PEPTIDES AND PEPTIDE MIMETICS TO TREAT PATHOLOGIES CHARACTERIZED BY AN INFLAMMATORY RESPONSE

[0001] This application claims priority to and benefit of USSN 60/697,495, filed July 7, 2005 and to USSN 60/676,431 filed on April 29, 2005, both of which are incorporated herein by reference in their entirety for all purposes.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This work was supported, in part, by Grant No: HL30568 from the National Heart Blood Lung Institute of the National Institutes of Health. The Government of the United States of America may have certain rights in this invention.

FIELD OF THE INVENTION

[0003] This invention relates to the field of atherosclerosis and other conditions characterized by inflammation and/or the formation of various oxidized species. In particular, this invention pertains to the identification of classes of active agents that are orally administrable and that ameliorate one or more symptoms of conditions characterized by an inflammatory response and/or the formation of various oxidized species.

BACKGROUND OF THE INVENTION

[0004] The introduction of statins (*e.g.*, Mevacor®, Lipitor®, *etc.*) has reduced mortality from heart attack and stroke by about one-third. However, heart attack and stroke remain the major cause of death and disability, particularly in the United States and in Western European countries. Heart attack and stroke are the result of a chronic inflammatory condition, which is called atherosclerosis.

[0005] Several causative factors are implicated in the development of cardiovascular disease including hereditary predisposition to the disease, gender, lifestyle factors such as smoking and diet, age, hypertension, and hyperlipidemia, including hypercholesterolemia. Several of these factors, particularly hyperlipidemia and hypercholesteremia (high blood cholesterol concentrations) provide a significant risk factor associated with atherosclerosis.

[0006] Cholesterol is present in the blood as free and esterified cholesterol within lipoprotein particles, commonly known as chylomicrons, very low density lipoproteins (VLDLs), low density lipoproteins (LDLs), and high density lipoproteins (HDLs). Concentration of total cholesterol in the blood is influenced by (1) absorption of cholesterol from the digestive tract, (2) synthesis of cholesterol from dietary constituents such as carbohydrates, proteins, fats and ethanol, and (3) removal of cholesterol from blood by tissues, especially the liver, and subsequent conversion of the cholesterol to bile acids, steroid hormones, and biliary cholesterol.

[0007] Maintenance of blood cholesterol concentrations is influenced by both genetic and environmental factors. Genetic factors include concentration of rate-limiting enzymes in cholesterol biosynthesis, concentration of receptors for low density lipoproteins in the liver, concentration of rate-limiting enzymes for conversion of cholesterols bile acids, rates of synthesis and secretion of lipoproteins and gender of person. Environmental factors influencing the hemostasis of blood cholesterol concentration in humans include dietary composition, incidence of smoking, physical activity, and use of a variety of pharmaceutical agents. Dietary variables include the amount and type of fat (saturated and polyunsaturated fatty acids), the amount of cholesterol, amount and type of fiber, and perhaps the amounts of vitamins such as vitamin C and D and minerals such as calcium.

[0008] Low density lipoprotein (LDL) oxidation has been strongly implicated in the pathogenesis of atherosclerosis. High density lipoprotein (HDL) has been found to be capable of protecting against LDL oxidation, but in some instances has been found to accelerate LDL oxidation. Important initiating factors in atherosclerosis include the production of LDL-derived oxidized phospholipids.

[0009] Normal HDL has the capacity to prevent the formation of these oxidized phospholipids and also to inactivate these oxidized phospholipids once they have formed. However, under some circumstances HDL can be converted from an anti-inflammatory molecule to a pro-inflammatory molecule that actually promotes the formation of these oxidized phospholipids.

[0010] It has been suggested that HDL and LDL function as part of the innate immune system (Navab *et al.* (2001) *Arterioscler. Thromb. Vasc. Biol.*, 21: 481-488). The generation of anti-inflammatory HDL has been achieved using class A amphipathic helical

peptides that mimic the major protein of HDL, apolipoprotein A-I (apo A-I) (*see, e.g.,* WO 02/15923).

SUMMARY OF THE INVENTION

[0011] This invention provides novel compositions and methods to ameliorate one or more symptoms of a vascular condition and/or a condition characterized by an inflammatory response and/or a condition characterized by the formation of oxidized reactive species in a mammal. The methods involve administration to a mammal (*e.g.* a human in need thereof) one or more of the active agents (*e.g.*, class A amphipathic helical peptides, certain tripeptides, tetrapeptides, pentapeptides, and amino acid pairs, certain Apo-J (G*) peptides, and certain small organic molecules.

[0012] In certain embodiments, this invention provides a peptide that ameliorates a symptom of atherosclerosis, wherein said peptide comprises the amino acid sequence or the retro amino acid sequence of a peptide listed in peptide listed in any of Tables 2-18 (*e.g.*, Table 4, Table 5, or Table 6, *etc.*). In certain embodiments the peptide(s) further comprise a protecting group coupled to the amino or carboxyl terminus. In certain embodiments the peptides comprise a first protecting group coupled to the amino terminus and a second protecting group coupled to the carboxyl terminus. In certain embodiments the protecting groups can be independently selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

[0013] In certain embodiments the peptide comprises a protecting group coupled to the amino terminal and the amino terminal protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl. In

certain embodiments the peptide comprises a protecting group coupled to the carboxyl terminal and the carboxyl terminal protecting group is an amide. In certain embodiments the peptide comprises: a first protecting group coupled to the amino terminus where the protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl; and a second protecting group coupled to the carboxyl terminal and the carboxyl terminal protecting group is an amide.

[0014] In various embodiments one or more amino acids comprising the peptide are "D" amino acids. In various embodiments, all amino acids comprising the peptide "D" amino acids. The peptide(s) can, optionally, be mixed/combined with a pharmacologically acceptable excipient. In certain embodiments the excipient is an excipient suitable for oral administration to a mammal.

[0015] In certain embodiments this invention provides methods of treating a vascular condition and/or a condition characterized by an inflammatory response and/or a condition characterized by the formation of oxidized reactive species in a mammal. The methods typically involve administering to a mammal in need thereof one or more of the active agents described in Tables 2-18 (*e.g.*, Table 4, Table 5, or Table 6, *etc.*), and/or a small organic molecule as described herein, in an amount sufficient to ameliorate one or more symptoms of the condition. In certain embodiments the active agent is a polypeptide comprising the amino acid sequence of 4F (SEQ ID NO:5). In certain embodiments the administration is by a route selected from the group consisting of oral administration, nasal administration, rectal administration, intraperitoneal injection, and intravascular injection, subcutaneous injection, transcutaneous administration, and intramuscular injection. In certain embodiments the active agent is administered in conjunction with a drug selected from the group consisting of CETP inhibitors, FTY720, Certican, DPP4 inhibitors, Calcium channel blockers, ApoA1 derivative or mimetic or agonist, PPAR agonists , Steroids, Gleevec, Cholesterol Absorption blockers (Zetia) , Vytorin, Any Renin Angiotensin pathway blockers, Angiotensin II receptor antagonist (Diovan etc), ACE inhibitors, Renin inhibitors, MR antagonist and Aldosterone synthase inhibitor, Beta-blockers, Alpha-adrenergic antagonists, LXR agonist, FXR agonist, Scavenger Receptor B1 agonist, ABCA1 agonist, Adiponectic receptor agonist or adiponectin inducers, Stearoyl-CoA Desaturase I (SCD1) inhibitor, Cholesterol synthesis inhibitors (non-statins), Diacylglycerol Acyltransferase I (DGAT1) inhibitor, Acetyl CoA Carboxylase 2 inhibitor, PAI-1 inhibitor, LP-PLA2 inhibitor, GLP-1, Glucokinase activator, CB-1

agonist, AGE inhibitor/breaker, PKC inhibitors, Anti-thrombotic/coagulants:, Aspirin, ADP receptor blockers *e.g.* Clopidigrel, Factor Xa inhibitor, GPIIb/IIIa inhibitor, Factor VIIa inhibitor, Warfarin, Low molecular weight heparin, Tissue factor inhibitor, Anti-inflammatory drugs:, Probucol and derivative *e.g.* AGI-1067 etc, CCR2 antagonist, CX3CR1 antagonist, IL-1 antagonist, Nitrates and NO donors, and Phosphodiesterase inhibitors.

[0016] Also provided is the use of a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6 in the treatment of a condition selected from the group consisting of atherosclerotic plaque formation, atherosclerotic lesion formation, myocardial infarction, stroke, congestive heart failure, arteriole function, arteriolar disease, arteriolar disease associated with aging, arteriolar disease associated with Alzheimer's disease, arteriolar disease associated with chronic kidney disease, arteriolar disease associated with hypertension, arteriolar disease associated with multi-infarct dementia, arteriolar disease associated with subarachnoid hemorrhage, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), , emphysema, asthma, idiopathic pulmonary fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, osteoporosis, Paget's disease , coronary calcification, rheumatoid arthritis, polyarteritis nodosa, polymyalgia rheumatica, lupus erythematosus, multiple sclerosis , Wegener's granulomatosis, central nervous system vasculitis (CNSV), Sjögren's syndrome, scleroderma, polymyositis., AIDS inflammatory response, bacterial infection, fungal infection, viral infection, parasitic infection, influenza, avian flu, viral pneumonia, endotoxic shock syndrome, sepsis , sepsis syndrome , trauma/wound, organ transplant, transplant atherosclerosis, transplant rejection , corneal ulcer, chronic/non-healing wound, ulcerative colitis, reperfusion injury (prevent and/or treat), ischemic reperfusion injury (prevent and/or treat), spinal cord injuries (mitigating effects) , cancers, myeloma/multiple myeloma, ovarian cancer, breast cancer, colon cancer, bone cancer, osteoarthritis, inflammatory bowel disease , allergic rhinitis, cachexia , diabetes , Alzheimer's disease , implanted prosthesis, biofilm formation, Crohns' disease, dermatitis, acute and chronic, eczema, psoriasis, contact dermatitis, scleroderma, Type I Diabetes, Type II Diabetes, juvenile onset diabetes, prevention of the onset of diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, erectile dysfunction, macular degeneration, multiple sclerosis, nephropathy, neuropathy, Parkinson's Disease, peripheral vascular disease, and meningitis.

[0017] In still another embodiment, this invention provides the use of a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6 for the manufacture of a medicament for the treatment of a condition selected from the group consisting of atherosclerotic plaque formation, atherosclerotic lesion formation, myocardial infarction, stroke, congestive heart failure, arteriole function, arteriolar disease, arteriolar disease associated with aging, arteriolar disease associated with Alzheimer's disease, arteriolar disease associated with chronic kidney disease, arteriolar disease associated with hypertension, arteriolar disease associated with multi-infarct dementia, arteriolar disease associated with subarachnoid hemorrhage, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), , emphysema, asthma, idiopathic pulmonary fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, osteoporosis, Paget's disease , coronary calcification, rheumatoid arthritis, polyarteritis nodosa, polymyalgia rheumatica, lupus erythematosus, multiple sclerosis , Wegener's granulomatosis, central nervous system vasculitis (CNSV), Sjögren's syndrome, scleroderma, polymyositis., AIDS inflammatory response, bacterial infection, fungal infection, viral infection, parasitic infection, influenza, avian flu, viral pneumonia, endotoxic shock syndrome, sepsis , sepsis syndrome , trauma/wound, organ transplant, transplant atherosclerosis, transplant rejection , corneal ulcer, chronic/non-healing wound, ulcerative colitis, reperfusion injury (prevent and/or treat), ischemic reperfusion injury (prevent and/or treat), spinal cord injuries (mitigating effects) , cancers, myeloma/multiple myeloma, ovarian cancer, breast cancer, colon cancer, bone cancer, osteoarthritis, inflammatory bowel disease , allergic rhinitis, cachexia , diabetes , Alzheimer's disease , implanted prosthesis, biofilm formation, Crohns' disease, dermatitis, acute and chronic, eczema, psoriasis, contact dermatitis, scleroderma, Type I Diabetes, Type II Diabetes, juvenile onset diabetes, prevention of the onset of diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, erectile dysfunction, macular degeneration, multiple sclerosis, nephropathy, neuropathy, Parkinson's Disease, peripheral vascular disease, and meningitis.

[0018] In certain embodiments this invention provides a stent for delivering drugs to a vessel in a body. The stent typically comprises a stent framework including a plurality of reservoirs formed therein, and a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Tables 2-18 (*e.g.,* Table 4, Table 5, or Table 6, *etc.*) and/or the inverse thereof. In certain embodiments the stent comprises a

peptide comprising the amino acid sequence of 4F (SEQ ID NO:5) or the inverse thereof. In certain embodiments the active agent is contained within a polymer. In certain embodiments the stent framework comprises one of a metallic base or a polymeric base. In certain embodiments the stent framework base comprises a material selected from the group consisting of stainless steel, nitinol, tantalum, MP35N alloy, platinum, titanium, a suitable biocompatible alloy, a suitable biocompatible polymer, and a combination thereof. The reservoir(s) comprising said stent can, in some embodiments, comprise micropores (*e.g.* having a diameter of about 20 microns or less). In certain embodiments the micropores have a diameter in the range of about 20 microns to about 50 microns. In various embodiments the micropores have a depth in the range of about 10 to about 50 microns. The micropores, in certain embodiments, extend through the stent framework having an opening on an interior surface of the stent and an opening on an exterior surface of the stent. In various embodiments the stent can further comprise a cap layer disposed on the interior surface of the stent framework, the cap layer covering at least a portion of the through-holes and providing a barrier characteristic to control an elution rate of a drug in the drug polymer from the interior surface of the stent framework. In various embodiments the reservoirs comprise channels along an exterior surface of the stent framework. In various embodiments the polymer comprises a first layer of a first drug polymer having a first pharmaceutical characteristic and the polymer layer comprises a second drug polymer having a second pharmaceutical characteristic. In certain embodiments the stent further comprises a barrier layer positioned between the polymer comprising the active agent. In various embodiments a catheter can be coupled to the stent framework. In certain embodiments the catheter can include a balloon used to expand the stent. In certain embodiments the catheter includes a sheath that retracts to allow expansion of the stent.

[0019] Also provided is a method of manufacturing a drug-polymer stent. The method typically involves providing a stent framework; cutting a plurality of reservoirs in the stent framework; applying a composition comprising one or more peptides comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in any of Tables 2-18 to at least one reservoir; and drying the composition. The method can further involve applying a polymer layer to the dried composition; and drying the polymer layer.

[0020] This invention also provides a method of treating a vascular condition. The method involves positioning a stent as described above, within a vessel of a body;

expanding the stent; and eluting at least one active agent (*e.g.*, an active agent from any of Tables 2-18) from at least a surface of the stent.

[0021] In certain embodiments, this invention expressly excludes one or more of the peptides described in U.S. Patent Nos: 6,037,323; 4,643,988; 6,933,279; 6,930,085; 6,664,230; 3,767,040; 6,037, 323; U.S. Patent Publications 2005/0164950; 2004/0266671; 2004/0254120; 2004/0057871; 2003/0229015; 2003/0191057; 2003/0171277; 2003/0045460; 2003/0040505; PCT Publications WO 2002/15923; WO 1999/16408; WO 1997/36927; and/or in Garber *et al.*(1992) *Arteriosclerosis and Thrombosis*, 12: 886-894, which are incorporated herein by reference .

Definitions.

[0022] The term "treat" when used with reference to treating, *e.g.* a pathology or disease refers to the mitigation and/or elimination of one or more symptoms of that pathology or disease, and/or a reduction in the rate of onset or severity of one or more symptoms of that pathology or disease, and/or the prevention of that pathology or disease.

[0023] The terms "isolated", "purified", or "biologically pure" when referring to an isolated polypeptide refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. With respect to nucleic acids and/or polypeptides the term can refer to nucleic acids or polypeptides that are no longer flanked by the sequences typically flanking them in nature. Chemically synthesized polypeptides are "isolated" because they are not found in a native state (*e.g.* in blood, serum, *etc.*). In certain embodiments, the term "isolated" indicates that the polypeptide is not found in nature.

[0024] The terms "polypeptide", "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residues is an artificial chemical analogue of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers.

[0025] The term "an amphipathic helical peptide" refers to a peptide comprising at least one amphipathic helix (amphipathic helical domain). Certain amphipathic helical peptides of this invention can comprise two or more (*e.g.*, 3, 4, 5, *etc.*) amphipathic helices.

[0026] The term " class A amphipathic helix" refers to a protein structure that forms an α-helix producing a segregation of a polar and nonpolar faces with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face (*see, e.g.,* Segrest *et al.* (1990) *Proteins: Structure, Function, and Genetics* 8: 103-117).

[0027] "Apolipoprotein J" (apo J) is known by a variety of names including clusterin, TRPM2, GP80, and SP 40 (*see, e.g.,* Fritz (1995) Pp 112 In: *Clusterin: Role in Vertebrate Development, Function, and Adaptation* (Harmony JAK Ed.), R.G. Landes, Georgetown, TX,). It was first described as a heterodimeric glycoprotein and a component of the secreted proteins of cultured rat Sertoli cells (*see, e.g.,* Kissinger *et al.* (1982) *Biol. Reprod.*; 27: 233240). The translated product is a single-chain precursor protein that undergoes intracellular cleavage into a disulfide-linked 34kDa α subunit and a 47 kDa β subunit (*see, e.g.,* Collard and Griswold (1987) *Biochem.*, 26: 3297-3303). It has been associated with cellular injury, lipid transport, apoptosis and it may be involved in clearance of cellular debris caused by cell injury or death. Clusterin has been shown to bind to a variety of molecules with high affinity including lipids, peptides, and proteins and the hydrophobic probe 1-anilino-8-naphthalenesulfonate (Bailey *et al.* (2001) *Biochem.*, 40: 11828-11840).

