu	Leu	Arg	Lys	Cys	Asn	Gln	Trp	Ser	Gly	Leu
Ser	Glu	Gly	Ser	Val	Thr 390	Cys	Ser	Ser	Ala	Ser	Thr	Thr	Glu	Asp	Cys 400
Ile	Ala	Leu	Val	Leu	Lys	Gly	Glu	Ala	Asp 410	Ala	Met	Ser	Leu	Asp	Gly 415
Gly	Tyr	Val	Tyr	Thr	Ala	Cys	Lys	Cys	Gly	Leu	Val	Pro	Val	Leu	Ala
Glu	Asn	Tyr 435	Lys	Ser	Gln	Gln	Ser	Ser	Asp 440	Pro	Asp	Pro	Asn	Cys	Val
Asp	Arg	Pro	Val	Glu	Gly	Tyr	Leu	Ala	Val	Ala	Val	Val	Arg	Arg	Ser
Asp	Thr	Ser	Leu	Thr	Trp 470	Asn	Ser	Val	Lys	Gly	Lys	Lys	Ser	Cys	His 480
Thr	Ala	Val	Asp	Arg	Thr	Ala	Gly	Trp	Asn 490	Ile	Pro	Met	Gly	Leu	Leu 495
Phe	Asn	Gln	Thr	Gly	Ser	Cys	Lys	Phe	Asp 505	Glu	Tyr	Phe	Ser	Gln	Ser
Cys	Ala	Pro	Gly	Ser	Asp	Pro	Arg	Ser	Asn 520	Leu	Cys	Ala	Leu	Cys	Ile
Gly	Asp	Glu	Gln	Gly	Glu	Asn	Lys	Cys	Val	Pro	Asn	Ser	Asn	Glu	Arg
Tyr	Tyr	Gly	Tyr	Thr	Gly	Ala	Phe	Arg	Cys	Leu	Ala	Glu	Asn	Ala	Gly

Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr Tyr Ala
 100 105 110
 Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu Leu Gln
 115 120 125
 Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly Trp Asn
 130 135 140
 Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly Pro Pro
 145 150 155 160
 Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser Cys Val
 165 170 175
 Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu Cys Arg Leu Cys Ala
 180 185 190
 Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro Tyr Phe
 195 200 205
 Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly Asp Val
 210 215 220
 Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp Glu Ala
 225 230 235 240
 Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg Lys Pro
 245 250 255
 Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser His Ala
 260 265 270
 Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp Asn Leu
 275 280 285
 Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro Lys Phe
 290 295 300
 Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe Lys Asp
 305 310 315 320
 Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser Gly Leu
 325 330 335
 Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg Lys Ser
 340 345 350
 Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys Ala Val
 355 360 365
 Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu Ser Glu
 370 375 380
 Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys Ile Ala
 385 390 395 400

Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Tyr
 405 410 415

Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn
 420 425 430

Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val Asp Arg
 435 440 445

Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser Asp Thr
 450 455 460

Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His Thr Ala
 465 470 475 480

Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu Phe Asn
 485 490 495

Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser Cys Ala
 500 505 510

Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile Gly Asp
 515 520 525

Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg Tyr Tyr
 530 535 540

Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly Asp Val
 545 550 555 560

Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly Asn Asn
 565 570 575

Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala Leu Leu
 580 585 590

Cys Leu Asp Gly Lys Arg Lys Pro Val Thr Glu Ala Arg Ser Cys His
 595 600 605

Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp Lys Val
 610 615 620

Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe Gly Arg
 625 630 635 640

Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser Glu Thr
 645 650 655

Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg Leu His
 660 665 670

Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val Ala Gly
 675 680 685

Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys
 690 695 700

Glu Phe Leu Arg Lys
705

<210> 32
<211> 708
<212> PRT
<213> GOAT

<400> 32

Met Lys Leu Phe Val Pro Ala Leu Leu Ser Leu Gly Ala Leu Gly Leu
1 5 10 15
Cys Leu Ala Ala Pro Arg Lys Asn Val Arg Trp Cys Ala Ile Ser Leu
20 25 30
Pro Glu Trp Ser Lys Cys Tyr Gln Trp Gln Arg Arg Met Arg Lys Leu
35 40 45
Gly Ala Pro Ser Ile Thr Cys Ile Arg Arg Thr Ser Ala Leu Glu Cys
50 55 60
Ile Arg Ala Ile Ala Gly Lys Asn Ala Asp Ala Val Thr Leu Asp Ser
65 70 75 80
Gly Met Val Phe Glu Ala Gly Leu Asp Pro Tyr Lys Leu Arg Pro Val
85 90 95
Ala Ala Glu Ile Tyr Gly Thr Glu Lys Ser Pro Gln Thr His Tyr Tyr
100 105 110
Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Gln Leu Asp Gln Leu
115 120 125
Gln Gly Gln Lys Ser Cys His Met Gly Leu Gly Arg Ser Ala Gly Trp
130 135 140
Asn Ile Pro Val Gly Ile Leu Arg Pro Phe Leu Ser Trp Thr Glu Ser
145 150 155 160
Ala Glu Pro Leu Gln Gly Ala Val Ala Arg Phe Phe Ser Ala Ser Cys
165 170 175
Val Pro Cys Val Asp Gly Lys Ala Tyr Pro Asn Leu Cys Gln Leu Cys
180 185 190
Lys Gly Val Gly Glu Asn Lys Cys Ala Cys Ser Ser Gln Glu Pro Tyr
195 200 205
Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
210 215 220
Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys
225 230 235 240
Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Thr Arg Ala
245 250 255