[0028] The class G amphipathic helix is found in globular proteins, and thus, the name class G. The feature of this class of amphipathic helix is that it possesses a random distribution of positively charged and negatively charged residues on the polar face with a narrow nonpolar face. Because of the narrow nonpolar face this class does not readily associate with phospholipid (*see, e.g.,* Segrest *et al.* (1990) *Proteins: Structure, Function, and Genetics.* 8: 103-117; Erratum (1991) *Proteins: Structure, Function and Genetics*, 9: 79). Several exchangeable apolipoproteins possess similar but not identical characteristics to the G amphipathic helix. Similar to the class G amphipathic helix, this other class possesses a random distribution of positively and negatively charged residues on the polar face. However, in contrast to the class G amphipathic helix which has a narrow nonpolar face, this class has a wide nonpolar face that allows this class to readily bind phospholipid and the class is termed G* to differentiate it from the G class of amphipathic helix (*see, e.g.,* Segrest *et al.* (1992) *J. Lipid Res.*, 33: 141-166; Anantharamaiah *et al.* (1993) Pp. 109-142 In: *The Amphipathic Helix,* Epand, R.M. Ed CRC Press, Boca Raton, Florida). Computer programs to identify and classify

amphipathic helical domains have been described by Jones *et al.*(1992) *J. Lipid Res.* 33: 287-296) and include, but are not limited to the helical wheel program (WHEEL or WHEEL/SNORKEL), helical net program (HELNET, HELNET/SNORKEL, HELNET/Angle), program for addition of helical wheels (COMBO or COMBO/SNORKEL), program for addition of helical nets (COMNET, COMNET/SNORKEL, COMBO/SELECT, COMBO/NET), consensus wheel program (CONSENSUS, CONSENSUS/SNORKEL), and the like.

[0029] The term "ameliorating" when used with respect to "ameliorating one or more symptoms of atherosclerosis" refers to a reduction, prevention, or elimination of one or more symptoms characteristic of atherosclerosis and/or associated pathologies. Such a reduction includes, but is not limited to a reduction or elimination of oxidized phospholipids, a reduction in atherosclerotic plaque formation and rupture, a reduction in clinical events such as heart attack, angina, or stroke, a decrease in hypertension, a decrease in inflammatory protein biosynthesis, reduction in plasma cholesterol, and the like.

[0030] The term "enantiomeric amino acids" refers to amino acids that can exist in at least two forms that are nonsuperimposable mirror images of each other. Most amino acids (except glycine) are enantiomeric and exist in a so-called L-form (L amino acid) or D-form (D amino acid). Most naturally occurring amino acids are "L" amino acids. The terms "D amino acid" and "L amino acid" are used to refer to absolute configuration of the amino acid, rather than a particular direction of rotation of plane-polarized light. The usage herein is consistent with standard usage by those of skill in the art. Amino acids are designated herein using standard 1-letter or three-letter codes, *e.g.* as designated in Standard ST.25 in the Handbook On Industrial Property Information and Documentation.

[0031] The term "protecting group" refers to a chemical group that, when attached to a functional group in an amino acid (*e.g.* a side chain, an alpha amino group, an alpha carboxyl group, *etc.*) blocks or masks the properties of that functional group. Preferred amino-terminal protecting groups include, but are not limited to acetyl, or amino groups. Other amino-terminal protecting groups include, but are not limited to alkyl chains as in fatty acids, propeonyl, formyl and others. Preferred carboxyl terminal protecting groups include, but are not limited to groups that form amides or esters.

[0032] The phrase "protect a phospholipid from oxidation by an oxidizing agent" refers to the ability of a compound to reduce the rate of oxidation of a phospholipid (or the amount of oxidized phospholipid produced) when that phospholipid is contacted with an oxidizing agent (*e.g.* hydrogen peroxide, 13-(S)-HPODE, 15-(S)-HPETE, HPODE, HPETE, HODE, HETE, *etc.*).

[0033] The terms "low density lipoprotein" or "LDL" is defined in accordance with common usage of those of skill in the art. Generally, LDL refers to the lipid-protein complex which when isolated by ultracentrifugation is found in the density range d = 1.019 to d = 1.063.

[0034] The terms "high density lipoprotein" or "HDL" is defined in accordance with common usage of those of skill in the art. Generally "HDL" refers to a lipid-protein complex which when isolated by ultracentrifugation is found in the density range of d = 1.063 to d = 1.21.

[0035] The term "Group I HDL" refers to a high density lipoprotein or components thereof (*e.g.* apo A-I, paraoxonase, platelet activating factor acetylhydrolase, *etc.*) that reduce oxidized lipids (*e.g.* in low density lipoproteins) or that protect oxidized lipids from oxidation by oxidizing agents.

[0036] The term "Group II HDL" refers to an HDL that offers reduced activity or no activity in protecting lipids from oxidation or in repairing (*e.g.* reducing) oxidized lipids.

[0037] The term "HDL component" refers to a component (*e.g.* molecules) that comprises a high density lipoprotein (HDL). Assays for HDL that protect lipids from oxidation or that repair (*e.g.* reduce oxidized lipids) also include assays for components of HDL (*e.g.* apo A-I, paraoxonase, platelet activating factor acetylhydrolase, *etc.*) that display such activity.

[0038] The term "human apo A-I peptide" refers to a full-length human apo A-I peptide or to a fragment or domain thereof comprising a class A amphipathic helix.

[0039] A "monocytic reaction" as used herein refers to monocyte activity characteristic of the "inflammatory response" associated with atherosclerotic plaque formation. The monocytic reaction is characterized by monocyte adhesion to cells of the vascular wall (*e.g.* cells of the vascular endothelium), and/or chemotaxis into the subendothelial space, and/or differentiation of monocytes into macrophages.

[0040] The term "absence of change" when referring to the amount of oxidized phospholipid refers to the lack of a detectable change, more preferably the lack of a statistically significant change (*e.g.* at least at the 85%, preferably at least at the 90%, more preferably at least at the 95%, and most preferably at least at the 98% or 99% confidence level). The absence of a detectable change can also refer to assays in which oxidized phospholipid level changes, but not as much as in the absence of the protein(s) described herein or with reference to other positive or negative controls.

[0041] The following abbreviations may be used herein: PAPC: L-α-1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; POVPC: 1-palmitoyl-2-(5-oxovaleryl)-*sn*-glycero-3-phosphocholine; PGPC: 1-palmitoyl-2-glutaryl-*sn*-glycero-3-phosphocholine; PEIPC: 1-palmitoyl-2-(5,6-epoxyisoprostane E_2)-*sn*-glycero-3-phosphocholine; ChC18:2: cholesteryl linoleate; ChC18:2-OOH: cholesteryl linoleate hydroperoxide; DMPC: 1,2-ditetradecanoyl-rac-glycerol-3-phosphocholine; PON: paraoxonase; HPF: Standardized high power field; PAPC: L-α-1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine; BL/6: C57BL/6J; C3H:C3H/HeJ.

[0042] The term "conservative substitution" is used in reference to proteins or peptides to reflect amino acid substitutions that do not substantially alter the activity (specificity (*e.g.* for lipoproteins)) or binding affinity (*e.g.* for lipids or lipoproteins)) of the molecule. Typically conservative amino acid substitutions involve substitution one amino acid for another amino acid with similar chemical properties (*e.g.* charge or hydrophobicity). The following six groups each contain amino acids that are typical conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

[0043] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection. With respect to the peptides of this invention sequence identity is determined over the full length of the peptide.

[0044] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0045] Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (*see generally* Ausubel *et al., supra*).

[0046] One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle (1987) *J. Mol. Evol.* 35:351-360. The method used is similar to the method described by Higgins & Sharp (1989) *CABIOS* 5: 151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The final alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

[0047] Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al.* (1990) *J. Mol. Biol.* 215: 403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff & Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

[0048] In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin & Altschul (1993) *Proc. Natl. Acad. Sci. USA* ,90: 5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[0049] The phrase "in conjunction with" when used in reference to the use of one or more drugs in conjunction with one or more active agents described herein indicates that the drug(s) and the active agent(s) are administered so that there is at least some chronological overlap in their physiological activity on the organism. Thus the drug(s) and active agent(s) can be administered simultaneously and/or sequentially. In sequential administration there may even be some substantial delay (*e.g.*, minutes or even hours or days) before administration of the second moiety as long as the first administered drug/agent has exerted some physiological alteration on the organism when the second administered agent is administered or becomes active in the organism.

[0050] The phrases "adjacent to each other in a helical wheel diagram of a peptide" or "contiguous in a helical wheel diagram of a peptide" when referring to residues in a helical peptide indicates that in the helical wheel representation the residuces appear adjacent or contiguous even though they may not be adjacent or contiguous in the linear peptide. Thus, for example, the residues "A, E, K, W, K, and F" are contiguous in the helical wheel diagrams shown in Figure 15 even though these residues are not contiguous in the linear peptide.

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] Figure 1 shows a comparison of the effect of D4F (Navab, *et al.* (2002) *Circulation*, 105: 290-292) and apo-J peptide 336 made from D amino acids (D-J336*) on the prevention of LDL-induced monocyte chemotactic activity *in vitro* in a co-incubation experiment. The data are mean ±SD of the number of migrated monocytes in nine high power fields in quadruple cultures. (D-J336 = Ac-LLEQLNEQFNWVSRLANLTQGE - NH_2, SEQ ID NO:1).

[0052] Figure 2 illustrates the prevention of LDL-induced monocyte chemotactic activity by pre-treatment of artery wall cells with D-J336 as compared to D-4F. The data are mean ±SD of the number of migrated monocytes in nine high power fields in quadruple cultures.

[0053] Figure 3 illustrates he effect of apo J peptide mimetics on HDL protective capacity in LDL receptor null mice. The values are the mean ± SD of the number of migrated monocytes in 9 high power fields from each of quadruple assay wells.

[0054] Figure 4 illustrates protection against LDL–induced monocyte chemotactic activity by HDL from apo E null mice given oral peptides. The values are the mean ± SD of the number of migrated monocytes in 9 high power fields from each of quadruple assay wells. Asterisks indicate significant difference ($p<0.05$) as compared to No Peptide mHDL.

[0055] Figure 5 illustrates the effect of oral apo A-1 peptide mimetic and apoJ peptide on LDL susceptibility to oxidation. The values are the mean ± SD of the number of migrated monocytes in 9 high power fields from each of quadruple assay wells. Asterisks indicate significant difference ($p<0.05$) as compared to No Peptide LDL.

[0056] Figure 6 illustrates the effect of oral apoA-1 peptide mimetic and apoJ peptide on HDL protective capacity. The values are the mean ± SD of the number of migrated monocytes in 9 high power fields from each of quadruple assay wells. Asterisks indicate significant difference ($p<0.05$) as compared to No Peptide mHDL.

[0057] Figure 7 illustrates the effect of oral apoA-1 peptide mimetic and apoJ peptide on plasma paraoxonase activity. The values are the mean ± SD of readings from quadruple plasma aliquots. Asterisks indicate significant differences ($p<0.05$) as compared to No Peptide control plasma.

[0058] Figure 8 shows the effect of oral G* peptides on HDL protective capacity in apoE-/- mice . The values are the mean ± SD of readings from quadruple plasma aliquots. Asterisks indicate significant differences ($p<0.05$) as compared to no peptide control plasma.

[0059] Figure 9 shows the effect of Oral G* peptide, 146-156, on HDL protective capacity in ApoE-/- mice.

[0060] Figures 10A through 10C illustrate helical wheel diagrams of certain peptides of this invention. Figure 10A: $V^2W^3A^5F^{10,17}$-D-4F; Figure 10B: W^3-D-4F; Figure 10C: $V^2W^3F^{10}$-D-4F:

[0061] Figure 11 A standard human LDL (LDL) was added to human artery wall cocultures without (No Addition) or with human HDL (+Control HDL) or with mouse HDL from apoE null mice given Chow overnight (+Chow HDL), or given D-4F in the chow overnight (+D4F HDL) or given G5-D-4F in the chow overnight (+G5 HDL), or given G5,10-D-4F in the chow overnight (+5-10 HDL), or given G5,11-D-4F in the chow

overnight (+5-11 HDL) and the resulting monocyte chemotactic activity determined as previously described (Navab *et al.* (2002) *Circulation*, 105: 290-292).

[0062] Figure 12 shows that peptides of this invention are effective in mitigating symptoms of diabetes (*e.g.*, blood glucose). Obese Zucker rats 26 weeks of age were bled and then treated with daily intraperitoneal injections of D-4F (5.0 mg/kg/day). After 10 days the rats were bled again plasma glucose and lipid hydroperoxides (LOOH) were determined. *p=0.027; ** p=0.0017.

[0063] Figure 13. Sixteen week old Obese Zucker Rats were injected with D-4F (5 mg/kg/daily) for 1 week at which time they underwent balloon injury of the common carotid artery. Two weeks later the rats were sacrificed and the intimal media ratio determined.

[0064] Figure 14 demonstrates that the product of the solution phase synthesis scheme is very biologically active in producing HDL and pre-beta HDL that inhibit LDL-induced monocyte chemotaxis in apo E null mice. ApoE null mice were fed 5 micrograms of the D-4F synthesized as described above (Frgmnt) or the mice were given the same amount of mouse chow without D-4F (Chow). Twelve hours after the feeding was started, the mice were bled and their plasma was fractionated on FPLC. LDL (100 micrograms LDL-cholesterol) was added to cocultures of human artery wall cells alone (LDL) or with a control human HDL (Control HDL) or with HDL (50 micrograms HDL-cholesterol) or post-HDL (pHDL; prebeta HDL) from mice that did (Frgmnt) or did not (Chow) receive the D-4F and the monocyte chemotactic activity produced was determined

[0065] Figure 15 illustrates a helical wheel representation of 4F and reverse (retro) 4F. Reverse-4F is a mirror image of 4F with the relative positions of the amino acids to each other and to the hydrophilic and hydrophobic faces being identical.

[0066] Figure 16 shows a comparison of the HDL inflammatory index of D-4F versus reverse D-4F.

DETAILED DESCRIPTION

I. Methods of treatment.

[0067] The active agents (*e.g.* peptides, small organic molecules, amino acid pairs, *etc.*) described herein are effective for mitigating one or more symptoms and/or reducing

the rate of onset and/or severity of one or more indications described herein. In particular, the active agents (*e.g.* peptides, small organic molecules, amino acid pairs, *etc.*) described herein are effective for mitigating one or more symptoms of atherosclerosis. Without being bound to a particular theory, it is believed that the peptides bind the "seeding molecules" required for the formation of pro-inflammatory oxidized phospholipids such as Ox-PAPC, POVPC, PGPC, and PEIPC.

[0068] In addition, since many inflammatory conditions and/or other pathologies are mediated at least in part by oxidized lipids, we believe that the peptides of this invention are effective in ameliorating conditions that are characterized by the formation of biologically active oxidized lipids. In addition, there are a number of other conditions for which the active agents described herein appear to be efficacious.

[0069] A number of pathologies for which the active agents described herein appear to be a palliative and/or a preventative are described below.

A) Atherosclerosis and associated pathologies.

[0070] We discovered that normal HDL inhibits three steps in the formation of mildly oxidized LDL. In particular, we demonstrated that treating human LDL *in vitro* with apo A-I or an apo A-I mimetic peptide (37pA) removed seeding molecules from the LDL that included HPODE and HPETE. These seeding molecules were required for cocultures of human artery wall cells to be able to oxidize LDL and for the LDL to induce the artery wall cells to produce monocyte chemotactic activity. We also demonstrated that after injection of apo A-I into mice or infusion into humans, the LDL isolated from the mice or human volunteers after injection/infusion of apo A-I was resistant to oxidation by human artery wall cells and did not induce monocyte chemotactic activity in the artery wall cell cocultures.

[0071] The protective function of various active agents of this invention is illustrated in the parent applications (09/645,454, filed August 24, 2000, 09/896,841, filed June 29, 2001, and WO 02/15923 (PCT/US01/26497), filed June 29, 2001, *see, e.g.*, Figures 1-5 in WO 02/15923. Figure 1, panels A, B, C, and D in WO 02/15923 show the association of ^{14}C-D-5F with blood components in an ApoE null mouse. It is also demonstrated that HDL from mice that were fed an atherogenic diet and injected with PBS failed to inhibit the oxidation of human LDL and failed to inhibit LDL-induced monocyte chemotactic activity in human artery wall coculures. In contrast, HDL from mice fed an

atherogenic diet and injected daily with peptides described herein was as effective in inhibiting human LDL oxidation and preventing LDL-induced monocyte chemotactic activity in the cocultures as was normal human HDL (Figures 2A and 2B in WO 02/15923). In addition, LDL taken from mice fed the atherogenic diet and injected daily with PBS was more readily oxidized and more readily induced monocyte chemotactic activity than LDL taken from mice fed the same diet but injected with 20 μg daily of peptide 5F. The D peptide did not appear to be immunogenic (Figure 4 in WO 02/15923).

[0072] The *in vitro* responses of human artery wall cells to HDL and LDL from mice fed the atherogenic diet and injected with a peptide according to this invention are consistent with the protective action shown by such peptides *in vivo*. Despite, similar levels of total cholesterol, LDL-cholesterol, IDL+VLDL-cholesterol, and lower HDL-cholesterol as a percent of total cholesterol, the animals fed the atherogenic diet and injected with the peptide had significantly lower lesion scores (Figure 5 in WO 02/15923). The peptides of this invention thus prevented progression of atherosclerotic lesions in mice fed an atherogenic diet.

[0073] Thus, in one embodiment, this invention provides methods for ameliorating and/or preventing one or more symptoms of atherosclerosis by administering one or more of the active agents described herein..

[0074] It is also noted that c-reactive protein, a marker for inflammation, is elevated in congestive heart failure. Also, in congestive heart failure there is an accumulation of reactive oxygen species and vasomotion abnormalities. Because of their effects in preventing/reducing the formation of various oxidized species and/or because of their effect in improving vasoreactivity and/or arteriole function (see below) the active agents described herein will be effective in treating congestive heart failure.

B) Arteriole/vascular indications.