Pro Val Asp Ala Phe Lys Glu Cys His Leu Ala Gln Val Pro Ser His
 260 265 270
 Ala Val Val Ala Arg Ser Val Asp Gly Lys Glu Asn Leu Ile Trp Glu
 275 280 285
 Leu Leu Arg Lys Ala Gln Glu Lys Phe Gly Lys Asn Lys Ser Gln Ser
 290 295 300
 Phe Gln Leu Phe Gly Ser Pro Glu Gly Arg Arg Asp Leu Leu Phe Lys
 305 310 315 320
 Asp Ser Ala Leu Gly Phe Val Arg Ile Pro Ser Lys Val Asp Ser Ala
 325 330 335
 Leu Tyr Leu Gly Ser Arg Tyr Leu Thr Ala Leu Lys Asn Leu Arg Glu
 340 345 350
 Thr Ala Glu Glu Leu Lys Ala Arg Cys Thr Arg Val Val Trp Cys Ala
 355 360 365
 Val Gly Pro Glu Glu Gln Ser Lys Cys Gln Gln Trp Ser Glu Gln Ser
 370 375 380
 Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile
 385 390 395 400
 Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Ser Leu Asp Gly Gly
 405 410 415
 Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Met Ala Glu
 420 425 430
 Asn Arg Lys Ser Ser Lys Tyr Ser Ser Leu Asp Cys Val Leu Arg Pro
 435 440 445
 Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly
 450 455 460
 Leu Thr Trp Asn Ser Leu Lys Gly Lys Lys Ser Cys His Thr Ala Val
 465 470 475 480
 Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Ala Asn Gln
 485 490 495
 Thr Gly Ser Cys Ala Phe Asp Glu Phe Phe Ser Gln Ser Cys Ala Pro
 500 505 510
 Gly Ala Asp Pro Lys Ser Ser Leu Cys Ala Leu Cys Ala Gly Asp Asp
 515 520 525
 Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540
 Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560

Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Ser
 565 570 575

Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590

Leu Asp Gly Thr Thr Lys Pro Val Thr Glu Ala Gln Ser Cys Tyr Leu
 595 600 605

Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ser Asp Arg Ala Ala
 610 615 620

His Val Glu Gln Val Leu Leu His Gln Gln Ala Leu Phe Gly Lys Asn
 625 630 635 640

Gly Lys Asn Cys Pro Asp Gln Phe Cys Leu Phe Lys Ser Glu Thr Lys
 645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
 660 665 670

Arg Pro Thr Tyr Glu Lys Tyr Leu Gly Thr Glu Tyr Val Thr Ala Ile
 675 680 685

Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700

Phe Leu Thr Arg
 705

<210> 33
 <211> 710
 <212> PRT
 <213> HUMAN

<400> 33
 Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
 1 5 10 15

Cys Leu Ala Gly Arg Arg Arg Ser Val Gln Trp Cys Ala Val Ser Gln
 20 25 30

Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys Val
 35 40 45

Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln Cys
 50 55 60

Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp Gly
 65 70 75 80

Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro Val
 85 90 95

Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr Tyr

			100					105						110		
Ala	Val	Ala	Val	Val	Lys	Lys	Gly	Gly	Ser	Phe	Gln	Leu	Asn	Glu	Leu	
		115					120					125				
Gln	Gly	Leu	Lys	Ser	Cys	His	Thr	Gly	Leu	Arg	Arg	Thr	Ala	Gly	Trp	
	130					135					140					
Asn	Val	Pro	Ile	Gly	Thr	Leu	Arg	Pro	Phe	Leu	Asn	Trp	Thr	Gly	Pro	
145					150					155					160	
Pro	Glu	Pro	Ile	Glu	Ala	Ala	Val	Ala	Arg	Phe	Phe	Ser	Ala	Ser	Cys	
				165					170					175		
Val	Pro	Gly	Ala	Asp	Lys	Gly	Gln	Phe	Pro	Asn	Leu	Cys	Arg	Leu	Cys	
			180					185					190			
Ala	Gly	Thr	Gly	Glu	Asn	Lys	Cys	Ala	Phe	Ser	Ser	Gln	Glu	Pro	Tyr	
		195					200					205				
Phe	Ser	Tyr	Ser	Gly	Ala	Phe	Lys	Cys	Leu	Arg	Asp	Gly	Ala	Gly	Asp	
	210					215					220					
Val	Ala	Phe	Ile	Arg	Glu	Ser	Thr	Val	Phe	Glu	Asp	Leu	Ser	Asp	Glu	
225					230					235					240	
Ala	Glu	Arg	Asp	Glu	Tyr	Glu	Leu	Leu	Cys	Pro	Asp	Asn	Thr	Arg	Lys	
				245					250					255		
Pro	Val	Asp	Lys	Phe	Lys	Asp	Cys	His	Leu	Ala	Arg	Val	Pro	Ser	His	
			260					265					270			
Ala	Val	Val	Ala	Arg	Ser	Val	Asn	Gly	Lys	Glu	Asp	Ala	Ile	Trp	Asn	
		275					280					285				
Leu	Leu	Arg	Gln	Ala	Gln	Glu	Lys	Phe	Gly	Lys	Asp	Lys	Ser	Pro	Lys	
	290					295					300					
Phe	Gln	Leu	Phe	Gly	Ser	Pro	Ser	Gly	Gln	Lys	Asp	Leu	Leu	Phe	Lys	
305					310					315					320	
Asp	Ser	Ala	Ile	Gly	Phe	Ser	Arg	Val	Pro	Pro	Arg	Ile	Asp	Ser	Gly	
				325					330					335		
Leu	Tyr	Leu	Gly	Ser	Gly	Tyr	Phe	Thr	Ala	Ile	Gln	Asn	Leu	Arg	Lys	
			340					345					350			
Ser	Glu	Glu	Glu	Val	Ala	Ala	Arg	Arg	Ala	Arg	Val	Val	Trp	Cys	Ala	
		355					360					365				
Val	Gly	Glu	Gln	Glu	Leu	Arg	Lys	Cys	Asn	Gln	Trp	Ser	Gly	Leu	Ser	
	370					375					380					
Glu	Gly	Ser	Val	Thr	Cys	Ser	Ser	Ala	Ser	Thr	Thr	Glu	Asp	Cys	Ile	
385					390					395					400	
Ala	Leu	Val	Leu	Lys	Gly	Glu	Ala	Asp	Ala	Met	Ser	Leu	Asp	Gly	Gly	