[0075] Vessels smaller than even the smallest arteries (*i.e.*, arterioles) thicken, become dysfunctional and cause end organ damage to tissues as diverse as the brain and the kidney. It is believed the active agents described herein can function to improve areteriole structure and function and/or to slow the rate and/or severity of arteriole dysfunction. Without being bound to a particular theory, it is believed that arteriole dysfunction is a causal factor in various brain and kidney disorders. Use of the agents

described herein thus provides a method to improve the structure and function of arterioles and preserve the function of end organs such as the brain and kidney.

[0076] Thus, for example, administration of one or more of the active agents described herein is expected to reduce one or more symptoms or to slow the onset or severity of arteriolar disease associated with aging, and/or Alzheimer's disease, and/or Parkinson's disease, and/or with multi-infarct dementia, and/or subarachnoid hemorrhage, and the like. Similarly, administration of one or more agents described herein is expected to mitigate one or more symptoms and/or to slow the onset and/or severity of chronic kidney disease, and/or hypertension.

[0077] Similarly, the agents described herein appear to improve vasoreactivity. Because of the improvement of vasoreactivity and/or arteriole function, the agents described herein are suitable for the treatment of peripheral vascular disease, erectile dysfunction, and the like.

C) Pulmonary indications.

[0078] The agents described herein are also suitable for treatment of a variety of pulmonary indications. These include, but are not limited to chronic obstructive pulmonary disease (COPD), emphysema, pulmonary disease, asthma, idiopathic pulmonary fibrosis, and the like.

D) Mitigation of a symptom or condition associated with coronary calcification and osteoporosis.

[0079] Vascular calcification and osteoporosis often co-exist in the same subjects (Ouchi *et al.* (1993) *Ann NY Acad Sci.,* 676: 297-307; Boukhris and Becker (`1972) *JAMA,* 219: 1307-1311; Banks *et al.* (1994) *Eur J Clin Invest.*, 24: 813-817; Laroche *et al.* (1994) *Clin Rheumatol.*, 13: 611-614; Broulik and Kapitola (1993) *Endocr Regul.*, 27: 57-60; Frye *et al.* (1992) *Bone Mine.,* 19: 185-194; Barengolts *et al.* (1998) *Calcif Tissue Int.,* 62: 209-213; Burnett and Vasikaran (2002) *Ann Clin Biochem.*, 39: 203-210. Parhami *et al.* (1997) *Arterioscl Thromb Vasc Biol.*, 17: 680-687, demonstrated that mildly oxidized LDL (MM-LDL) and the biologically active lipids in MM-LDL [*i.e.* oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine) (Ox-PAPC)], as well as the isoprostane, 8-iso prostaglandin E_2, but not the unoxidized phospholipid (PAPC) or isoprostane 8-iso progstaglandin $F_{2\alpha}$ induced alkaline phosphatase activity and osteoblastic differentiation

of calcifying vascular cells (CVCs) in vitro, but inhibited the differentiation of MC3T3-E1 bone cells.

[0080] The osteon resembles the artery wall in that the osteon is centered on an endothelial cell-lined lumen surrounded by a subendothelial space containing matrix and fibroblast-like cells, which is in turn surrounded by preosteoblasts and osteoblasts occupying a position analogous to smooth muscle cells in the artery wall (*Id.*). Trabecular bone osteoblasts also interface with bone marrow subendothelial spaces (*Id.*). Parhami *et al.* postulated that lipoproteins could cross the endothelium of bone arteries and be deposited in the subendothelial space where they could undergo oxidation as in coronary arteries (*Id.*). Based on their *in vitro* data they predicted that LDL oxidation in the subendothelial space of bone arteries and in bone marrow would lead to reduced osteoblastic differentiation and mineralization which would contribute to osteoporosis (*Id.*). Their hypothesis further predicted that LDL levels would be positively correlated with osteoporosis as they are with coronary calcification (Pohle *et al.* (2001) *Circulation*, 104: 1927-1932), but HDL levels would be negatively correlated with osteoporosis (Parhami *et al.* (1997) *Arterioscl Thromb Vasc Biol.*, 17: 680-687).

[0081] *In vitro,* the osteoblastic differentiation of the marrow stromal cell line M2-10B4 was inhibited by MM-LDL but not native LDL (Parhami *et al.* (1999) *J Bone Miner Res.*, 14: 2067-2078). When marrow stromal cells from atherosclerosis susceptible C57BL/6 (BL6) mice fed a low fat chow diet were cultured there was robust osteogenic differentiation (*Id.*). In contrast, when the marrow stromal cells taken from the mice after a high fat, atherogenic diet were cultured they did not undergo osteogenic differentiation (*Id.*). This observation is particularly important since it provides a possible explanation for the decreased osteogenic potential of marrow stromal cells in the development of osteoporosis (Nuttall and Gimble (2000) *Bone,* 27: 177-184). *In vivo* the decrease in osteogenic potential is accompanied by an increase in adipogenesis in osteoporotic bone (*Id.*).

[0082] It was found that adding D-4F to the drinking water of apoE null mice for 6 weeks dramatically increased trabecular bone mineral density and it is believed that the other active agents of this invention will act similarly.

[0083] Our data indicate that osteoporosis can be regarded as an "atherosclerosis of bone". It appears to be a result of the action of oxidized lipids. HDL destroys these

oxidized lipids and promotes osteoblastic differentiation. Our data indicate that administering active agent (s) of this invention to a mammal (*e.g.*, in the drinking water of apoE null mice) dramatically increases trabecular bone in just a matter of weeks.

[0084] This indicates that the active agents, described herein are useful for mitigation one or more symptoms of osteoporosis (*e.g.*, for inhibiting decalcification) or for inducing recalcification of osteoporotic bone. The active agents are also useful as prophylactics to prevent the onset of symptom(s) of osteoporosis in a mammal (*e.g.*, a patient at risk for osteoporosis).

[0085] We believe similar mechanisms are a cause of coronary calcification, *e.g.*, calcific aortic stenosis. Thus, in certain embodiments, this invention contemplates the use of the active agents described herein to inhibit or prevent a symptom of a disease such as coronary calcification, calcific aortic stenosis, osteoporosis, and the like.

E) Inflammatory and Autoimmune Indications.

[0086] Chronic inflammatory and/or autoimmune conditions are also characterized by the formation of a number of reactive oxygen species and are amenable to treatment using one or more of the active agents described herein. Thus, without being bound to a particular theory, we also believe the active agents described herein are useful, prophylactically or therapeutically, to mitigate the onset and/or more or more symptoms of a variety of other conditions including, but not limited to rheumatoid arthritis, lupus erythematous, polyarteritis nodosa, polymyalgia rheumatica, scleroderma, multiple sclerosis, and the like.

[0087] In certain embodiments, the active agents are useful in mitigating one or more symptoms caused by, or associated with, an inflammatory response in these conditions.

[0088] Also, in certain embodiments , the active agents are useful in mitigating one or more symptoms caused by or associated with an inflammatory response associated with AIDS.

F) Infections/trauma/transplants.

0089] We have observed that a consequence of influenza infection and other infections is the diminution in paraoxonase and platelet activating acetylhydrolase activity

in the HDL. Without being bound by a particular theory, we believe that, as a result of the loss of these HDL enzymatic activities and also as a result of the association of pro-oxidant proteins with HDL during the acute phase response, HDL is no longer able to prevent LDL oxidation and is no longer able to prevent the LDL-induced production of monocyte chemotactic activity by endothelial cells.

[0090] We observed that in a subject injected with very low dosages of certain agents of this invention (*e.g.*, 20 micrograms for mice) daily after infection with the influenza A virus paraoxonase levels did not fall and the biologically active oxidized phospholipids were not generated beyond background. This indicates that 4F, D4F (and/or other agents of this invention) can be administered (*e.g.* orally or by injection) to patients (including, for example with known coronary artery disease during influenza infection or other events that can generate an acute phase inflammatory response, *e.g.* due to viral infection, bacterial infection, trauma, transplant, various autoimmune conditions, *etc.*) and thus we can prevent by this short term treatment the increased incidence of heart attack and stroke associated with pathologies that generate such inflammatory states.

[0091] In addition, by restoring and/or maintaining paroxonase levels and/or monocyte activity, the agent(s) of this invention are useful in the treatment of infection (*e.g.*, viral infection, bacterial infection, fungal infection) and/or the inflammatory pathologies associated with infection (*e.g.* meningitis) and/or trauma.

[0092] In certain embodiments, because of the combined anti-inflammatory activity and anti-infective activity, the agents described herein are also useful in the treatment of a wound or other trauma, mitigating adverse effects associated with organ or tissue transplant, and/or organ or tissue transplant rejection, and/or implanted prostheses, and/or transplant atherosclerosis, and/or biofilm formation. In addition, we believe that L-4F, D-4F, and/or other agents described herein are also useful in mitigating the effects of spinal cord injuries.

G) Diabetes and associated conditions.

[0093] Various active agents described herein have also been observed to show efficacy in reducing and/or preventing one or more symptoms associated with diabetes. Thus, in various embodiments, this invention provides methods of treating (therapeutically and/or prophylactically) diabetes and/or associated pathologies (*e.g.*, Type I diabetes,

Type II diabetes, juvenile onset diabetes, diabetic nephropathy, nephropathy, diabetic neuropathy, diabetic retinopathy, and the like.

H) Cancer.

[0094] NFκB is a transcription factor that is normally activated in response to proinflammatory cytokines and that regulates the expression of more than 200 genes. Many tumor cell lines show constitutive activation of NFκB signaling. Various studies of mouse models of intestinal, and mammary tumors conclude that activation of the NFκB pathway enhances tumor development and may act primarily in the late stages of tumorigenesis (*see, e.g.,* (2004) Cell 118: 285; (2004) *J. Clin. Invest., 114: 569*). Inhibition of NFκB signaling suppressed tumor development. Without being bound to a particular theory, mechanisms for this suppression are believed to include an increase in tumor cell apoptosis, reduced expression of tumor cell growth factors supplied by surrounding stromal cells, and/or abrogation of a tumor cell dedifferentiation program that is critical for tumor invasion/metastasis.

[0095] Without being bound by a particular theory, it is believed the administration of one or more active agents described herein will inhibit expression and/or secretion, and/or activity of NFκB. Thus, in certain embodiments, this invention provides methods of treating a pathology characterized by elevated NFκB by administering one or more active agents described herein. Thus, In various embodiments this invention contemplates inhibiting NFκB activation associated with cancer by administering one ore more active agents described herein, optionally in combination with appropriate cancer therapeutics.

I) Biochemical Activity.

[0096] The active agent(s) described herein have been shown to exhibit a number of specific biological activities. Thus, for example, they increase heme oxygenase 1, they increase extracellular superoxide dismutase, they reduce or prevent the association of myeloperoxidase with apoA-I, they reduce or prevent the nitrosylation of tyrosine in apoA-I, they render HDL Anti-inflammatory or more anti-inflammatory, and they increase the formation cycling of pre-β HDL, they promote reverse cholesterol transport, in particular, reverse cholesterol transport from macrophages, and they synergize the activity of statins. The active agents described herein can thus be administered to a mammal to

promote any of these activities, *e.g.* to treat a condition/pathology whose severity, and/or likelihood of onset is reduced by one or more of these activities.

J) Mitigation of a symptom of atherosclerosis associated with an acute inflammatory response.

[0097] The active agents, of this invention are also useful in a number of contexts. For example, we have observed that cardiovascular complications (*e.g.*, atherosclerosis, stroke, *etc.*) frequently accompany or follow the onset of an acute phase inflammatory response, *e.g.*, such as that associated with a recurrent inflammatory disease, a viral infection (*e.g.*, influenza), a bacterial infection, a fungal infection, an organ transplant, a wound or other trauma, and so forth.

[0098] Thus, in certain embodiments, this invention contemplates administering one or more of the active agents described herein to a subject at risk for, or incurring, an acute inflammatory response and/or at risk for or incurring a symptom of atherosclerosis and/or an associated pathology (*e.g.*, stroke).

[0099] Thus, for example, a person having or at risk for coronary disease may prophylactically be administered a one or more active agents of this invention during flu season. A person (or animal) subject to a recurrent inflammatory condition, *e.g.*, rheumatoid arthritis, various autoimmune diseases, *etc.*, can be treated with a one or more agents described herein to mitigate or prevent the development of atherosclerosis or stroke. A person (or animal) subject to trauma, *e.g.*, acute injury, tissue transplant, *etc.* can be treated with a polypeptide of this invention to mitigate the development of atherosclerosis or stroke.

[0100] In certain instances such methods will entail a diagnosis of the occurrence or risk of an acute inflammatory response. The acute inflammatory response typically involves alterations in metabolism and gene regulation in the liver. It is a dynamic homeostatic process that involves all of the major systems of the body, in addition to the immune, cardiovascular and central nervous system. Normally, the acute phase response lasts only a few days; however, in cases of chronic or recurring inflammation, an aberrant continuation of some aspects of the acute phase response may contribute to the underlying tissue damage that accompanies the disease, and may also lead to further complications, for example cardiovascular diseases or protein deposition diseases such as amyloidosis.

[0101] An important aspect of the acute phase response is the radically altered biosynthetic profile of the liver. Under normal circumstances, the liver synthesizes a characteristic range of plasma proteins at steady state concentrations. Many of these proteins have important functions and higher plasma levels of these acute phase reactants (APRs) or acute phase proteins (APPs) are required during the acute phase response following an inflammatory stimulus. Although most APRs are synthesized by hepatocytes, some are produced by other cell types, including monocytes, endothelial cells, fibroblasts and adipocytes. Most APRs are induced between 50% and several-fold over normal levels. In contrast, the major APRs can increase to 1000-fold over normal levels. This group includes serum amyloid A (SAA) and either C-reactive protein (CRP) in humans or its homologue in mice, serum amyloid P component (SAP). So-called negative APRs are decreased in plasma concentration during the acute phase response to allow an increase in the capacity of the liver to synthesize the induced APRs.

[0102] In certain embodiments, the acute phase response, or risk therefore is evaluated by measuring one or more APPs. Measuring such markers is well known to those of skill in the art, and commercial companies exist that provide such measurement (*e.g.*, AGP measured by Cardiotech Services, Louisville, KY).

K) Other indications.

[0103] In various embodiments it is contemplated that the active agents described herein are useful in the treatment (*e.g.* mitigation and/or prevention) of corneal ulcers, endothelial sloughing, Crohn's disease, acute and chronic dermatitis (including, but not limited to eczema and/or psoriasis), macular degeneration, neuropathy, scleroderma, and ulcerative colitis.

[0104] A summary of indications/conditions for which the active agents have been shown to be effective and/or are believed to be effective is shown in Table 1.

[0105] Table 1. Summary of conditions in which the active agents (*e.g.*, D-4F) have been shown to be or are believed to be effective.

atherosclerosis/symptoms/consequences thereof
plaque formation
lesion formation
myocardial infarction
stroke

congestive heart failure

vascular function:
- arteriole function
- arteriolar disease
  - associated with aging
  - associated with alzheimer's disease
  - associated with chronic kidney disease
  - associated with hypertension
  - associated with multi-infarct dementia
  - associated with subarachnoid hemorrhage
- peripheral vascular disease

pulmonary disease:
- chronic obstructive pulmonary disease (COPD),
- emphysema
- asthma
- idiopathic pulmonary fibrosis
- Pulmonary fibrosis
- adult respiratory distress syndrome

osteoporosis

Paget's disease

coronary calcification

autoimmune:
- rheumatoid arthritis
- polyarteritis nodosa
- polymyalgia rheumatica
- lupus erythematosus
- multiple sclerosis
- Wegener's granulomatosis
- central nervous system vasculitis (CNSV)
- Sjögren's syndrome
- Scleroderma
- polymyositis.

AIDS inflammatory response

infections:
- bacterial
- fungal
- viral
- parasitic
- influenza
  - avian flu
- viral pneumonia
- endotoxic shock syndrome
- sepsis

sepsis syndrome (clinical syndrome where it appears that the patient is septic but no organisms are recovered from the blood)
trauma/wound: organ transplant transplant atherosclerosis transplant rejection corneal ulcer chronic/non-healing wound ulcerative colitis reperfusion injury (prevent and/or treat) ischemic reperfusion injury (prevent and/or treat) spinal cord injuries (mitigating effects)
cancers myeloma/multiple myeloma ovarian cancer breast cancer colon cancer bone cancer
osteoarthritis
inflammatory bowel disease
allergic rhinitis
cachexia
diabetes
Alzheimer's disease
implanted prosthesis
biofilm formation
Crohns' disease
dermatitis, acute and chronic eczema psoriasis contact dermatitis scleroderma
diabetes and related conditions Type I Diabetes Type II Diabetes Juvenile Onset Diabetes Prevention of the onset of diabetes Diabetic Nephropathy Diabetic Neuropathy Diabetic Retinopathy
erectile dysfunction
macular degeneration

multiple sclerosis
nephropathy
neuropathy
Parkinson's Disease
peripheral Vascular Disease
meningitis
Specific biological activities:
increase Heme Oxygenase 1
increase extracellular superoxide dismutase
prevent endothelial sloughing
prevent the association of myeloperoxidase with ApoA-I
prevent the nitrosylation of tyrosine in ApoA-I
render HDL anti-inflammatory
improve vasoreactivity
increase the formation of pre-beta HDL
promote reverse cholesterol transport
promote reverse cholesterol transport from macrophages
synergize the action of statins

[0106] It is noted that the conditions listed in Table 1 are intended to be illustrative and not limiting.

L) Administration.

[0107] Typically the active agent(s) will be administered to a mammal (*e.g.*,. a human) in need thereof. Such a mammal will typically include a mammal (*e.g.* a human) having or at risk for one or more of the pathologies described herein.

[0108] The active agent(s) can be administered, as described herein, according to any of a number of standard methods including, but not limited to injection, suppository, nasal spray, time-release implant, transdermal patch, and the like. In one particularly preferred embodiment, the peptide(s) are administered orally (*e.g.* as a syrup, capsule, or tablet).