				405					410					415		
Tyr	Val	Tyr	Thr	Ala	Gly	Lys	Cys	Gly	Leu	Val	Pro	Val	Leu	Ala	Glu	
			420					425					430			
Asn	Tyr	Lys	Ser	Gln	Gln	Ser	Ser	Asp	Pro	Asp	Pro	Asn	Cys	Val	Asp	
		435					440					445				
Arg	Pro	Val	Glu	Gly	Tyr	Leu	Ala	Val	Ala	Val	Val	Arg	Arg	Ser	Asp	
	450					455					460					
Thr	Ser	Leu	Thr	Trp	Asn	Ser	Val	Lys	Gly	Lys	Lys	Ser	Cys	His	Thr	
465					470					475					480	
Ala	Val	Asp	Arg	Thr	Ala	Gly	Trp	Asn	Ile	Pro	Met	Gly	Leu	Leu	Phe	
				485					490						495	
Asn	Gln	Thr	Gly	Ser	Cys	Lys	Phe	Asp	Glu	Tyr	Phe	Ser	Gln	Ser	Cys	
			500					505					510			
Ala	Pro	Gly	Ser	Asp	Pro	Arg	Ser	Asn	Leu	Cys	Ala	Leu	Cys	Ile	Gly	
		515					520					525				
Asp	Glu	Gln	Gly	Glu	Asn	Lys	Cys	Val	Pro	Asn	Ser	Asn	Glu	Arg	Tyr	
	530					535					540					
Tyr	Gly	Tyr	Thr	Gly	Ala	Phe	Arg	Cys	Leu	Ala	Glu	Asn	Ala	Gly	Asp	
545					550					555					560	
Val	Ala	Phe	Val	Lys	Asp	Val	Thr	Val	Leu	Gln	Asn	Thr	Asp	Gly	Asn	
				565					570					575		
Asn	Asn	Glu	Ala	Trp	Ala	Lys	Asp	Leu	Lys	Leu	Ala	Asp	Phe	Ala	Leu	
			580					585					590			
Leu	Cys	Leu	Asp	Gly	Lys	Arg	Lys	Pro	Val	Thr	Glu	Ala	Arg	Ser	Cys	
		595					600					605				
His	Leu	Ala	Met	Ala	Pro	Asn	His	Ala	Val	Val	Ser	Arg	Met	Asp	Lys	
	610					615					620					
Val	Glu	Arg	Leu	Lys	Gln	Val	Leu	Leu	His	Gln	Gln	Ala	Lys	Phe	Gly	
625					630					635					640	
Arg	Asn	Gly	Ser	Asp	Cys	Pro	Asp	Lys	Phe	Cys	Leu	Phe	Gln	Ser	Glu	
				645					650					655		
Thr	Lys	Asn	Leu	Leu	Phe	Asn	Asp	Asn	Thr	Glu	Cys	Leu	Ala	Arg	Leu	
			660					665					670			
His	Gly	Lys	Thr	Thr	Tyr	Glu	Lys	Tyr	Leu	Gly	Pro	Gln	Tyr	Val	Ala	
		675					680					685				
Gly	Ile	Thr	Asn	Leu	Lys	Lys	Cys	Ser	Thr	Ser	Pro	Leu	Leu	Glu	Ala	
	690					695					700					
Cys	Glu	Phe	Leu	Arg	Lys											

705

710

<210> 34
 <211> 711
 <212> PRT
 <213> HUMAN

<400> 34

Met Lys Leu Val Phe Leu Val Leu Leu Phe Leu Gly Ala Leu Gly Leu
 1 5 10 15
 Cys Leu Ala Gly Arg Arg Arg Arg Ser Val Gln Trp Cys Ala Val Ser
 20 25 30
 Gln Pro Glu Ala Thr Lys Cys Phe Gln Trp Gln Arg Asn Met Arg Lys
 35 40 45
 Val Arg Gly Pro Pro Val Ser Cys Ile Lys Arg Asp Ser Pro Ile Gln
 50 55 60
 Cys Ile Gln Ala Ile Ala Glu Asn Arg Ala Asp Ala Val Thr Leu Asp
 65 70 75 80
 Gly Gly Phe Ile Tyr Glu Ala Gly Leu Ala Pro Tyr Lys Leu Arg Pro
 85 90 95
 Val Ala Ala Glu Val Tyr Gly Thr Glu Arg Gln Pro Arg Thr His Tyr
 100 105 110
 Tyr Ala Val Ala Val Val Lys Lys Gly Gly Ser Phe Gln Leu Asn Glu
 115 120 125
 Leu Gln Gly Leu Lys Ser Cys His Thr Gly Leu Arg Arg Thr Ala Gly
 130 135 140
 Trp Asn Val Pro Ile Gly Thr Leu Arg Pro Phe Leu Asn Trp Thr Gly
 145 150 155 160
 Pro Pro Glu Pro Ile Glu Ala Ala Val Ala Arg Phe Phe Ser Ala Ser
 165 170 175
 Cys Val Pro Gly Ala Asp Lys Gly Gln Phe Pro Asn Leu Cys Arg Leu
 180 185 190
 Cys Ala Gly Thr Gly Glu Asn Lys Cys Ala Phe Ser Ser Gln Glu Pro
 195 200 205
 Tyr Phe Ser Tyr Ser Gly Ala Phe Lys Cys Leu Arg Asp Gly Ala Gly
 210 215 220
 Asp Val Ala Phe Ile Arg Glu Ser Thr Val Phe Glu Asp Leu Ser Asp
 225 230 235 240
 Glu Ala Glu Arg Asp Glu Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg
 245 250 255

Lys Pro Val Asp Lys Phe Lys Asp Cys His Leu Ala Arg Val Pro Ser
 260 265 270
 His Ala Val Val Ala Arg Ser Val Asn Gly Lys Glu Asp Ala Ile Trp
 275 280 285
 Asn Leu Leu Arg Gln Ala Gln Glu Lys Phe Gly Lys Asp Lys Ser Pro
 290 295 300
 Lys Phe Gln Leu Phe Gly Ser Pro Ser Gly Gln Lys Asp Leu Leu Phe
 305 310 315 320
 Lys Asp Ser Ala Ile Gly Phe Ser Arg Val Pro Pro Arg Ile Asp Ser
 325 330 335
 Gly Leu Tyr Leu Gly Ser Gly Tyr Phe Thr Ala Ile Gln Asn Leu Arg
 340 345 350
 Lys Ser Glu Glu Glu Val Ala Ala Arg Arg Ala Arg Val Val Trp Cys
 355 360 365
 Ala Val Gly Glu Gln Glu Leu Arg Lys Cys Asn Gln Trp Ser Gly Leu
 370 375 380
 Ser Glu Gly Ser Val Thr Cys Ser Ser Ala Ser Thr Thr Glu Asp Cys
 385 390 395 400
 Ile Ala Leu Val Leu Lys Gly Glu Ala Asp Ala Met Ser Leu Asp Glu
 405 410 415
 Gly Tyr Val Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala
 420 425 430
 Glu Asn Tyr Lys Ser Gln Gln Ser Ser Asp Pro Asp Pro Asn Cys Val
 435 440 445
 Asp Arg Pro Val Glu Gly Tyr Leu Ala Val Ala Val Val Arg Arg Ser
 450 455 460
 Asp Thr Ser Leu Thr Trp Asn Ser Val Lys Gly Lys Lys Ser Cys His
 465 470 475 480
 Thr Ala Val Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Leu
 485 490 495
 Phe Asn Gln Thr Gly Ser Cys Lys Phe Asp Glu Tyr Phe Ser Gln Ser
 500 505 510
 Cys Ala Pro Gly Ser Asp Pro Arg Ser Asn Leu Cys Ala Leu Cys Ile
 515 520 525
 Gly Asp Glu Gln Gly Glu Asn Lys Cys Val Pro Asn Ser Asn Glu Arg
 530 535 540
 Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asn Ala Gly
 545 550 555 560

Asp Val Ala Phe Val Lys Asp Val Thr Val Leu Gln Asn Thr Asp Gly
 565 570 575

Asn Asn Asn Glu Ala Trp Ala Lys Asp Leu Lys Leu Ala Asp Phe Ala
 580 585 590

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

Cys His Leu Ala Met Ala Pro Asn His Ala Val Val Ser Arg Met Asp
 610 615 620

Lys Val Glu Arg Leu Lys Gln Val Leu Leu His Gln Gln Ala Lys Phe
 625 630 635 640

Gly Arg Asn Gly Ser Asp Cys Pro Asp Lys Phe Cys Leu Phe Gln Ser
 645 650 655

Glu Thr Lys Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Arg
 660 665 670

Leu His Gly Lys Thr Thr Tyr Glu Lys Tyr Leu Gly Pro Gln Tyr Val
 675 680 685

Ala Gly Ile Thr Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu
 690 695 700

Ala Cys Glu Phe Leu Arg Lys
 705 710

<210> 35
 <211> 708
 <212> PRT
 <213> COW

<400> 35
 Met Lys Leu Phe Val Pro Ala Leu Leu Ser Leu Gly Ala Leu Gly Leu
 1 5 10 15