[0109] The methods involve the administration of a single active agent of this invention or the administration of two or more different active agents. The active agents can be provided as monomers (*e.g.*, in separate or combined formulations), or in dimeric, oligomeric or polymeric forms. In certain embodiments, the multimeric forms may comprise associated monomers (*e.g.*, ionically or hydrophobically linked) while certain

other multimeric forms comprise covalently linked monomers (directly linked or through a linker).

[0110] While the invention is described with respect to use in humans, it is also suitable for animal, *e.g.* veterinary use. Thus certain preferred organisms include, but are not limited to humans, non-human primates, canines, equines, felines, porcines, ungulates, largomorphs, and the like.

[0111] The methods of this invention are not limited to humans or non-human animals showing one or more symptom(s) of the pathologies described herein, but are also useful in a prophylactic context. Thus, the active agents of this invention can be administered to organisms to prevent the onset/development of one or more symptoms of the pathologies described herein (*e.g.,* atherosclerosis, stroke, *etc.*). Particularly preferred subjects in this context are subjects showing one or more risk factors for the pathology. Thus, for example, in the case of atherosclerosis risk factors include family history, hypertension, obesity, high alcohol consumption, smoking, high blood cholesterol, high blood triglycerides, elevated blood LDL, VLDL, IDL, or low HDL, diabetes, or a family history of diabetes, high blood lipids, heart attack, angina or stroke, *etc.*.

II. Active Agents.

[0112] A wide variety of active agents are suitable for the treatment of one or more of the indications discussed above. These agents include, but are not limited to class A amphipathic helical peptides, class A amphipathic helical peptide mimetics of apoA-I having aromatic or aliphatic residues in the non-polar face, small peptides including penta-peptides, tetrapeptides, tripeptides, dipeptides and pairs of amino acids, Apo-J (G* peptides), and peptide mimetics, *e.g.,* as described below.

A) Class A amphipathic helical peptides.

[0113] In certain embodiments, the activate agents for use in the method of this invention include class A amphipathic helical peptides, *e.g.* as described in U.S. Patent 6,664,230, and PCT Publications WO 02/15923 and WO 2004/034977. It was discovered that peptides comprising a class A amphipathic helix ("class A peptides"), in addition to being capable of mitigating one or more symptoms of atherosclerosis are also useful in the treatment of one or more of the other indications described herein.

[0114] Class A peptides are characterized by formation of an α-helix that produces a segregation of polar and non-polar residues thereby forming a polar and a nonpolar face with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face (*see, e.g.,* Anantharamaiah (1986) *Meth. Enzymol*, 128: 626-668). It is noted that the fourth exon of apo A-I, when folded into 3.667 residues/turn produces a class A amphipathic helical structure.

[0115] One class A peptide, designated 18A (*see, e.g.,* Anantharamaiah (1986) *Meth. Enzymol*, 128: 626-668) was modified as described herein to produce peptides orally administrable and highly effective at inhibiting or preventing one or more symptoms of atherosclerosis and/or other indications described herein.. Without being bound by a particular theory, it is believed that the peptides of this invention may act *in vivo* may by picking up seeding molecule(s) that mitigate oxidation of LDL.

[0116] We determined that increasing the number of Phe residues on the hydrophobic face of 18A would theoretically increase lipid affinity as determined by the computation described by Palgunachari *et al.* (1996) *Arteriosclerosis, Thrombosis, & Vascular Biol.* 16: 328-338. Theoretically, a systematic substitution of residues in the nonpolar face of 18A with Phe could yield six peptides. Peptides with an additional 2, 3 and 4 Phe would have theoretical lipid affinity (λ) values of 13, 14 and 15 units, respectively. However, the λ values jumped four units if the additional Phe were increased from 4 to 5 (to 19 λ units). Increasing to 6 or 7 Phe would produce a less dramatic increase (to 20 and 21 λ units, respectively).

[0117] A number of these class A peptides were made including, the peptide designated 4F, D4F, 5F, and D5F, and the like. Various class A peptides inhibited lesion development in atherosclerosis-susceptible mice. In addition, the peptides show varying, but significant degrees of efficacy in mitigating one or more symptoms of the various pathologies described herein. A number of such peptides are illustrated in Table 2.

[0118] Table 2. Illustrative class A amphipathic helical peptides for use in this invention.

Peptide Name	Amino Acid Sequence	SEQ ID NO.
18A	D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F	1

2F	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	2
3F	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	3
3F14	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	4
4F	Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	5
5F	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	6
6F	Ac-D-W-L-K-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	7
7F	Ac-D-W-F-K-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	8
	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	9
	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	10
	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	11
	Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	12
	Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	13
	Ac-E-W-L-K-L-F-Y-E-K-V-L-E-K-F-K-E-A-F-NH_2	14
	Ac-E-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	15
	Ac-E-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	16
	Ac-E-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	17
	Ac-E-W-L-K-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	18
	Ac-E-W-L-K-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	19
	Ac-E-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	20
	AC-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2	21
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	22
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	23
	Ac-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	24
	Ac-A-F-Y-D-K-F-F-E-K-F-K-E-F-F-NH_2	25
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	26
	Ac-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	27
	Ac-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	28
	Ac-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	29
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	30
	Ac-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-NH_2	31
	Ac-L-F-Y-E-K-V-L-E-K-F-K-E-A-F-NH_2	32
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	33
	Ac-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-NH_2	34
	Ac-A-F-Y-D-K-V-F-E-K-F-K-E-A-F-NH_2	35
	Ac-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH_2	36
	Ac-A-F-Y-D-K-V-A-E-K-F-K-E-F-F-NH_2	37
	Ac-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	38
	Ac-D-W-L-K-A-L-Y-D-K-V-A-E-K-L-K-E-A-L-NH_2	39
	Ac-D-W-F-K-A-F-Y-E-K-V-A-E-K-L-K-E-F-F-NH_2	40
	Ac-D-W-F-K-A-F-Y-E-K-F-F-E-K-F-K-E-F-F-NH_2	41
	Ac-E-W-L-K-A-L-Y-E-K-V-A-E-K-L-K-E-A-L-NH_2	42

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-K-L-K-E-A-F-NH_2 43

Ac-E-W-F-K-A-F-Y-E-K-V-A-E-K-L-K-E-F-F-NH_2 44

Ac-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2 45

Ac-E-W-L-K-A-F-Y-E-K-F-F-E-K-F-K-E-F-F-NH_2 46

Ac-E-W-F-K-A-F-Y-E-K-F-F-E-K-F-K-E-F-F-NH_2 47

Ac-D-F-L-K-A-W-Y-D-K-V-A-E-K-L-K-E-A-W-NH_2 48

Ac-E-F-L-K-A-W-Y-E-K-V-A-E-K-L-K-E-A-W-NH_2 49

Ac-D-F-W-K-A-W-Y-D-K-V-A-E-K-L-K-E-W-W-NH_2 50

Ac-E-F-W-K-A-W-Y-E-K-V-A-E-K-L-K-E-W-W-NH_2 51

Ac-D-K-L-K-A-F-Y-D-K-V-F-E-W-A-K-E-A-F-NH_2 52

Ac-D-K-W-K-A-V-Y-D-K-F-A-E-A-F-K-E-F-L-NH_2 53

Ac-E-K-L-K-A-F-Y-E-K-V-F-E-W-A-K-E-A-F-NH_2 54

Ac-E-K-W-K-A-V-Y-E-K-F-A-E-A-F-K-E-F-L-NH_2 55

Ac-D-W-L-K-A-F-V-D-K-F-A-E-K-F-K-E-A-Y-NH_2 56

Ac-E-K-W-K-A-V-Y-E-K-F-A-E-A-F-K-E-F-L-NH_2 57

Ac-D-W-L-K-A-F-V-Y-D-K-V-F-K-L-K-E-F-F-NH_2 58

Ac-E-W-L-K-A-F-V-Y-E-K-V-F-K-L-K-E-F-F-NH_2 59

Ac-D-W-L-R-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH_2 60

Ac-E-W-L-R-A-F-Y-E-K-V-A-E-K-L-K-E-A-F-NH_2 61

Ac-D-W-L-K-A-F-Y-D-R-V-A-E-K-L-K-E-A-F-NH_2 62

Ac-E-W-L-K-A-F-Y-E-R-V-A-E-K-L-K-E-A-F-NH_2 63

Ac-D-W-L-K-A-F-Y-D-K-V-A-E-R-L-K-E-A-F-NH_2 64

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-R-L-K-E-A-F-NH_2 65

Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-R-E-A-F-NH_2 66

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-K-L-R-E-A-F-NH_2 67

Ac-D-W-L-K-A-F-Y-D-R-V-A-E-R-L-K-E-A-F-NH_2 68

Ac-E-W-L-K-A-F-Y-E-R-V-A-E-R-L-K-E-A-F-NH_2 69

Ac-D-W-L-R-A-F-Y-D-K-V-A-E-K-L-R-E-A-F-NH_2 70

Ac-E-W-L-R-A-F-Y-E-K-V-A-E-K-L-R-E-A-F-NH_2 71

Ac-D-W-L-R-A-F-Y-D-R-V-A-E-K-L-K-E-A-F-NH_2 72

Ac-E-W-L-R-A-F-Y-E-R-V-A-E-K-L-K-E-A-F-NH_2 73

Ac-D-W-L-K-A-F-Y-D-K-V-A-E-R-L-R-E-A-F-NH_2 74

Ac-E-W-L-K-A-F-Y-E-K-V-A-E-R-L-R-E-A-F-NH_2 75

Ac-D-W-L-R-A-F-Y-D-K-V-A-E-R-L-K-E-A-F-NH_2 76

Ac-E-W-L-R-A-F-Y-E-K-V-A-E-R-L-K-E-A-F-NH2 77

D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-**-P-**D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F 78

D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F-**-P-**D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-F-F 79

D-W-F-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-**-P-**D-W-F-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F 80

D-K-L-K-A-F-Y-D-K-V-F-E-W-A-K-E-A-F-**-P-**D-K- 81

L-K-A-F-Y-D-K-V-F-E-W-L-K-E-A-F	
D-K-W-K-A-V-Y-D-K-F-A-E-A-F-K-E-F-L-**P**-D-K-W-K-A-V-Y-D-K-F-A-E-A-F-K-E-F-L	82
D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-**P**-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F	83
D-W-L-K-A-F-V-Y-D-K-V-F-K-L-K-E-F-F-**P**-D-W-L-K-A-F-V-Y-D-K-V-F-K-L-K-E-F-F	84
D-W-L-K-A-F-Y-D-K-F-A-E-K-F-K-E-F-F-**P**-D-W-L-K-A-F-Y-D-K-F-A-E-K-F-K-E-F-F	85
Ac-E-W-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-A-F-NH_2	86
Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-NH_2	87
Ac-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-NH_2	88
Ac-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-NH_2	89
NMA-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-NH_2	90
NMA-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-NH_2	91
NMA-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	92
NMA-E-W-F-K-A-F-Y-E-K-V-A-E-K-F-K-E-A-F-NH_2	93
NMA-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2	94
NMA-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-NH_2	95
Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	96
NMA-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	97
NMA-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	98
NMA-A-F-Y-D-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	99
NMA-A-F-Y-E-K-V-F-E-K-F-K-E-F-F-NH_2	
Ac-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-NH_2	100
NMA-D-W-L-K-A-F-Y-D-K-V-F-E-K-F-NH_2	
Ac-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-NH_2	101
NMA-E-W-L-K-A-F-Y-E-K-V-F-E-K-F-NH_2	
Ac-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-NH_2	102
NMA-L-K-A-F-Y-D-K-V-F-E-K-F-K-E-NH_2	
Ac-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-NH_2	103
NMA-L-K-A-F-Y-E-K-V-F-E-K-F-K-E-NH_2	

[1]Linkers are underlined.

NMA is N-Methyl Anthranilyl.

[0119] In certain preferred embodiments, the peptides include variations of 4F ((SEQ ID NO:5 in Table 2), also known as L-4F, where all residues are L form amino acids) or D-4F where one or more residues are D form amino acids). In any of the

peptides described herein, the C-terminus, and/or N-terminus, and/or internal residues can be blocked with one or more blocking groups as described herein.

[0120] While various peptides of Table 2, are illustrated with an acetyl group or an N-methylanthranilyl group protecting the amino terminus and an amide group protecting the carboxyl terminus, any of these protecting groups may be eliminated and/or substituted with another protecting group as described herein. In particularly preferred embodiments, the peptides comprise one or more D-form amino acids as described herein. In certain embodiments, every amino acid (*e.g.,* every enantiomeric amino acid) of the peptides of Table 2 is a D-form amino acid.

[0121] It is also noted that Table 2 is not fully inclusive. Using the teachings provided herein, other suitable class A amphipathic helical peptides can routinely be produced (*e.g.,* by conservative or semi-conservative substitutions (*e.g.,* D replaced by E), extensions, deletions, and the like). Thus, for example, one embodiment utilizes truncations of any one or more of peptides shown herein (*e.g.,* peptides identified by SEQ ID Nos:2-20 and 39- in Table 2). Thus, for example, SEQ ID NO:21 illustrates a peptide comprising 14 amino acids from the C-terminus of 18A comprising one or more D amino acids, while SEQ ID NOS:22-38 illustrate other truncations.

[0122] Longer peptides are also suitable. Such longer peptides may entirely form a class A amphipathic helix, or the class A amphipathic helix (helices) can form one or more domains of the peptide. In addition, this invention contemplates multimeric versions of the peptides (*e.g.,* concatamers). Thus, for example, the peptides illustrated herein can be coupled together (directly or through a linker (*e.g.,* a carbon linker, or one or more amino acids) with one or more intervening amino acids). Illustrative polymeric peptides include 18A-Pro-18A and the peptides of SEQ ID NOs:78-85, in certain embodiments comprising one or more D amino acids, more preferably with every amino acid a D amino acid as described herein and/or having one or both termini protected.

[0123] It will also be appreciated in addition to the peptide sequences expressly illustrated herein, this invention also contemplates retro and retro-inverso forms of each of these peptides. In retro forms, the direction of the sequence is reversed. In inverse forms, the chirality of the constituent amino acids is reversed (*i.e.,* L form amino acids become D form amino acids and D form amino acids become L form amino acids). In the retro-inverso form, both the order and the chirality of the amino acids is reversed. Thus, for

example, a retro form of the 4F peptide (DWFKAFYDKVAEKFKEAF, SEQ ID NO:5), where the amino terminus is at the aspartate (D) and the carboxyl terminus is at the phenylalanine (F), has the same sequence, but the amino terminus is at the phenylalanine and the carboxy terminus is at the aspartate (*i.e.*, FAEKFKEAVKDYFAKFWD, SEQ ID NO:104). Where the 4F peptide comprises all L amino acids, the retro-inverso form will have the sequence shown above (SEQ ID NO:104) and comprise all D form amino acids. As illustrated in the helical wheel diagrams of Figure 15, 4F and retroinverso (Rev-4F) are mirror images of each other with identical segregation of the polar and nonpolar faces with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face. These mirror images of the same polymer of amino acids are identical in terms of the segregation of the polar and nonpolar faces with the positively charged residues residing at the polar-nonpolar interface and the negatively charged residues residing at the center of the polar face. Thus, 4F and Rev-4F are enantiomers of each other. For a discussion of retro- and retro-inverso peptides *see, e.g.,* Chorev and Goodman, (1995) *TibTech,* 13: 439-445.

[0124] Where reference is made to a sequence and orientation is not expressly indicated, the sequence can be viewed as representing the amino acid sequence in the amino to carboxyl orientation, the retro form (*i.e.,* the amino acid sequence in the carboxyl to amino orientation), the retro form where L amino acids are replaced with D amino acids or D amino acids are replaced with L amino acids, and the retro-inverso form where both the order is reversed and the amino acid chirality is reversed.

C) Class A amphipathic helical peptide mimetics of apoA-I having Aromatic or aliphatic residues in the non-polar face.

[0125] In certain embodiments, this invention also provides modified class A amphipathic helix peptides. Certain preferred peptides incorporate one or more aromatic residues at the center of the nonpolar face, *e.g.,* $3F^{C\pi}$, (as present in 4F), or with one or more aliphatic residues at the center of the nonpolar face, *e.g.,* $3F^{I\pi}$, *see, e.g.,* Table 3. Without being bound to a particular theory, we believe the central aromatic residues on the nonpolar face of the peptide $3F^{C\pi}$, due to the presence of π electrons at the center of the nonpolar face, allow water molecules to penetrate near the hydrophobic lipid alkyl chains of the peptide-lipid complex, which in turn would enable the entry of reactive oxygen species (such as lipid hydroperoxides) shielding them from the cell surface. Similarly, we

also believe the peptides with aliphatic residues at the center of the nonpolar face, *e.g.*, $3F^{I\pi}$, will act similarly but not quite as effectively as $3F^{C\pi}$.

[0126] Preferred peptides will convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory, and/or decrease LDL-induced monocyte chemotactic activity generated by artery wall cells equal to or greater than D4F or other peptides shown in Table 2.

[0127] Table 3. Examples of certain preferred peptides.

Name	Sequence	SEQ ID NO
($3F^{C\pi}$)	Ac-DKWKAVYDKFAEAFKEFL-NH_2	105
($3F^{I\pi}$)	Ac-DKLKAFYDKVFEWAKEAF-NH_2	106

C) Other class A and some class Y amphipathic helical peptides.

[0128] In certain embodiments this invention also contemplates class a amphipathic helical peptides that have an amino acid composition identical to one or more of the class a amphipathic helical peptides described above. Thus, for example, in certain embodiments this invention contemplates peptides having an amino acid composition identical to 4F. Thus, in certain embodiments, this invention includes active agents that comprise a peptide that consists of 18 amino acids, where the 18 amino acids consist of 3 alanines (A), 2 aspartates (D), 2 glutamates (E), 4 phenylalanines (F), 4 lysines (K), 1 valine (V), 1 tryptophan (W), and 1 tyrosine (Y); and where the peptide forms a class A amphipathic helix; and protects a phospholipid against oxidation by an oxidizing agent. In various embodiments, the peptides comprise least one "D" amino acid residue; and in certain embodimemtns, the peptides comprise all "D: form amino acid residues. A variety of such peptides are illustrated in Table 4. Reverse (retro-), inverse, retro-inverso-, and circularly permuted forms of these peptides are also contemplated.