Cys Leu Ala Ala Pro Arg Lys Asn Val Arg Trp Cys Thr Ile Ser Gln
 20 25 30

Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu
 35 40 45

Gly Ala Pro Ser Ile Thr Cys Val Arg Arg Ala Phe Ala Leu Glu Cys
 50 55 60

Ile Arg Ala Ile Ala Glu Lys Lys Ala Asp Ala Val Thr Leu Asp Gly
 65 70 75 80

Gly Met Val Phe Glu Ala Gly Arg Asp Pro Tyr Lys Leu Arg Pro Val
 85 90 95

Ala Ala Glu Ile Tyr Gly Thr Lys Glu Ser Pro Gln Thr His Tyr Tyr
 100 105 110

Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Gln Leu Asp Gln Leu
115 120 125

Gln Gly Arg Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
130 135 140

Val Ile Pro Met Gly Ile Leu Arg Pro Tyr Leu Ser Trp Thr Glu Ser
145 150 155 160

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

Val Pro Cys Ile Asp Arg Gln Ala Tyr Pro Asn Leu Cys Gln Leu Cys
180 185 190

Lys Gly Glu Gly Glu Asn Gln Cys Ala Cys Ser Ser Arg Glu Pro Tyr
195 200 205

Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
210 215 220

Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys
225 230 235 240

Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Ser Arg Ala
245 250 255

Pro Val Asp Ala Phe Lys Glu Cys His Leu Ala Gln Val Pro Ser His
260 265 270

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

Leu Leu Ser Lys Ala Gln Glu Lys Phe Gly Lys Asn Lys Ser Arg Ser
290 295 300

Phe Gln Leu Phe Gly Ser Pro Pro Gly Gln Arg Asp Leu Leu Phe Lys
305 310 315 320

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

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

Thr Ala Glu Glu Val Lys Ala Arg Tyr Thr Arg Val Val Trp Cys Ala
355 360 365

Val Gly Pro Glu Glu Gln Lys Lys Cys Gln Gln Trp Ser Gln Gln Ser
370 375 380

Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile
385 390 395 400

Val Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Asn Leu Asp Gly Gly
405 410 415

Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu
 420 425 430
 Asn Arg Lys Thr Ser Lys Tyr Ser Ser Leu Asp Cys Val Leu Arg Pro
 435 440 445
 Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly
 450 455 460
 Leu Thr Trp Asn Ser Leu Lys Asp Lys Lys Ser Cys His Thr Ala Val
 465 470 475 480
 Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Val Asn Gln
 485 490 495
 Thr Gly Ser Cys Ala Phe Asp Glu Phe Phe Ser Gln Ser Cys Ala Pro
 500 505 510
 Gly Arg Asp Pro Lys Ser Arg Leu Cys Ala Leu Cys Ala Gly Asp Asp
 515 520 525
 Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540
 Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560
 Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Thr
 565 570 575
 Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590
 Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala Gln Ser Cys His Leu
 595 600 605
 Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ser Asp Arg Ala Ala
 610 615 620
 His Val Lys Gln Val Leu Leu His Gln Gln Ala Leu Phe Gly Lys Asn
 625 630 635 640
 Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe Lys Ser Glu Thr Lys
 645 650 655
 Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
 660 665 670
 Arg Pro Thr Tyr Glu Glu Tyr Leu Gly Thr Glu Tyr Val Thr Ala Ile
 675 680 685
 Ala Asn Leu Lys Lys Cys Ser Thr Ser Pro Leu Leu Glu Ala Cys Ala
 690 695 700
 Phe Leu Thr Arg
 705

<210> 36
 <211> 686
 <212> PRT
 <213> PIG

<400> 36

Met Lys Leu Phe Ile Pro Ala Leu Leu Phe Leu Trp Thr Leu Gly Leu
 1 5 10 15
 Cys Leu Ala Ala Pro Lys Lys Gly Val Arg Trp Cys Val Ile Ser Thr
 20 25 30
 Ala Glu Tyr Ser Lys Cys Arg Gln Trp Gln Ser Lys Ile Arg Arg Thr
 35 40 45
 Asn Pro Ile Phe Cys Ile Arg Arg Ala Ser Pro Thr Asp Cys Ile Arg
 50 55 60
 Ala Ile Ala Ala Lys Arg Ala Asp Ala Val Thr Leu Asp Gly Gly Leu
 65 70 75 80
 Val Phe Glu Ala Gly Gln Tyr Lys Leu Arg Pro Val Ala Ala Glu Ile
 85 90 95
 Tyr Gly Thr Glu Glu Asn Pro Gln Thr Tyr Tyr Tyr Ala Val Ala Val
 100 105 110
 Val Lys Lys Gly Phe Asn Phe Gln Leu Asn Gln Leu Gln Gly Arg Lys
 115 120 125
 Ser Cys His Ile Gly Leu Gly Arg Ser Ala Gly Trp Asn Ile Pro Ile
 130 135 140
 Gly Leu Leu Arg Arg Phe Leu Asp Trp Ala Gly Pro Pro Glu Pro Leu
 145 150 155 160
 Gln Lys Ala Val Ala Lys Phe Phe Ser Gln Ser Cys Val Pro Cys Ala
 165 170 175
 Asp Gly Asn Ala Tyr Pro Asn Leu Cys Gln Leu Cys Ile Gly Lys Gly
 180 185 190
 Lys Asp Lys Cys Ala Cys Ser Ser Gln Glu Pro Tyr Phe Gly Tyr Ser
 195 200 205
 Gly Ala Phe Asn Cys Leu His Lys Gly Ile Gly Asp Val Ala Phe Val
 210 215 220
 Lys Glu Ser Thr Val Phe Glu Asn Leu Pro Gln Lys Ala Asp Arg Asp
 225 230 235 240
 Lys Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg Lys Pro Val Glu Ala
 245 250 255
 Phe Arg Glu Cys His Leu Ala Arg Val Pro Ser His Ala Val Val Ala

			260					265					270			
Arg	Ser	Val	Asn	Gly	Lys	Glu	Asn	Ser	Ile	Trp	Ser	Leu	Leu	Tyr	Gln	
		275					280					285				
Ser	Gln	Lys	Lys	Phe	Gly	Lys	Ser	Asn	Pro	Gln	Glu	Phe	Gln	Leu	Phe	
	290					295					300					
Gly	Ser	Pro	Gly	Gln	Gln	Lys	Asp	Leu	Leu	Phe	Arg	Asp	Ala	Thr	Ile	
305					310					315					320	
Gly	Phe	Leu	Lys	Ile	Pro	Ser	Lys	Ile	Asp	Ser	Lys	Leu	Tyr	Leu	Gly	
				325					330						335	
Leu	Pro	Tyr	Leu	Thr	Ala	Ile	Gln	Gly	Leu	Arg	Glu	Thr	Ala	Ala	Glu	
			340					345					350			
Val	Glu	Ala	Arg	Gln	Ala	Lys	Val	Val	Trp	Cys	Ala	Val	Gly	Pro	Glu	
		355					360					365				
Glu	Leu	Arg	Lys	Cys	Arg	Gln	Trp	Ser	Ser	Gln	Ser	Ser	Gln	Asn	Leu	
	370					375					380					
Asn	Cys	Ser	Leu	Ala	Ser	Thr	Thr	Glu	Asp	Cys	Ile	Val	Gln	Val	Leu	
385					390					395					400	
Lys	Gly	Glu	Ala	Asp	Ala	Met	Ser	Leu	Asp	Gly	Gly	Phe	Ile	Tyr	Thr	
				405					410					415		
Ala	Gly	Lys	Cys	Gly	Leu	Val	Pro	Val	Leu	Ala	Glu	Asn	Gln	Lys	Ser	
			420					425					430			
Arg	Gln	Ser	Ser	Ser	Ser	Asp	Cys	Val	His	Arg	Pro	Thr	Gln	Gly	Tyr	
		435					440					445				
Phe	Ala	Val	Ala	Val	Val	Arg	Lys	Ala	Asn	Gly	Gly	Ile	Thr	Trp	Asn	
	450					455					460					
Ser	Val	Arg	Gly	Thr	Lys	Ser	Cys	His	Thr	Ala	Val	Asp	Arg	Thr	Ala	
465					470					475					480	
Gly	Trp	Asn	Ile	Pro	Met	Gly	Leu	Leu	Val	Asn	Gln	Thr	Gly	Ser	Cys	
				485					490					495		
Lys	Phe	Asp	Glu	Phe	Phe	Ser	Gln	Ser	Cys	Ala	Pro	Gly	Ser	Gln	Pro	
			500					505					510			
Gly	Ser	Asn	Leu	Cys	Ala	Leu	Cys	Val	Gly	Asn	Asp	Gln	Gly	Val	Asp	
		515					520					525				
Lys	Cys	Val	Pro	Asn	Ser	Asn	Glu	Arg	Tyr	Tyr	Gly	Tyr	Thr	Gly	Ala	
	530					535					540					
Phe	Arg	Cys	Leu	Ala	Glu	Asn	Ala	Gly	Asp	Val	Ala	Phe	Val	Lys	Asp	
545					550					555					560	
Val	Thr	Val	Leu	Asp	Asn	Thr	Asn	Gly	Gln	Asn	Thr	Gln	Glu	Trp	Ala	