[0129] Table 4. Illustrative 18 amino acid length class A amphipathic helical peptides with the amino acid composition 3 alanines (A), 2 aspartates (D), 2 glutamates (E), 4 phenylalanines (F), 4 lysines (K), 1 valine (V), 1 tryptophan (W), and 1 tyrosine (Y).

Name	Sequence	SEQ ID NO
[Switch D-E]-4F analogs		107
[Switch D-E]-1-4F	Ac-**E**WFKAFY**E**KVA**D**KFK**D**AF-NH2	108
[Switch D-E]-2-4F	Ac-**E**WFKAFYDKVADKFK**E**AF-NH2	109

[Switch D-E]-3-4F	Ac-DWFKAFY**E**KVA**D**KFKEAF-NH2	110
[Switch D-E]-4-4F	Ac-DWFKAFY**E**KVAEKFK**D**AF-NH2	111
[W-2,F-3 positions reversed]		112
4F-2	Ac-D**FW**KAFYDKVAEKFKEAF-NH_2	113
[Switch D-E]-1-4F-2	Ac-**E**FWKAFY**E**KVA**D**KFK**D**AF-NH2	114
[Switch D-E]-2-4F-2	Ac-**E**FWKAFYDKVADKFK**E**AF-NH2	115
[Switch D-E]-3-4F-2	Ac-DFWKAFY**E**KVA**D**KFKEAF-NH2	116
[Switch D-E]-4-4F-2	Ac-DFWKAFY**E**KVAEKFK**D**AF-NH2	117
[F-6 and Y-7 positions switched]		118
4F-3	Ac-DWFKA**YF**DKVAEKFKEAF-NH_2	119
[Switch D-E]-1-4F-5	Ac-**E**WFKAYF**E**KVA**D**KFK**D**AF-NH2	120
[Switch D-E]-2-4F-5	Ac-**E**WFKAYFDKVADKFK**E**AF-NH2	121
[Switch D-E]-3-4F-5	Ac-DWFKAYF**E**KVA**D**KFKEAF-NH2	122
[Switch D-E]-4-4F-5	Ac-DWFKAYF**E**KVAEKFK**D**AF-NH2	123
[Y-7and 10V positions switched]		124
4F-4	Ac-DWFKAF**V**DK**Y**AEKFKEAF-NH_2	125
[Switch D-E]-1-4F-4	Ac-**E**WFKAFV**E**KYA**D**KFK**D**AF-NH2	126
[Switch D-E]-2-4F-4	Ac-**E**WFKAFVDKYADKFK**E**AF-NH2	127
[Switch D-E]-3-4F-4	Ac-DWFKAFV**E**KYA**D**KFKEAF-NH2	128
[Switch D-E]-4-4F	Ac-DWFKAFV**E**KYAEKFK**D**AF-NH2	129
[V-10 and A-11 switched]		130
4-F-5	Ac-DWFKAFYDK**AV**EKFKEAF-NH_2	131
[Switch D-E]-1-4F-5	Ac-**E**WFKAFY**E**KAV**D**KFK**D**AF-NH2	132
[Switch D-E]-2-4F-5	Ac-**E**WFKAFYDKAVDKFK**E**AF-NH2	133
[Switch D-E]-3-4F-5	Ac-DWFKAFY**E**KAV**D**KFKEAF-NH2	134
[Switch D-E]-4-4F-5	Ac-DWFKAFY**E**KAVEKFK**D**AF-NH2	135
[A-11 and F-14 switched]		136
4F-6	Ac-DWFKAFYDKV**F**EK**A**KEAF-NH_2	137
[Switch D-E]-1-4F-6	Ac-**E**WFKAFY**E**KVF**D**KAK**D**AF-NH2	138
[Switch D-E]-2-4F-6	Ac-**E**WFKAFYDKVFDKAK**E**AF-NH2	139
[Switch D-E]-3-4F-6	Ac-DWFKAFY**E**KVF**D**KAKEAF-NH2	140
[Switch D-E]-4-4F-6	Ac-DWFKAFY**E**KVFEKAK**D**AF-NH2	141
[F-14 and A-17 switched]		142
4F-7	Ac-DWFKAFYDKVAEK**A**KE**F**F-NH_2	143
[Switch D-E]-1-4F-7	Ac-**E**WFKAFY**E**KVA**D**KAK**D**FF-NH2	144
[Switch D-E]-2-4F-7	Ac-**E**WFKAFYDKVADKAK**E**FF-NH2	145
[Switch D-E]-3-4F-7	Ac-DWFKAFY**E**KVA**D**KAKEFF-NH2	146
[Switch D-E]-4-4F-7	Ac-DWFKAFY**E**KVAEKAK**D**FF-NH2	147
[A-17 and F-18 switched]		148
4F-8	Ac-DWFKAFYDKVAEKFKE**FA**-NH_2	149
[Switch D-E]-1-4F-8	Ac-**E**WFKAFY**E**KVA**D**KFK**D**FA-NH2	150
[Switch D-E]-2-4F-8	Ac-**E**WFKAFYDKVADKFK**E**FA-NH2	151
[Switch D-E]-3-4F-8	Ac-DWFKAFY**E**KVA**D**KFKEFA-NH2	152
[Switch D-E]-4-4F-8	Ac-DWFKAFY**E**KVAEKFK**D**FA-NH2	153
[W-2 and A-17 switched]		154
4F-9	Ac-D**A**FKAFYDKVAEKFKE**W**F-NH_2	155
[Switch D-E]-1-4F-9	Ac-**E**AFKAFY**E**KVA**D**KFK**D**WF-NH2	156
[Switch D-E]-2-4F-9	Ac-**E**AFKAFYDKVADKFK**E**WF-NH2	157
[Switch D-E]-3-4F-9	Ac-DAFKAFY**E**KVA**D**KFKEWF-NH2	158
[Switch D-E]-4-4F-9	Ac-DAFKAFY**E**KVAEKFK**D**WF-NH2	159
[W-2 and A-11 switched]		160
4F-10	Ac-D**A**FKAFYDKV**W**EKFKEAF-NH_2	161
[Switch D-E]-1-4F-10	Ac-**E**AFKAFY**E**KVW**D**KFK**D**AF-NH2	162

[Switch D-E]-2-4F-10	Ac-EAFKAFYDKVWDKFKEAF-NH2	163
[Switch D-E]-3-4F-10	Ac-DAFKAFYEKVWDKFKEAF-NH2	164
[Switch D-E]-4-4F-10	Ac-DAFKAFYEKVWEKFKDAF-NH2	165
[W-2 and Y-7 switched]		166
4F-11	Ac-DYFKAFWDKVAEKFKEAF-NH_2	167
[Switch D-E]-1-4F-11	Ac-EYFKAFWEKVADKFKDAF-NH2	168
[Switch D-E]-2-4F-11	Ac-EYFKAFWDKVADKFKEAF-NH2	169
[Switch D-E]-3-4F-11	Ac-DYFKAFWEKVADKFKEAF-NH2	170
[Switch D-E]-4-4F-11	Ac-DYFKAFWEKVAEKFKDAF-NH2	171
[F-3 and A-17 switched]		172
4F-12	Ac-DWAKAFYDKVAEKFKEFF-NH_2	173
[Switch D-E]-1-4F-12	Ac-EWAKAFYEKVADKFKDFF-NH2	174
[Switch D-E]-2-4F-12	Ac-EWAKAFYDKVADKFKEFF-NH2	175
[Switch D-E]-3-4F-12	Ac-DWAKAFYEKVADKFKEFF-NH2	176
[Switch D-E]-4-4F-12	Ac-DWAKAFYEKVAEKFKDFF-NH2	177
[F-6 and A-17 switched]		178
4F-13	Ac-DWFKAAYDKVAEKFKEFF-NH_2	179
[Switch D-E]-1-4F-13	Ac-EWFKAAYEKVADKFKDFF-NH2	180
[Switch D-E]-2-4F-13	Ac-EWFKAAYDKVADKFKEFF-NH2	181
[Switch D-E]-3-4F-13	Ac-DWFKAAYEKVADKFKEFF-NH2	182
[Switch D-E]-4-4F-13	Ac-DWFKAAYEKVAEKFKDFF-NH2	183
[Y-7 and A-17 switched		184
4F-14	Ac-DWFKAFADKVAEKFKEYF-NH_2	185
[Switch D-E]-1-4F-14	Ac-EWFKAFAEKVADKFKDYF-NH2	186
[Switch D-E]-2-4F-14	Ac-EWFKAFADKVADKFKEYF-NH2	187
[Switch D-E]-3-4F-14	Ac-DWFKAFAEKVADKFKEYF-NH2	188
[Switch D-E]-4-4F	Ac-DWFKAFAEKVAEKFKDYF-NH2	189
[V-10 and A-17 switched]		190
4F-15	Ac-DWFKAFYDKAAEKFKEVF-NH_2	191
[Switch D-E]-1-4F-15	Ac-EWFKAFYEKAADKFKDVF-NH2	192
[Switch D-E]-2-4F-15	Ac-EWFKAFYDKAADKFKEVF-NH2	193
[Switch D-E]-3-4F-15	Ac-DWFKAFYEKAADKFKEVF-NH2	194
[Switch D-E]-4-4F-15	Ac-DWFKAFYEKAAEKFKDVF-NH2	195
[F3 and Y-7 switched]		196
4F-16	Ac-DWYKAFFDKVAEKFKEAF-NH_2	197
[Switch D-E]-1-4F-16	Ac-EWYKAFFEKVADKFKDAF-NH2	198
[Switch D-E]-2-4F-16	Ac-EWYKAFFDKVADKFKEAF-NH2	199
[Switch D-E]-3-4F-16	Ac-DWYKAFFEKVADKFKEAF-NH2	200
[Switch D-E]-4-4F-16	Ac-DWYKAFFEKVAEKFKDAF-NH2	201
[F-3 and V-10 switched]		202
4F-17	Ac-DWVKAFYDKFAEKFKEAF-NH_2	203
[Switch D-E]-1-4F-17	Ac-EWVKAFYEKFADKFKDAF-NH2	204
[Switch D-E]-2-4F-17	Ac-EWVKAFYDKFADKFKEAF-NH2	205
[Switch D-E]-3-4F-17	Ac-DWVKAFYEKFADKFKEAF-NH2	206
[Switch D-E]-4-4F-17	Ac-DWVKAFYEKFAEKFKDAF-NH2	207
[Y-7 and F-14 switched]		208
4F-18	Ac-DWFKAFFDKVAEKYKEAF-NH_2	209
[Switch D-E]-1-4F-18	Ac-EWFKAFFEKVADKYKDAF-NH2	210
[Switch D-E]-2-4F-18	Ac-EWFKAFFDKVADKYKEAF-NH2	211
[Switch D-E]-3-4F-18	Ac-DWFKAFFEKVADKYKEAF-NH2	212
[Switch D-E]-3-4F-18	Ac-DWFKAFFEKVADKYKEAF-NH2	213
[Y-7 and F-18 switched]		214
4F-19	Ac-DWFKAFFDKVAEKFKEAY-NH_2	215

[Switch D-E]-1-4F-19	Ac-**E**WFKAFF**E**KVA**D**KFK**D**AY-NH2	216
[Switch D-E]-2-4F-19	Ac-**E**WFKAFFDKVADKFK**E**AY-NH2	217
[Switch D-E]-3-4F-19	Ac-DWFKAFF**E**KVA**D**KFKEAY-NH2	218
[Switch D-E]-4-4F-19	Ac-DWFKAFF**E**KVAEKFK**D**AY-NH2	219
[V-10 and F-18 switched		220
4F-20	Ac-DWFKAFYDK**F**AEKFKEA**V**-NH_2	221
[Switch D-E]-1-4F-20	Ac-**E**WFKAFY**E**KFA**D**KFK**D**AV-NH2	222
[Switch D-E]-2-4F-20	Ac-**E**WFKAFYDKFADKFK**E**AV-NH2	223
[Switch D-E]-3-4F-20	Ac-DWFKAFY**E**KFA**D**KFKEAV-NH2	224
[Switch D-E]-4-4F-20	Ac-DWFKAFY**E**KFAEKFK**D**AV-NH2	225
[W-2 and K13 switched]		226
4F-21	Ac-D**K**FKAFYDKVAEKF**W**EAF-NH_2	227
[Switch D-E]-1-4F-21	Ac-**E**KFKAFY**E**KVA**D**KFW**D**AF-NH2	228
[Switch D-E]-2-4F-21	Ac-**E**KFKAFYDKVADKFW**E**AF-NH2	229
[Switch D-E]-3-4F-21	Ac-DKFKAFY**E**KVA**D**KFWEAF-NH2	230
[Switch D-E]-4-4F-21	Ac-DKFKAFY**E**KVAEKFW**D**AF-NH2	231
[W-3, F-13 and K-2 4F]		232
4F-22	Ac-D**KW**KAFYDKVAEKF**F**EAF-NH_2	233
[Switch D-E]-1-4F-22	Ac-**E**KWKAFY**E**KVA**D**KFF**D**AF-NH2	234
[Switch D-E]-2-4F-22	Ac-**E**KWKAFYDKVADKFF**E**AF-NH2	235
[Switch D-E]-3-4F-22	Ac-DKWKAFY**E**KVA**D**KFFEAF-NH2	236
[Switch D-E]-4-4F-22	Ac-DKWKAFY**E**KVAEKFF**D**AF-NH2	237
[K-2, W10, V-13]		238
4F-23	Ac-D**K**FKAFYDK**W**AE**V**FKEAF-NH_2	239
[Switch D-E]-4F analogs		240
[Switch D-E]-1-4F-23	Ac-**E**KFKAFY**E**KWA**D**VFK**D**AF-NH2	241
[Switch D-E]-2-4F-23	Ac-**E**KFKAFYDKWADVFK**E**AF-NH2	242
[Switch D-E]-3-4F-23	Ac-DKFKAFY**E**KWA**D**VFKEAF-NH2	243
[Switch D-E]-4-4F-23	Ac-DKFKAFY**E**KWAEVFK**D**AF-NH2	244
[K-2, F-13, W-14 4F]		245
4F-24	Ac-D**K**FKAFYDKVAE**FW**KEAF-NH_2	246
[Switch D-E]-4F analogs		247
[Switch D-E]-1-4F-24	Ac-**E**KFKAFY**E**KVA**D**FWK**D**AF-NH2	248
[Switch D-E]-2-4F-24	Ac-**E**KFKAFYDKVADFWK**E**AF-NH2	249
[Switch D-E]-3-4F-24	Ac-DKFKAFY**E**KVA**D**FWKEAF-NH2	250
[Switch D-E]-4-4F-24	Ac-DKFKAFY**E**KVAEFWK**D**AF-NH2	251
Reverse 4F analogs		252
Rev-4F	Ac-FAEKFKEAVKDYFAKFWD-NH2	253
[Switch D-E]-1-Rev-4F	Ac-FA**D**KFK**D**AVK**E**YFAKFW**E**-NH2	254
[Switch D-E]-2-Rev-4F	Ac-FA**D**KFKEAVKDYFAKFW**E**-NH2	255
[Switch D-E]-3-Rev-4F	Ac-FAEKFK**D**AVK**E**YFAKFWD-NH2	256
[Switch D-E]-4-Rev-4F	Ac-FAEKFK**D**AVKDYFAKFW**E**-NH2	257
[A-2 and W-17 switched]		258
Rev-4F-1	Ac-F**W**EKFKEAVKDYFAKF**A**D-NH2	259
[Switch D-E]-1-Rev-4F-1	Ac-FW**D**KFK**D**AVK**E**YFAKFA**E**-NH2	260
[Switch D-E]-2-Rev-4F-1	Ac-FA**D**KFKEAVKDYFAKFW**E**-NH2	261
[Switch D-E]-3-Rev-4F-1	Ac-FAEKFK**D**AVK**E**YFAKFWD-NH2	262
[Switch D-E]-4-Rev-4F-1	Ac-FAEKFK**D**AVKDYFAKFW**E**-NH2	263
[Switch A-2 and F-16]		264
Rev-4F-2	Ac-F**F**EKFKEAVKDYFAK**A**WD-NH2	265
[Switch D-E]-1-Rev-4F-2	Ac-FF**D**KFK**D**AVK**E**YFAKAW**E**-NH2	266
[Switch D-E]-2-Rev-4F-2	Ac-FF**D**KFKEAVKDYFAKAW**E**-NH2	267
[Switch D-E]-3-Rev-4F-2	Ac-FFEKFK**D**AVK**E**YFAKAWD-NH2	268