				565					570					575			
Arg	Glu	Leu	Arg	Ser	Asp	Asp	Phe	Glu	Leu	Leu	Cys	Leu	Asn	Gly	Thr		
			580					585					590				
Arg	Lys	Pro	Val	Thr	Glu	Ala	Gln	Asn	Cys	His	Leu	Ala	Val	Ala	Pro		
		595					600					605					
Ser	His	Ala	Val	Val	Ser	Arg	Lys	Glu	Lys	Ala	Ala	Gln	Val	Glu	Gln		
	610					615					620						
Met	Leu	Leu	Thr	Glu	Gln	Ala	Gln	Phe	Gly	Arg	Tyr	Gly	Lys	Asp	Cys		
625					630					635					640		
Pro	Asp	Lys	Phe	Cys	Leu	Phe	Arg	Ser	Glu	Thr	Lys	Asn	Leu	Leu	Phe		
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Asn	Asp	Asn	Thr	Glu	Cys	Leu	Ala	Gln	Leu	Gln	Gly	Lys	Thr	Thr	Tyr		
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Cys	Leu	Ala	Ala	Pro	Lys	Lys	Gly	Val	Arg	Trp	Cys	Val	Ile	Ser	Thr		
		20						25					30				
Ala	Glu	Tyr	Ser	Lys	Cys	Arg	Gln	Trp	Gln	Ser	Lys	Ile	Arg	Arg	Thr		
		35					40					45					
Asn	Pro	Met	Phe	Cys	Ile	Arg	Arg	Ala	Ser	Pro	Thr	Asp	Cys	Ile	Arg		
		50				55					60						
Ala	Ile	Ala	Ala	Lys	Arg	Ala	Asp	Ala	Val	Thr	Leu	Asp	Gly	Gly	Leu		
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Val	Phe	Glu	Ala	Asp	Gln	Tyr	Lys	Leu	Arg	Pro	Val	Ala	Ala	Glu	Ile		
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Tyr	Gly	Thr	Glu	Glu	Asn	Pro	Gln	Thr	Tyr	Tyr	Tyr	Ala	Val	Ala	Val		
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Val	Lys	Lys	Gly	Phe	Asn	Phe	Gln	Asn	Gln	Leu	Gln	Gly	Arg	Lys	Ser		
		115					120					125					
Cys	His	Thr	Gly	Leu	Gly	Arg	Ser	Ala	Gly	Trp	Asn	Ile	Pro	Ile	Gly		
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Lys Ala Val Ala Lys Phe Phe Ser Gln Ser Cys Val Pro Cys Ala Asp
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Gly Asn Ala Tyr Pro Asn Leu Cys Gln Leu Cys Ile Gly Lys Gly Lys
 180 185 190

Asp Lys Cys Ala Cys Ser Ser Gln Glu Pro Tyr Phe Gly Tyr Ser Gly
 195 200 205

Ala Phe Asn Cys Leu His Lys Gly Ile Gly Asp Val Ala Phe Val Lys
 210 215 220

Glu Ser Thr Val Phe Glu Asn Leu Pro Gln Lys Ala Asp Arg Asp Lys
 225 230 235 240

Tyr Glu Leu Leu Cys Pro Asp Asn Thr Arg Lys Pro Val Glu Ala Phe
 245 250 255

Arg Glu Cys His Leu Ala Arg Val Pro Ser His Ala Val Val Ala Arg
 260 265 270

Ser Val Asn Gly Lys Glu Asn Ser Ile Trp Glu Leu Leu Tyr Gln Ser
 275 280 285

Gln Lys Lys Phe Gly Lys Ser Asn Pro Gln Glu Phe Gln Leu Phe Gly
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Ser Pro Gly Gln Gln Lys Asp Leu Leu Phe Arg Asp Ala Thr Ile Gly
 305 310 315 320

Phe Leu Lys Ile Pro Ser Lys Ile Asp Ser Lys Leu Tyr Leu Gly Leu
 325 330 335

Pro Tyr Leu Thr Ala Ile Gln Gly Leu Arg Glu Thr Ala Ala Glu Val
 340 345 350

Glu Ala Arg Gln Ala Lys Val Val Trp Cys Ala Val Gly Pro Glu Glu
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Leu Arg Lys Cys Arg Gln Trp Ser Ser Gln Ser Ser Gln Asn Leu Asn
 370 375 380

Cys Ser Leu Ala Ser Thr Thr Glu Asp Cys Ile Val Gln Val Leu Lys
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Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Phe Ile Tyr Thr Ala
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Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Gln Lys Ser Arg
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Gln Ser Ser Ser Ser Asp Cys Val His Arg Pro Thr Gln Gly Tyr Phe
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Ala Val Ala Val Val Arg Lys Ala Asn Gly Gly Ile Thr Trp Asn Ser
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Val Arg Gly Thr Lys Ser Cys His Thr Ala Val Asp Arg Thr Ala Gly
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Trp Asn Ile Pro Met Gly Leu Leu Val Asn Gln Thr Gly Ser Cys Lys
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Phe Asp Glu Phe Phe Ser Gln Ser Cys Ala Pro Gly Ser Gln Pro Gly
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Ser Asn Leu Cys Ala Leu Cys Val Gly Asn Asp Gln Gly Val Asp Lys
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Cys Val Pro Asn Ser Asn Glu Arg Tyr Tyr Gly Tyr Thr Gly Ala Phe
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Arg Cys Leu Ala Glu Asn Ala Gly Asp Val Ala Phe Val Lys Asp Val
 545 550 555 560

Thr Val Leu Asp Asn Thr Asn Gly Gln Asn Thr Glu Glu Trp Ala Arg
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Glu Leu Arg Ser Asp Asp Phe Glu Leu Leu Cys Leu Asp Gly Thr Arg
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Lys Pro Val Thr Glu Ala Gln Asn Cys His Leu Ala Val Ala Pro Ser
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His Ala Val Val Ser Arg Lys Glu Lys Ala Ala Gln Val Glu Gln Val
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Leu Leu Thr Glu Gln Ala Gln Phe Gly Arg Tyr Gly Lys Asp Cys Pro
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Asp Lys Phe Cys Leu Phe Arg Ser Glu Thr Lys Asn Leu Leu Phe Asn
 645 650 655