[Switch D-E]-4-Rev-4F-2	Ac-FFEKFK**D**AVKDYFAKAW**E**-NH2	269
[switch F-5 and A-8]		270
Rev-4F-3	Ac-FAEK**A**KE**F**VKDYFAKFWD-NH2	271
[Switch D-E]-1-Rev-4F-3	Ac-FA**D**KAK**D**FVK**E**YFAKFW**E**-NH2	272
[Switch D-E]-2-Rev-4F-3	Ac-FA**D**KAKEFVKDYFAKFW**E**-NH2	273
[Switch D-E]-3-Rev-4F-3	Ac-FAEKAK**D**FVK**E**YFAKFWD-NH2	274
[Switch D-E]-4-Rev-4F-3	Ac-FAEKAK**D**FVKDYFAKFW**E**-NH2	275
[Switch A-8 and V9]		276
Rev-4F-4	Ac-FAEKFKE**VA**KDYFAKFWD-NH2	277
[Switch D-E]-1-Rev-4F-4	Ac-FA**D**KFK**D**VAK**E**YFAKFW**E**-NH2	278
[Switch D-E]-2-Rev-4F-4	Ac-FA**D**KFKEVAKDYFAKFW**E**-NH2	279
[Switch D-E]-3-Rev-4F-4	Ac-FAEKFK**D**VAK**E**YFAKFWD-NH2	280
[Switch D-E]-4-Rev-4F-4	Ac-FAEKFK**D**VAKDYFAKFW**E**-NH2	281
[Switch V-9 to Y-12]		282
Rev-4F-5	Ac-FAEKFKEA**Y**KD**V**FAKFWD-NH2	283
[Switch D-E]-1-Rev-4F-5	Ac-FA**D**KFK**D**AYK**E**VFAKFW**E**-NH2	284
[Switch D-E]-2-Rev-4F-5	Ac-FA**D**KFKEAYKDVFAKFW**E**-NH2	285
[Switch D-E]-3-Rev-4F-5	Ac-FAEKFK**D**AYK**E**VFAKFWD-NH2	286
[Switch D-E]-4-Rev-4F-5	Ac-FAEKFK**D**AYKDVFAKFW**E**-NH2	287
[Switch Y-12 and F-13]		288
Rev-4F-6	Ac-FAEKFKEAVKD**FY**AKFWD-NH2	289
[Switch D-E]-1-Rev-4F-6	Ac-FA**D**KFK**D**AVK**E**FYAKFW**E**-NH2	290
[Switch D-E]-2-Rev-4F-6	Ac-FA**D**KFKEAVKDFYAKFW**E**-NH2	291
[Switch D-E]-3-Rev-4F-6	Ac-FAEKFK**D**AVK**E**FYAKFWD-NH2	292
[Switch D-E]-4-Rev-4F-6	Ac-FAEKFK**D**AVKDFYAKFW**E**-NH2	293
[Switch K-6 and W-17]		294
Rev-4F-7	Ac-FAEKF**W**EAVKDYFAKF**K**D-NH2	295
[Switch D-E]-1-Rev-4F-7	Ac-FA**D**KFW**D**AVK**E**YFAKFK**E**-NH2	296
[Switch D-E]-2-Rev-4F-7	Ac-FA**D**KFWEAVKDYFAKFK**E**-NH2	297
[Switch D-E]-3-Rev-4F-7	Ac-FAEKFW**D**AVK**E**YFAKFKD-NH2	298
[Switch D-E]-4-Rev-4F-7	Ac-FAEKFW**D**AVKDYFAKFK**E**-NH2	299
[Switch F-1 and A-2]		300
Rev-4F-8	Ac-**AF**EKFKEAVKDYFAKFWD-NH2	301
[Switch D-E]-1-Rev-4F-8	Ac-AF**D**KFK**D**AVK**E**YFAKFW**E**-NH2	302
[Switch D-E]-2-Rev-4F-8	Ac-AF**D**KFKEAVKDYFAKFW**E**-NH2	303
[Switch D-E]-3-Rev-4F-8	Ac-AFEKFK**D**AVK**E**YFAKFWD-NH2	304
[Switch D-E]-4-Rev-4F-8	Ac-AFEKFK**D**AVKDYFAKFW**E**-NH2	305
[F-1 and V-9 are switched]		306
Rev-F-9	Ac-**V**AEKFKEA**F**KDYFAKFWD-NH2	307
[Switch D-E]-1-Rev-4F-9	Ac-VA**D**KFK**D**AFK**E**YFAKFW**E**-NH2	308
[Switch D-E]-2-Rev-4F-9	Ac-VA**D**KFKEAFKDYFAKFW**E**-NH2	309
[Switch D-E]-3-Rev-4F-9	Ac-VAEKFK**D**AFK**E**YFAKFWD-NH2	310
[Switch D-E]-4-Rev-4F-9	Ac-VAEKFK**D**AFKDYFAKFW**E**-NH2	311
[F-1 and Y-12 are switched]		312
Rev-4F-10	Ac-**Y**AEKFKEAVKD**F**FAKFWD-NH2	313
[Switch D-E]-1-Rev-4F-10	Ac-YA**D**KFK**D**AVK**E**FFAKFW**E**-NH2	314
[Switch D-E]-2-Rev-4F-10	Ac-YA**D**KFKEAVKDFFAKFW**E**-NH2	315
[Switch D-E]-3-Rev-4F-10	Ac-YAEKFK**D**AVK**E**FFAKFWD-NH2	316
[Switch D-E]-4-Rev-4F-10	Ac-YAEKFK**D**AVKDFFAKFW**E**-NH2	317
[F-1 and A-8 are switched]		318
Rev-4F-11	Ac-**A**AEKFKE**F**VKDYFAKFWD-NH2	319
[Switch D-E]-1-Rev-4F-11	Ac-AA**D**KFK**D**FVK**E**YFAKFW**E**-NH2	320
[Switch D-E]-2-Rev-4F-11	Ac-AA**D**KFKEFVKDYFAKFW**E**-NH2	321

[Switch D-E]-3-Rev-4F-11	Ac-AAEKFK**D**FVK**E**YFAKFWD-NH2	322
Switch D-E]-4-Rev-4F-11	Ac-AAEKFK**D**FVKDYFAKFW**E**-NH2	323
[A-2 and F-5 are switched]		324
Rev-4F-12	Ac-F**F**EK**A**KEAVKDYFAKFWD-NH2	325
[Switch D-E]-1-Rev-4F-12	Ac-FF**D**KAK**D**AVK**E**YFAKFW**E**-NH2	326
[Switch D-E]-2-Rev-4F-12	Ac-FF**D**KAKEAVKDYFAKFW**E**-NH2	327
[Switch D-E]-3-Rev-4F-12	Ac-FFEKAK**D**AVK**E**YFAKFWD-NH2	328
[Switch D-E]-4-Rev-4F-12	Ac-FFEKAK**D**AVKDYFAKFW**E**-NH2	329
[A-2 and Y12 are switched		330
Rev-4F-13	Ac-F**Y**EKFKEAVKD**A**FAKFWD-NH2	331
[Switch D-E]-1-Rev-4F-13	Ac-FY**D**KFK**D**AVK**E**AFAKFW**E**-NH2	332
[Switch D-E]-2-Rev-4F-13	Ac-FY**D**KFKEAVKDAFAKFW**E**-NH2	333
[Switch D-E]-3-Rev-4F-13	Ac-FYEKFK**D**AVK**E**AFAKFWD-NH2	334
[Switch D-E]-4-Rev-4F-13	Ac-FYEKFK**D**AVKDAFAKFW**E**-NH2	335
[A-2 and V-9 are switched]		336
Rev-4F-14	Ac-F**V**EKFKEA**A**KDYFAKFWD-NH2	337
[Switch D-E]-1-Rev-4F-14	Ac-FV**D**KFK**D**AAK**E**YFAKFW**E**-NH2	338
[Switch D-E]-2-Rev-4F-14	Ac-FV**D**KFKEAAKDYFAKFW**E**-NH2	339
[Switch D-E]-3-Rev-4F-14	Ac-FVEKFK**D**AAK**E**YFAKFWD-NH2	340
[Switch D-E]-4-Rev-4F-14	Ac-FVEKFK**D**AAKDYFAKFW**E**-NH2	341
[F-5 and Y-12 are switched]		342
Rev-4F-15	Ac-FAEK**Y**KEAVKD**F**FAKFWD-NH2	343
[Switch D-E]-1-Rev-4F-15	Ac-FA**D**KYK**D**AVK**E**FFAKFW**E**-NH2	344
[Switch D-E]-2-Rev-4F-15	Ac-FA**D**KYKEAVKDFFAKFW**E**-NH2	345
[Switch D-E]-3-Rev-4F-15	Ac-FAEKYK**D**AVK**E**FFAKFWD-NH2	346
[Switch D-E]-4-Rev-4F-15	Ac-FAEKYK**D**AVKDFFAKFW**E**-NH2	347
[F-5 and V-9 are switched]		348
Rev-4F-16	Ac-FAEK**V**KEA**F**KDYFAKFWD-NH2	349
[Switch D-E]-1-Rev-4F-16	Ac-FA**D**KVK**D**AFK**E**YFAKFW**E**-NH2	350
[Switch D-E]-2-Rev-4F-16	Ac-FA**D**KVKEAFKDYFAKFW**E**-NH2	351
[Switch D-E]-3-Rev-4F-16	Ac-FAEKVK**D**AFK**E**YFAKFWD-NH2	352
[Switch D-E]-4-Rev-4F-16	Ac-FAEKVK**D**AFKDYFAKFW**E**-NH2	353
[A-8 and Y-12 switched]		354
Rev-4F-17	Ac-FAEKFKE**Y**VKD**A**FAKFWD-NH2	355
[Switch D-E]-1-Rev-4F-17	Ac-FA**D**KFK**D**YVK**E**AFAKFW**E**-NH2	356
[Switch D-E]-2-Rev-4F-17	Ac-FA**D**KFKEYVKDAFAKFW**E**-NH2	357
[Switch D-E]-3-Rev-4F-17	Ac-FAEKFK**D**YVK**E**AFAKFWD-NH2	358
[Switch D-E]-4-Rev-4F-17	Ac-FAEKFK**D**YVKDAFAKFW**E**-NH2	359
[V-9 and F-13 are switched]		360
Rev-4F-18	Ac-FAEKFKEA**F**KDY**V**AKFWD-NH2	361
[Switch D-E]-1-Rev-4F-18	Ac-FA**D**KFK**D**AFK**E**YVAKFW**E**-NH2	362
[Switch D-E]-2-Rev-4F-18	Ac-FA**D**KFKEAFKDYVAKFW**E**-NH2	363
[Switch D-E]-3-Rev-4F-18	Ac-FAEKFK**D**AFK**E**YVAKFWD-NH2	364
[Switch D-E]-4-Rev-4F-18	Ac-FAEKFK**D**AFKDYVAKFW**E**-NH2	365
[V-9 and F-16 switched]		366
Rev-4F-19	Ac-FAEKFKEA**F**KDYFAK**V**WD-NH2	367
[Switch D-E]-1-Rev-4F-19	Ac-FA**D**KFK**D**AFK**E**YFAKVW**E**-NH2	368
[Switch D-E]-2-Rev-4F-19	Ac-FA**D**KFKEAFKDYFAKVW**E**-NH2	369
[Switch D-E]-3-Rev-4F-19	Ac-FAEKFK**D**AFK**E**YFAKVWD-NH2	370
Switch D-E]-4-Rev-4F-19	Ac-FAEKFK**D**AFKDYFAKVW**E**-NH2	371
[Y-12 and F-16 are switched		372
Rev-4F-20	Ac-FAEKFKEAVKD**F**FAK**Y**WD-NH2	373
[Switch D-E]-1-Rev-4F-20	Ac-FA**D**KFK**D**AVK**E**FFAKYW**E**-NH2	374

[Switch D-E]-2-Rev-4F-20	Ac-FA**D**KFKEAVKDFFAKYW**E**-NH2	375
[Switch D-E]-3-Rev-4F-20	Ac-FAEKFK**D**AVK**E**FFAKYWD-NH2	376
[Switch D-E]-4-Rev-4F-20	Ac-FAEKFK**D**AVKDFFAKYW**E**-NH2	377
[W-1, F-6 and K-17 Rev 4F]		378
Rev-4F-21	Ac-**W**AEKF**F**EAVKDYFAKF**K**D-NH2	379
[Switch D-E]-1-Rev-4F-7	Ac-WA**D**KFF**D**AVK**E**YFAKFK**E**-NH2	380
[Switch D-E]-2-Rev-4F-7	Ac-WA**D**KFFEAVKDYFAKFK**E**-NH2	381
[Switch D-E]-3-Rev-4F-7	Ac-WAEKFF**D**AVK**E**YFAKFKD-NH2	382
Switch D-E]-4-Rev-4F-7	Ac-WAEKFF**D**AVKDYFAKFK**E**-NH2	383
[W-5, F-6 and K-17 Rev-4F]		384
Rev-4F-22	Ac-FAEK**W**F**F**EAVKDYFAKF**K**D-NH2	385
[Switch D-E]-1-Rev-4F-22	Ac-FA**D**KWF**D**AVK**E**YFAKFK**E**-NH2	386
[Switch D-E]-2-Rev-4F-22	Ac-FA**D**KWFEAVKDYFAKFK**E**-NH2	387
[Switch D-E]-3-Rev-4F-22	Ac-FAEKWF**D**AVK**E**YFAKFKD-NH2	388
[Switch D-E]-4-Rev-4F-22	Ac-FAEKWF**D**AVKDYFAKFK**E**-NH2	389
[V-6, W-9, K-17 Rev-4F]		390
Rev-4F-23	Ac-FAEKF**V**EA**W**KDYFAKF**K**D-NH2	391
[Switch D-E]-1-Rev-4F-23	Ac-FA**D**KFV**D**AWK**E**YFAKFK**E**-NH2	392
[Switch D-E]-2-Rev-4F-23	Ac-FA**D**KFVEAWKDYFAKFK**E**-NH2	393
[Switch D-E]-3-Rev-4F-23	Ac-FAEKFV**D**AWK**E**YFAKFKD-NH2	394
[Switch D-E]-4-Rev-4F-23	Ac-FAEKFV**D**AWKDYFAKFK**E**-NH2	395
[Y-2, A-4, W-12, K-17 Rev-4F]		396
Rev-4F-24	Ac-F**Y**EKF**A**EAVKD**W**FAKF**K**D-NH2	397
[Switch D-E]-1-Rev-4F-24	Ac-FY**D**KFA**D**AVK**E**WFAKFK**E**-NH2	398
[Switch D-E]-2-Rev-4F-24	Ac-FY**D**KFAEAVKDWFAKFK**E**-NH2	399
[Switch D-E]-3-Rev-4F-24	Ac-FYEKFA**D**AVK**E**WFAKFKD-NH2	400
[Switch D-E]-4-Rev-4F-24	Ac-FYEKFA**D**AVKDWFAKFK**E**-NH2	401

[0130] Based on the helical wheel diagrams shown in Figure 15 it is possible to readily identify biologically active and useful peptides. Thus, for example, the following peptides have been accurately identified as active: 3F1; 3F2; 4F the reverse (retro) forms thereof and the retro-inverso forms thereof. Thus, in certain embodiments, this invention contemplates active agents comprising a peptide that is 18 amino acids in length and forms a class A amphipathic helix where the peptide has the amino acid composition 2 aspartates, 2 glutamates, 4 lysines, 1 tryptophan, 1 tyrosine, no more than one leucine, no more than 1 valine, no less than 1 and no more than 3 alanines, and with 3 to 6 amino acids from the group: phenylalanine, alpha-naphthalanine, beta-naphthalanine, histidine, and contains either 9 or 10 amino acids on the polar face in a helical wheel representation of the class A amphipathic helix including 4 amino acids with positive charge at neutral pH with two of the positively charged residues residing at the interface between the polar and non-polar faces and with two of the four positively charged residues on the polar face that are contiguous and on the non-polar face two of the amino acid residues from the group: phenylalanine, alpha-naphthalanine, beta-naphthalanine, histidine are also

contiguous and if there are 4 or more amino acids from this group on the non-polar face there are also at least 2 residues from this group that are not contiguous.

[0131] In certain embodiments, this invention also contemplates certain class Y as well as class A amphipathic helical peptides. Class Y amphipathic helical peptides are known to those of skill in the art (*see, e.g.,* Segrest *et al.* (1992) *J. Lipid Res.* 33: 141-166; Oram and Heinecke (2005) *Physiol Rev.* 85: 1343-1372, and the like). In various embodiments these peptides include, but are not limited to an 18 amino acid peptide that forms a class A amphipathic helix or a class Y amphipathic helix described by formula III (SEQ ID NO:402):

D X X K Y X X D K X Y D KX K D Y X III

where the D's are independently Asp or Glu; the Ks are independently Lys or Arg; the Xs are independently Leu, norLeu, Val, Ile, Trp, Phe, Tyr, β–Nal, or α–Nal and all X residues are on the non-polar face (*e.g.,* when viewed in a helical wheel diagram) except for one that can be on the polar face between two K residues; the Y's are independently Ala, His, Ser, Gln, Asn, or Thr non-polar face (*e.g.,* when viewed in a helical wheel diagram) and the Y's are independently one Ala on the polar face, one His, one Ser, one Gln one Asn, or one Thr on the polar face (*e.g.,* when viewed in a helical wheel diagram), where no more than two K are be contiguous (*e.g.,* when viewed in a helical wheel diagram); and where no more than 3 D's are contiguous (*e.g.,* when viewed in a helical wheel diagram) and the fourth D is be separated from the other D's by a Y. Illustrative peptides of this kind which include peptides with histidine, and/or alpha- and/or beta-napthalanine are shown in Table 5. Reverse (retro-), inverse, retro-inverso-, and circularly permuted forms of these peptides are also contemplated.

[0132] Table 5. Illustrates various class A and/or class Y peptide analogs with His incorporated into the sequence.

Short name	**Peptide sequence**	**SEQ ID NO**
[A-5>H] 4F	Ac-DWFK**H**FYDKVAEKFKEAF-NH_2	403
[A-5>H, D-E switched]4F	Ac-**E**WFK**H**FY**E**KVA**D**KFK**D**AF-NH_2	404
[A-5>H, D-1>E]4F	Ac-**E**WFK**H**FYDKVAEKFKEAF-NH_2	405
[A-5>H, D-8>E]4-F	Ac-DWFK**H**FY**E**KVAEKFKEAF-NH_2	406
[A-5>H, E-12>D] 4F	Ac-DWFK**H**FYDKVA**D**KFKEAF-NH_2	407
[A-5>H, E-16>D] 4F	Ac-DWFK**H**FYDKVAEKFK**D**AF-NH_2	408
[F-3>H,A-5>F] -4F	Ac-DW**H**K**F**FYDKVAEKFKEAF-NH_2	409
[F-3>H,A-5>F, D-E switched] -4F	Ac-**E**W**H**K**F**FY**E**KVA**D**KFK**D**AF-NH_2	410

[F-3>H,A-5>F,D-1>E] -4F	Ac-**E**W**H**K**F**FYDKVAEKFKEAF-NH_2	411
[F-3>H,A-5>F,D-8>E] -4F	Ac-DW**H**K**F**FY**E**KVAEKFKEAF-NH_2	412
[F-3>H,A-5>F,E-12>D] -4F	Ac-DW**H**K**F**FYDKVA**D**KFKEAF-NH_2	413
[F-3>H,A-5>F, E-16>D] -4F	Ac-DW**H**K**F**FYDKVAEKFK**D**AF-NH_2	414
[A-5>F,F-6>H]4F	Ac-DWFK**FH**YDKVAEKFKEAF-NH_2	415
[A-5>F,F-6>H,D-E switched]4F	Ac-**E**WFK**FH**Y**E**KVA**D**KFK**D**AF-NH_2	416
[[A-5>F,F-6>H, D-1>E]4F	Ac-**E**WFK**FH**YDKVAEKFKEAF-NH_2	417
[A-5>F,F-6>H, D-8>E]4F	Ac-DWFK**FH**Y**E**KVAEKFKEAF-NH_2	418
[A-5>F,F-6>H, E-12>D]4F	Ac-DWFK**FH**YDKVA**D**KFKEAF-NH_2	419
[A-5>F,F-6>H,E-16>D]4F	Ac-DWFK**FH**YDKVAEKFK**D**AF-NH_2	420
[A-5>V, V-10>H]4F	Ac-DWFK**V**FYDK**H**AEKFKEAF-NH_2	421
[A-5>V, V-10>H,D-E switched]4F	Ac-**E**WFK**V**FY**E**K**H**A**D**KFK**D**AF-NH_2	422
[A-5>V, V-10>H,D-1>E]4F	Ac-**E**WFK**V**FYDK**H**AEKFKEAF-NH_2	423
[A-5>V, V-10>H, D-8>E] 4F	Ac-DWFK**V**FY**E**K**H**AEKFKEAF-NH_2	424
[A-5>V, V-10>H,E-12>D] 4F	Ac-DWFK**V**FYDK**H**A**D**KFKEAF-NH_2	425
[A-5>V, V-10>H,E16>D] 4F	Ac-DWFK**V**FYDK**H**AEKFK**D**AF-NH_2	426
[[A-17>H]4F	Ac-DWFKAFYDKVAEKFKE**H**F-NH_2	427
[A-17>H, D-E switched] 4F	Ac-**E**WFKAFY**E**KVA**D**KFK**DH**F-NH_2	428
[[A-17>H,D-1>E]4F	Ac-**E**WFKAFYDKVAEKFKE**H**F-NH_2	429
[[A-17>H, D-8>E]4F	Ac-DWFKAFY**E**KVAEKFKE**H**F-NH_2	430
[[A-17>H,E-12>D]4F	Ac-DWFKAFYDKVA**D**KFKE**H**F-NH_2	431
[[A-17>H, E16>D]4F	Ac-DWFKAFYDKVAEKFK**DH**F-NH_2	432
[A-17>F, F-18>H] 4F	Ac-DWFKAFYDKVAEKFKE**FH**-NH_2	433
[A-17>F, F-18>H,D-E switched] 4F	Ac-**E**WFKAFY**E**KVA**D**KFK**DFH**-NH_2	434
[A-17>F, F-18>H,D-1>E] -4F	Ac-**E**WFKAFYDKVAEKFKE**FH**-NH_2	435
[A-17>F, F-18>H] 4F	Ac-DWFKAFYDKVAEKFKE**FH**-NH_2	436
[A-17>F, F-18>H,D-8>E] -4F	Ac-DWFKAFY**E**KVAEKFKE**FH**-NH_2	437
[A-17>F, F-18>H,E-12>D] 4F	Ac-DWFKAFYDKVAEKFKE**FH**-NH_2	438
[A-17>F, F-18>H],E-16>D]-4F	Ac-DWFKAFYDKVAEKFK**DFH**-NH_2	439
Rev-4F	Ac-FAEKFKEAVKDYFAKFWD-NH_2	440
[A-2>H]Rev4F	Ac-F**H**EKFKEAVKDYFAKFWD-NH_2	441
Rev-[A-2>H, D>E]-4F	Ac-F**H**EKFKEAVK**E**YFAKFW**E**-NH_2	442
Rev-[A-2>H, E>D]4F	Ac-F**HD**KFK**D**AVKDYFAKFWD-NH_2	443
[A-2>H, D-E switched] Rev-4F	Ac-F**HD**KFK**D**AVK**E**YFAKFW**E**-NH_2	444
[A-2>H, E-3>D]Rev-4F	Ac-F**HD**KFKEAVKDYFAKFWD-NH_2	445
[A-2>H, E-7>D]Rev-4F	Ac-F**H**EKFK**D**AVKDYFAKFWD-NH_2	446
[A-2>H, D-11>E]Rev-4F	Ac-F**H**EKFKEAVK**E**YFAKFWD-NH_2	447
[A-2>H, D-18>E]Rev-4F	Ac-F**H**EKFKEAVKDYFAKFW**E**-NH_2	448
[F-1>H, A-2>F]Rev-4F	Ac-**HF**EKFKEAVKDYFAKFWD-NH_2	449
[F-1>H, A-2>F,D-E switched]Rev-4F	Ac-**HFD**KFK**D**AVK**E**YFAKFW**E**-NH_2	450
[F-1>H, A-2>F, D>E]Rev-4F	Ac-**HF**EKFKEAVK**E**YFAKFW**E**-NH_2	451
[F-1>H, A-2>F,E-3>D]Rev-4F	Ac-**HFD**KFKEAVKDYFAKFWD-NH_2	452
[F-1>H, A-2>F,E-7>D]Rev-4F	Ac-**HF**EKFK**D**AVKDYFAKFWD-NH_2	453
[F-1>H, A-2>F,D-11>E]Rev-4F	Ac-**HF**EKFKEAVK**E**YFAKFWD-NH_2	454
[F-1>H, A-2>F, D-18>E]Rev-4F	Ac-**HF**EKFKEAVKDYFAKFW**E**-NH_2	455
[A-2>F, F-5>H] Rev D-4F	Ac-F**F**EK**H**KEAVKDYFAKFWD-NH_2	456
[A-2>F, F-5>H,D-E switched] Rev D-4F	Ac-F**FD**K**H**K**D**AVK**E**YFAKFW**E**-NH_2	457
[A-2>F, F-5>H, D>E] Rev D-4F	Ac-F**F**EK**H**KEAVK**E**YFAKFW**E**-NH_2	458
[A-2>F, F-5>H,E>D] Rev D-4F	Ac-F**FD**K**H**K**D**AVKDYFAKFWD-NH_2	459
[A-2>F, F-5>H,E-3>D] Rev D-4F	Ac-F**FD**K**H**KEAVKDYFAKFWD-NH_2	460
[A-2>F, F-5>H,D-11>E] Rev D-4F	Ac-F**F**EK**H**K**E**AVK**E**YFAKFWD-NH_2	461
[A-2>F, F-5>H,D-18>E] Rev D-4F	Ac-F**F**EK**H**KEAVKDYFAKFW**E**-NH_2	462
[A-2>V, V-9>H] Rev D-4F	Ac-F**V**EKFKEA**H**KDYFAKFWD-NH_2	463

[A-2>V, V-9>H,D-E switched] Rev D-4F	Ac-F**V**D**H**K**E**YFAKFW**E**-NH_2	464
[A-2>V, V-9>H,D>E] Rev D-4F	Ac-F**V**EKFKEA**H**K**E**YFAKFW**E**-NH_2	465
[A-2>V, V-9>H,E>D] Rev D-4F	Ac-F**V**D**H**K**D**A**H**KDYFAKFWD-NH_2	466
[A-2>V, V-9>H,E-3>D] Rev D-4F	Ac-F**V**D**H**K**D**KEA**H**KDYFAKFWD-NH_2	467
[A-2>V, V-9>H,E-7>D] Rev D-4F	Ac-F**V**EKFK**D**A**H**KDYFAKFWD-NH_2	468
[A-2>V, V-9>H,D-11>E] Rev D-4F	Ac-F**V**EKFKEA**H**K**E**YFAKFWD-NH_2	469
[A-2>V, V-9>H,D-18>E] Rev D-4F	Ac-F**V**EKFKEA**H**KDYFAKFW**E**-NH_2	470
[A-8>H]Rev-4F	Ac-FAEKFKE**H**VKDYFAKFWD-NH_2	471
[A-8>H,D-E switched]Rev-4F	Ac-FA**D**KFK**DH**VK**E**YFAKFW**E**-NH_2	472
[A-8>H,D>E]Rev-4F	Ac-FAEKFKE**H**VK**E**YFAKFW**E**-NH_2	473
[A-8>H,E>D]Rev-4F	Ac-FA**D**KFK**DH**VKDYFAKFWD-NH_2	474
[A-8>H,E-3>D]Rev-4F	Ac-FA**D**KFKE**H**VKDYFAKFWD-NH_2	475
[A-8>H, E-7>D]Rev-4F	Ac-FAEKFK**DH**VKDYFAKFWD-NH_2	476
[A-8>H, D-11>E]Rev-4F	Ac-FAEKFKE**H**VK**E**YFAKFWD-NH_2	477
[A-8>H, D-18>E]Rev-4F	Ac-FAEKFKE**H**VKDYFAKFW**E**-NH_2	478
[A-8>F,F-13>H]Rev-4F	Ac-FAEKFKE**F**VKDY**H**AKFWD-NH_2	479
[A-8>F,F-13>H,D-E switched]Rev-4F	Ac-FA**D**KFK**DF**VK**E**Y**H**AKFW**E**-NH_2	480
[A-8>F,F-13>H, E-3>D]Rev-4F	Ac-FA**D**KFKE**F**VKDY**H**AKFWD-NH_2	481
[A-8>F,F-13>H, E-7>D]Rev-4F	Ac-FAEKFK**DF**VKDY**H**AKFWD-NH_2	482
[A-8>F,F-13>H, E>D]Rev-4F	Ac-FA**D**KFK**DF**VKDY**H**AKFWD-NH_2	483
[A-8>F,F-13>H,D>E]Rev-4F	Ac-FAEKFKE**F**VK**E**Y**H**AKFW**E**-NH_2	484
[A-8>F,F-13>H,D-11>E]Rev-4F	Ac-FAEKFKE**F**VK**E**Y**H**AKFWD-NH_2	485
[A-8>F,F-13>H, D-18>E]Rev-4F	Ac-FAEKFKE**F**VKDY**H**AKFW**E**-NH_2	486
[A-8>F, F16>H]Rev.-4F	Ac-FAEKFKE**F**VKDYFAK**H**WD-NH_2	487
[A-8>F, F16>H,D-E switched]Rev.-4F	Ac-FA**D**KFK**DF**VK**E**YFAK**H**W**E**-NH_2	488
[A-8>F, F16>H,D>E]Rev.-4F	Ac-FAEKFKE**F**VK**E**YFAK**H**W**E**-NH_2	489
[A-8>F, F16>H, E>D]Rev.-4F	Ac-FA**D**KFK**DF**VKDYFAK**H**WD-NH_2	490
[A-8>F, F16>H,E-3>D]Rev.-4F	Ac-FA**D**KFKE**F**VKDYFAK**H**WD-NH_2	491
[A-8>F, F16>H,E-7>D]Rev.-4F	Ac-FAEKFK**DF**VKDYFAK**H**WD-NH_2	492
[A-8>F, F16>H,D-11>E]Rev.-4F	Ac-FAEKFKE**F**VK**E**YFAK**H**WD-NH_2	493
[A-8>F, F16>H,D-18>E]Rev.-4F	Ac-FAEKFKE**F**VKDYFAK**H**W**E**-NH_2	494

Examples of class A 4F and Rev 4F analogs with beta-Nph. Similarly, alpha-Nph analogs can be designed. Similarly to the above analogs, His can be incorporated to Nph analogs. D>E analogs, E>D analogs and D-E switch analogs are additional possibilities similarly to the above described analogs.

4Nph	Ac-DW**Nph**KA**Nph**YDKVAEK**Nph**KEA**Nph**-NH2	495
[D-E switched]4Nph	Ac-**E**W**Nph**KA**Nph**Y**E**KVA**D**K**Nph**K**D**A**Nph**-NH2	496
[D>E]4Nph	Ac-**E**W**Nph**KA**Nph**Y**E**KVAEK**Nph**KEA**Nph**-NH2	497
[E>D]4Nph	Ac-DW**Nph**KA**Nph**YDKVA**D**K**Nph**K**D**A**Nph**-NH2	498
[D-1>E] 4Nph	Ac-**E**W**Nph**KA**Nph**YDKVAEK**Nph**KEA**Nph**-NH2	499
[D-8>E]4Nph	Ac-DW**Nph**KA**Nph**Y**E**KVAEK**Nph**KEA**Nph**-NH2	500
[E-12>D]4Nph	Ac-DW**Nph**KA**Nph**YDKVA**D**K**Nph**KEA**Nph**-NH2	501
[E-16>D]4Nph	Ac-DW**Nph**KA**Nph**YDKVAEK**Nph**K**D**A**Nph**-NH2	502

As described above for 4Nph, a minimum of 7 additional analogs for each of the analogs given below.

[F-3,6,>Nph]4F	Ac-DW**Nph**KA**Nph**YDKVAEKFKEAF-NH2	503
[F-14,18>Nph]4F	Ac-DWFKAFYDKVAEK**Nph**KEA**Nph**-NH2	504
[[F-3>Nph]4F	Ac-DW**Nph**KAFYDKVAEKFKEAF-NH2	505
[F-6>Nph]4F	Ac-DWFKA**Nph**YDKVAEKFKEAF-NH2	506
[F-14>Nph]4F	Ac-DWFKAFYDKVAEK**Nph**KEAF-NH2	507
[F-18>Nph]4F	Ac-DWFKAFYDKVAEKFKEA**Nph**-NH2	508

For each of the analog described below, a minimum of 7 additional analogs are

possible as described above by switching D-E, D>E and E>D and single D or E analogs.

Rev-4Nph	Ac-**Nph**AEK**Nph**KEAVKDY**Nph**AK**Nph**WD-NH2	509
[F-3,6>Nph]Rev 4F	Ac-**Nph**AEK**Nph**KEAVKDYFAKFWD-NH2	510
[F-13,16]Rev-4F	Ac-FAEKFKEAVKDY**Nph**AK**Nph**WD-NH2	511
[F-3>Nph]Rev-4F	Ac-**Nph**AEKFKEAVKDYFAKFWD-NH2	512
[F-6>Nph]Rev-4F	Ac-FAEK**Nph**KEAVKDYFAKFWD-NH2	513
[F-13>Nph]Rev-4F	Ac-FAEKFKEAVKDY**Nph**AKFWD-NH2	514
[F-16>Nph]Rev-4F	Ac-FAEKFKEAVKDYFAK**Nph**WD-NH2	515

For the analogs described below, additional analogs are possible by incorporating His or alpha-Nph and beta-Nph

Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH2	516
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH2	517
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH2	518
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH2	519
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH2	520
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH2	521
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH2	522
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH2	523
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH2	524
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH2	525
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH2	526
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH2	527
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH2	528
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH2	529
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH2	530
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH2	531
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH2	532
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH2	533
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH2	534
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH2	535
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH2	536
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH2	537
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH2	538
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH2	539
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH2	540
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH2	541
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH2	542
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH2	543

For each of the analogs below, additional H and Nph analogs are possible using the examples described above. Each analog can yield 7 analogs with the changes described in the examples given above.