Asp Asn Thr Glu Val Leu Ala Gln Leu Gln Gly Lys Thr Thr Tyr Glu
 660 665 670

Lys Tyr Leu Gly Ser Glu Tyr Val Thr Ala Ile Ala Asn Leu Lys Gln
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 Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu
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 Gly Ala Pro Ser Ile Thr Cys Val Arg Arg Ala Phe Ala Leu Glu Cys
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 Ile Pro Gly Ile Ala Glu Lys Lys Ala Asp Ala Val Thr Leu Asp Gly
 65 70 75 80
 Gly Met Val Phe Glu Ala Gly Arg Asp Pro Tyr Lys Leu Arg Pro Val
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 Ala Ala Glu Ile Tyr Gly Thr Lys Glu Ser Pro Gln Thr His Tyr Tyr
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 Ala Val Ala Val Val Lys Lys Gly Ser Asn Phe Gln Leu Asp Gln Leu
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 Gln Gly Arg Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
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 Ile Ile Pro Met Gly Ile Leu Arg Pro Tyr Leu Ser Trp Thr Glu Ser
 145 150 155 160
 Leu Glu Pro Leu Gln Gly Ala Val Ala Lys Phe Phe Ser Ala Ser Cys
 165 170 175
 Val Pro Cys Ile Asp Arg Gln Ala Tyr Pro Asn Leu Cys Gln Leu Cys
 180 185 190
 Lys Gly Glu Gly Glu Asn Gln Cys Ala Cys Ser Ser Arg Glu Pro Tyr
 195 200 205
 Phe Gly Tyr Ser Gly Ala Phe Lys Cys Leu Gln Asp Gly Ala Gly Asp
 210 215 220
 Val Ala Phe Val Lys Glu Thr Thr Val Phe Glu Asn Leu Pro Glu Lys
 225 230 235 240
 Ala Asp Arg Asp Gln Tyr Glu Leu Leu Cys Leu Asn Asn Ser Arg Ala
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 Pro Val Asp Ala Phe Lys Glu Cys His Leu Ala Gln Val Pro Ser His
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 Ala Val Val Ala Arg Ser Val Asp Gly Lys Glu Asp Leu Ile Trp Lys
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 Leu Leu Ser Lys Ala Gln Glu Lys Ser Gly Lys Asn Lys Ser Arg Ser
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 305 310 315 320

Asp Ser Ala Leu Gly Phe Leu Arg Ile Pro Ser Lys Val Asp Ser Ala
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 Thr Ala Glu Glu Val Lys Ala Arg Tyr Thr Arg Val Val Trp Cys Ala
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 Val Gly Pro Glu Glu Gln Lys Lys Cys Gln Gln Trp Ser Gln Gln Ser
 370 375 380
 Gly Gln Asn Val Thr Cys Ala Thr Ala Ser Thr Thr Asp Asp Cys Ile
 385 390 395 400
 Val Leu Val Leu Lys Gly Glu Ala Asp Ala Leu Asn Leu Asp Gly Gly
 405 410 415
 Tyr Ile Tyr Thr Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu
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 Asn Arg Lys Ser Ser Lys His Ser Ser Leu Asp Cys Val Leu Arg Pro
 435 440 445
 Thr Glu Gly Tyr Leu Ala Val Ala Val Val Lys Lys Ala Asn Glu Gly
 450 455 460
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 465 470 475 480
 Asp Arg Thr Ala Gly Trp Asn Ile Pro Met Gly Leu Ile Val Asn Gln
 485 490 495
 Thr Gly Ser Cys Ala Phe Asp Glu Phe Phe Ser Gln Ser Cys Ala Pro
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 Gln Gly Leu Asp Lys Cys Val Pro Asn Ser Lys Glu Lys Tyr Tyr Gly
 530 535 540
 Tyr Thr Gly Ala Phe Arg Cys Leu Ala Glu Asp Val Gly Asp Val Ala
 545 550 555 560
 Phe Val Lys Asn Asp Thr Val Trp Glu Asn Thr Asn Gly Glu Ser Thr
 565 570 575
 Ala Asp Trp Ala Lys Asn Leu Asn Arg Glu Asp Phe Arg Leu Leu Cys
 580 585 590
 Leu Asp Gly Thr Arg Lys Pro Val Thr Glu Ala Gln Ser Cys His Leu
 595 600 605
 Ala Val Ala Pro Asn His Ala Val Val Ser Arg Ser Asp Arg Ala Ala
 610 615 620

His Val Lys Gln Val Leu Leu His Gln Gln Ala Leu Phe Gly Lys Asn
625 630 635 640

Gly Lys Asn Cys Pro Asp Lys Phe Cys Leu Phe Lys Ser Glu Thr Lys
645 650 655

Asn Leu Leu Phe Asn Asp Asn Thr Glu Cys Leu Ala Lys Leu Gly Gly
660 665 670

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

Pro Glu Trp Phe Lys Cys Arg Arg Trp Gln Trp Arg Met Lys Lys Leu
35 40 45

Gly Ala Pro Ser Ile Thr Cys Val Arg Arg Ala Phe Ala Leu Glu Cys
50 55 60

Ile Arg Ala Ile Ala Glu Lys Lys Ala Asp Ala Val Thr Leu Asp Gly
65 70 75 80

Gly Met Val Phe Glu Ala Gly Arg Asp Pro Tyr Lys Leu Arg Pro Val
85 90 95

Ala Ala Glu Ile Tyr Gly Thr Lys Glu Ser Pro Gln Thr His Tyr Tyr
100 105 110

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

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