Rev3F-2	Ac-LFEKFAEAFKDYVAKWKD-NH2	544
RevR4-3F-2	Ac-LFE**R**FAEAFKDYVAKWKD-NH2	545
RevR10-3F2	Ac-LFEKFAEAF**R**DYVAKWKD-NH2	546
RevR15-3F-2	Ac-LFEKFAEAFKDYVA**R**WKD-NH2	547
Rev R17-3F-2	Ac-LFEKFAEAFKDYVAKW**R**D-NH2	548
Rev[D>E]3F2	Ac-LFEKFAEAFK**E**YVAKWK**E**-NH2	549
Rev[E>D]3F-2	Ac-LF**D**KFA**D**AFKDYVAKWKD-NH2	550
Rev-[E3>D]-3F-2	Ac-LF**D**KFAEAFKDYVAKWKD-NH2	551
Rev-[E7>D]-3F-2	Ac-LFEKFA**D**AFKDYVAKWKD-NH2	552

Rev[D11>E]3F-2	Ac-LFEKFAEAFK**E**YVAKWKD-NH2	553
Rev-[D18>E]3F-2	Ac-LFEKFAEAFKDYVAKWK**E**-NH2	554
Rev3F-1	Ac-FAEKAWEFVKDYFAKLKD-NH2	555
RevR4-3F-1	Ac-FAE**R**AWEFVKDYFAKLKD-NH2	556
RevR10-3F-1	Ac-FAEKAWEFV**K**DYFAKLKD-NH2	557
RevR15-3F-1	Ac- FAEKAWEFVKDYFA**K**LKD-NH2	558
RevR17-3F-1	Ac-FAEKAWEFVKDYFAKL**R**D-NH2	559
Rev[D>E]3F-1	Ac- FAEKAWEFVK**E**YFAKLK**E**-NH2	560
Rev[E>D}3F-1	Ac-FA**D**KAW**D**FVKDYFAKLKD-NH2	561
Rev[E3>D]-3F-1	Ac- FA**D**KAWEFVKDYFAKLKD-NH2	562
Rev[E7>D]3F-1	Ac- FAEKAW**D**FVKDYFAKLKD-NH2	563
Rev-[D11>E]3F-1	Ac- FAEKAWEFVK**E**YFAKLKD-NH2	564
Rev-[D18>E]3F-1	Ac- FAEKAWEFVKDYFAKLK**E**-NH2	565
Rev-5F	Ac-FFEKFKEFVKDYFAKLWD-NH2	566
Rev-[D>E]5F	Ac-FFEKFKEFVK**E**YFAKLW**E**-NH2	567
Rev-[E>D]5F	Ac-FF**D**KFK**D**FVKDYFAKLWD-NH2	568
Rev-R4-5F	Ac-FFE**R**FKEFVKDYFAKLWD-NH2	569
Rev-R6-5F	Ac-FFEKF**R**EFVKDYFAKLWD-NH2	570
Rev-R10-5F	Ac-FFEKFKEFV**R**DYFAKLWD-NH2	571
Rev-R15-5F	Ac-FFEKFKEFVKDYFA**R**LWD-NH2	572
Rev-[E3>D]-5F	Ac-FF**D**KFKEFVKDYFAKLWD-NH2	573
Rev-[E7>D]5F	Ac-FFEKFK**D**FVKDYFAKLWD-NH2	574
Rev-[D11>E]-5F	Ac-FFEKFKEFVK**E**YFAKLWD-NH2	575
Rev-[D18>E]-5F	Ac-FFEKFKEFVKDYFAKLW**E**-NH2	576
Rev-5F-2	Ac-F**L**EKFKEFVKDYFAK**F**WD-NH2	577
Rev-[D>E]-5F-2	Ac-FLEKFKEFVK**E**YFAKFW**E**-NH2	578
Rev-[E>D]-5F-2	Ac-FL**D**KFK**E**FVKDYFAKFWD-NH2	579
Rev-[E3>D]-5F-2	Ac-FL**D**KFKEFVKDYFAKFWD-NH2	580
Rev-[E7>D]-5F-2	Ac-FLEKFK**D**FVKDYFAKFWD-NH2	581
Rev-[D11>E]-5F-2	Ac-FLEKFKEFVK**E**YFAKFWD-NH2	582
Rev-[D18>E]-5F-2	Ac-FLEKFKEFVKDYFAKFW**E**-NH2	583
Rev-R4-5F-2	Ac-FLE**R**FKEFVKDYFAKFWD-NH2	584
Rev-R6-5F-2	Ac-FLEKF**R**EFVKDYFAKFWD-NH2	585
RevR10-5F-2	Ac-FLEKFKEFV**R**DYFAKFWD-NH2	586
Rev-R16-5F-2	Ac-FLEKFKEFVKDYFA**R**FWD-NH2	587
Rev-6F	Ac-F**F**EK**F**KE**FF**KDYFAKLWD-NH2	588

Rev-[D>E]-6F	Ac-FFEKFKEFFK**E**YFAKLW**E**-NH2	589
Rev-[E>D]-6F	Ac-FF**D**KFK**D**FFKDYFAKLWD-NH2	590
Rev-R4-6F	Ac-FF**E**F**R**FKEFFKDYFAKLWD-NH2	591
Rev-R6-6F	Ac-FF**E**KF**R**EFFKDYFAKLWD-NH2	592
Rev-R10-6F	Ac-FF**E**KFKEFF**R**DYFAKLWD-NH2	593
Rev-R14-6F	Ac-FF**E**RFKEFFKDYFA**R**LWD-NH2	594
Rev-[E3>D]-6F	Ac-FF**D**KFKEFFKDYFAKLWD-NH2	595
Rev-[E7>D]-6F	Ac-FFEKFK**D**FFKDYFAKLWD-NH2	596
Rev-[D11>E]-6F	Ac-FFEKFKEFFK**E**YFAKLWD-NH2	597
Rev-[D18>E]-6F	Ac-FFEKFKEFFKDYFAKLW**E**-NH2	598
Rev-4F	Ac-FAEKFKEAVKDYFAKFWD-NH2	599
Rev-[D>E]-4F	Ac-FAEKFKEAVK**E**YFAKFW**E**-NH2	600
Rev-[E>D]4F	Ac-FA**D**KFK**D**AVKDYFAKFWD-NH2	601
Rev-R4-4F	Ac-FAE**R**FREAVKDYFAKFWD-NH2	602
Rev-R6-4F	Ac-FAEKF**R**EAVKDYFAKFWD-NH2	603
Rev-R10-4F	Ac-FAEKFKEAV**R**DYFAKFWD-NH2	604
Rev-R14 -4F	Ac-FAEKFKEAVKDYFA**R**FWD-NH2	605
4F-2	Ac-DKWKAVYDKFAEAFKEFF-NH2	606
[D>E]-4F-2	Ac-EKWKAVYEKFAEAFKEFF-NH2	607
[E>D]-4F-2	Ac-DKWKAVYDKFA**D**AFK**D**FF-NH2	608
R2-4F-2	Ac-D**R**WKAVYDKFAEAFKEFF-NH2	609
R4-4F-2	Ac-DKW**R**AVYDKFAEAFKEFF-NH2	610
R9-4F-2	Ac-DKWKAVYD**R**FAEAFKEFF-NH2	611
R14-4F-2	Ac-DKWKAVYDKFAEAF**R**EFF-NH2	612
Rev4F-2	Ac-FFEKFAEAFKDYVAKWKD-NH2	613
Rev-[D>E]-4F-2	Ac-FFEKFAEAFK**E**YVAKWK**E**-NH2	614
Rev-[E>D]-3F-2	Ac-FF**D**KFA**D**AFKDYVAKWKD-NH2	615
Rev-R4-4F-2	Ac-FFE**R**FAEAFKDYVAKWKD-NH2	616
Rev-R10-4F-2	Ac-FFERFAEAF**R**DYVAKWKD-NH2	617
Rev-R15-4F-2	Ac-FFEKFAEAFKDYVA**R**WKD-NH2	618
Rev-R17-4F-2	Ac-FFE**R**FAEAFKDYVAKW**R**D-NH2	619
Rev-[E3>D]-4F-2	Ac-FF**D**KFAEAFKDYVAKWKD-NH2	620
Rev-[E7>D]-4F-2	Ac-FFEKFA**D**AFKDYVAKWKD-NH2	621
Rev-[D11>E]-4F-2	Ac-FFERFAEAFK**E**YVAKWKD-NH2	622
Rev-[D18>E]-4F-2	Ac-FFERFAEAFKDYVAKWK**E**-NH2	623
Rev-7F	Ac-FFEKFKEFFKDYFAKFWD-NH2	624

Rev-[E>D]-7F	Ac-FF**D**KFK**D**FFKDYFAKFWD-NH2	625
Rev-[D>E]-7F	Ac-FFEKFKEFFK**E**YFAKFW**E**-NH2	626
Rev-R4-7F	Ac-FFE**R**FKEFFKDYFAKFWD-NH2	627
Rev-R6-7F	Ac-FFEKF**R**EFFKDYFAKFWD-NH2	628
Rev-R10-7F	Ac-FFEKFKEFF**R**DYFAKFWD-NH2	629
Rev-R14-7F	Ac-FFEKFKEFFKDYFA**R**FWD-NH2	630
Rev-[E3>D]-7F	Ac-FF**D**KFKEFFKDYFAKFWD-NH2	631
Rev-[E7>D]7F	Ac-FFEKFK**D**FFKDYFAKFWD-NH2	632
Rev-[D11>E]-7F	Ac-FFEKFKEFFK**E**YFAKFWD-NH2	633
Rev-[D18>E]-7F	Ac-FFEKFKEFFKDYFAKFW**E**-NH2	634

[0133] It is also noted that any of the pepides described herein can comprise non-natural amino acids in addition to or instead of the corresponding the natural amino acids identified herien. Such modifications include, but are not limited to acetylation, amidation, formylation, methylation, sulfation, and the like. Illustrative non-natural amino acids include, but are not limited to Ornithine, norleucine, norvaline, N-methylvaline, 6-N-methyllysine, N-methylisoleucine, N-methylglycine, sarcosine, inosine, allo-isoleucine, isodesmolysine, 4-hydroxyproline, 3-hydroxyproline, allo-hydroxylysine, hydoxylisine, N-ethylasparagine, N-ethylglycine, 2,3-diaminopropionic acid, 2,2'-diaminopropionic acid, desmosine, 2,4-diaminobutyric acid, 2-aminopimelic acid, 3-aminoisobutyric acid, 2-aminoisobutyric acid, 2-aminoheptanoic acid, 6-aminocaproic acid, 4-aminobutyric acid, 2-aminobutyric acid, beta-alanine, 3-aminoadipic acid, 2-aminoadipic acid, and the like. In certain embodiments andy one or more of the "natural" amino acids of the peptides described herein, can be substituted with the correspondign non-natural amino acid (*e.g.* as describe above).

[0134] In certain embodiments, this invneiton contemplates particularly the use of modified lysines. Such modifications include, but are not limited to, biotin modification of epsilon lysines and/or methylation of the epsilon lysines. Illustative peptide comprising epsilon methylated lysines include, but are not limited to: Ac-D-W-F-K(eCH_3)$_2$-A-F-Y-D-K(eCH_3)$_2$-V-A-E-K(eCH_3)$_2$-F-K(eCH_3)$_2$-E-A-F-NH(CH_3)$_2$ (SEQ ID NO:635) and : Ac-DWFK(eCH_3)$_2$AFYDK(eCH_3)$_2$VAEK(eCH_3)$_2$FK(eCH_3)$_2$EAF-NH(CH_3) (SEQ ID NO:636). Other modified amino acids include but are not limited to ornithine analogs and homoaminoalanine analogs (instead of $(CH_2)_4$-NH_2 for Lys it can be -$(CH_2)_2$-NH_2 for Haa and -$(CH_2)_3$-NH_2 for Orn] and the like. It is noted that these modifications are illustrative

and not intended to be limiting. Illustrative 4F analogues that possess modified amino acids are shown in Table 6.

[0135] Table 6. Illustrative 4F analogs that comprise modified amino acids.

εN-Dimethyl-Lys derivative of 4F (εN-Dime)	
Ac-D-W-F-K(εN-Dime)-A-F-Y-D-K(εN-Dime)-V-A-E-K(εN-Dime)-F-K(εN-Dime)-E-A-F-NH_2	637
Ac-D-W-F-K-(εN-Dime)-A-F-Y-D-K(εN-Dime)-V-A-E-K(εN-Dime)-F-K((εN-Dime)-E-A-F-NH-Me	638
Ac-D-W-F-K-(εN-Dime)-A-F-Y-D-K(εN-Dime)-V-A-E-K(εN-Dime)-F-K(εN-Dime)-E-A-F-N-$(Me)_2$	639
εN-Diethyl-Lys derivatives of 4F (εN-Diet)	
Ac-D-W-F-K(εN-Diet)-A-F-Y-D-K(εN-Diet)-V-A-E-K(εN-Diet)-F-K(εN-Diet)-E-A-F-NH_2	640
Ac-D-W-F-K(εN-Diet)-A-F-Y-D-K(εN-Diet)-V-A-E-K(εN-Diet)-F-K(εN-Diet)-E-A-F-NH-Et	641
Ac-D-W-F-K(εN-Diet)-A-F-Y-D-K(εN-Diet)-V-A-E-K(εN-Diet)-F-K(εN-Diet)-E-A-F-NH-$(Et)_2$	642
εN-Monomethyl-Lys derivative of 4F (εN–Me)	
Ac-D-W-F-K(εN–Me)-A-F-Y-D-K(εN–Me)-V-A-E-K(εN–Me)-F-K(εN–Me)-E-A-F-NH_2	643
Ac-D-W-F-K(εN–Me)-A-F-Y-D-K(εN–Me)-V-A-E-K(εN–Me)-F-K(εN–Me)-E-A-F-NH-Me	644
Ac-D-W-F-K(εN–Me)-A-F-Y-D-K(εN–Me)-V-A-E-K(εN–Me)-F-K(εN–Me)-E-A-F-N-$(Me)_2$	645
εN-ethylLys derivative of 4F (εN–Et)	
Ac—D-W-F-K(εN–Et)-A-F-Y-D-K(εN–Et)-V-A-E-K(εN–Et)-F-K(εN–Et)-E-A-F-NH_2	646
Ac—D-W-F-K(εN–Et)-A-F-Y-D-K(εN–Et)-V-A-E-K(εN–Et)-F-K(εN–Et)-E-A-F-NH-Et	647
Ac—D-W-F-K(εN–Et)-A-F-Y-D-K(εN–Et)-V-A-E-K(εN–Et)-F-K(εN–Et)-E-A-F-NH-$(Et)_2$	648
HomoLys analogs of 4F (hK) $(-CH_2)_5-NH_2$	
Ac—D-W-F-hK-A-F-Y-D-hK-V-A-E-hK-F-hK-E-A-F-NH_2	649
Ac—D-W-F-hK(εN-Dime)-A-F-Y-D-hK(εN-Dime)-V-A-E-hK(εN-Dime)-F-hK(εN-Dime)-E-A-F-NH_2	650
Ac—D-W-F-hK(εN-Dime)-A-F-Y-D-hK(εN-Dime)-V-A-E-hK(εN-Dime)-F-hK(εN-Dime)-E-A-F-N-$(Me)_2$	651
Ac—D-W-F-hK(εN-Dime)-A-F-Y-D-hK(εN-Dime)-V-A-E-hK(εN-Dime)-F-hK(εN-Dime)-E-A-F-NH-Me	652
Ac—D-W-F-hK(εN-Diet)-A-F-Y-D-hK(εN-Diet)-V-A-E-hK(εN-Diet)-F-hK(εN-Diet)-E-A-F-NH-Et	653
Ac-D-W-F-hK(εN–Me)-A-F-Y-D-hK(εN–Me)-V-A-E-hK(εN–Me)-F-hK(εN–Me)-E-A-F-NH_2	654
Ac-D-W-F-hK(εN–Me)-A-F-Y-D-hK(εN–Me)-V-A-E-hK(εN–Me)-F-hK(εN–Me)-E-A-F-NH-Me	655
Ac-D-W-F-hK(εN–Me)-A-F-Y-D-hK(εN–Me)-V-A-E-hK(εN–Me)-F-hK(εN–Me)-E-A-F-N-$(Me)_2$	656
Ac—D-W-F-hK(εN–Et)-A-F-Y-D-hK(εN–Et)-V-A-E-hK(εN–Et)-F-	657

hK(εN–Et)-E-A-F-NH_2	
Ac—D-W-F-hK(εN–Et)-A-F-Y-D-hK(εN–Et)-V-A-E-hK(εN–Et)-F-hK(εN–Et)-E-A-F-NH-Et	658
Ac—D-W-F-hK(εN–Et)-A-F-Y-D-hK(εN–Et)-V-A-E-hK(εN–Et)-F-hK(εN–Et)-E-A-F-NH-$(Et)_2$	659
4F analogs in which K is replaced O (O=Ornithine, -$(CH_2)_3$-NH_2)	660
Ac—D-W-F-O-A-F-Y-D-O-V-A-E-O-F-O-E-A-F-NH_2	661
Ac—D-W-F-O(δN-Dime)-A-F-Y-D-O(δN-Dime)-V-A-E-O(δN-Dime)-F-O(δN-Dime)-E-A-F-NH_2	662
Ac—D-W-F-O(δN-Dime)-A-F-Y-D-)(δN-Dime)-V-A-E-O(δN-Dime)-F-O(δN-Dime)-E-A-F-N-$(Me)_2$	663
Ac—D-W-F-O(δN-Dime)-A-F-Y-D-O(δN-Dime)-V-A-E-O(δN-Dime)-F-O(δN-Dime)-E-A-F-NH-Me	664
Ac—D-W-F-O(δN-Diet)-A-F-Y-D-O(δN-Diet)-V-A-E-O(δN-Diet)-F-O(δN-Diet)-E-A-F-NH-Et	665
Ac-D-W-F-O(δN–Me)-A-F-Y-D-O(δN–Me)-V-A-E-O(δN–Me)-F-O(δN–Me)-E-A-F-NH_2	666
Ac-D-W-F-O(δN–Me)-A-F-Y-D-O(δN–Me)-V-A-E-O(δN–Me)-F-O(δN–Me)-E-A-F-NH-Me	667
Ac-D-W-F-O(δN–Me)-A-F-Y-D-O(δN–Me)-V-A-E-O(δN–Me)-F-O(δN–Me)-E-A-F-N-$(Me)_2$	668
Ac—D-W-F-O(δN–Et)-A-F-Y-D-O(δN–Et)-V-A-E-O(δN–Et)-F-O(δN–Et)-E-A-F-NH_2	669
Ac—D-W-F-O(δN–Et)-A-F-Y-D-O(δN–Et)-V-A-E-O(δN–Et)-F-O(δN–Et)-E-A-F-NH-Et	670
Ac—D-W-F-O(δN–Et)-A-F-Y-D-O(δN–Et)-V-A-E-OdεN–Et)-F-O(δN–Et)-E-A-F-NH-$(Et)_2$	671

[0136] The peptides and modifications shown above are intended to be illustrative and not limiting.

D) Smaller peptides.

[0137] It was also a surprising discovery that certain small peptides consisting of a minimum of three amino acids preferentially (but not necessarily) with one or more of the amino acids being the D-stereoisomer of the amino acid, and possessing hydrophobic domains to permit lipid protein interactions, and hydrophilic domains to permit a degree of water solubility also possess significant anti-inflammatory properties and are useful in treating one ore more of the pathologies described herein. The "small peptides" typically range in length from 2 amino acids to about 15 amino acids, more preferably from about 3 amino acids to about 10 or 11 amino acids, and most preferably from about 4 to about 8 or 10 amino acids. In various embodiments the peptides are typically characterized by having hydrophobic terminal amino acids or terminal amino acids rendered hydrophobic

by the attachment of one or more hydrophobic "protecting" groups. Various "small peptides" are described in copending applications USSN 10/649,378, filed August 26, 2003, and in USSN 10/913,800, filed on August 6, 2004, and in PCT Application PCT/US2004/026288.

[0138] In certain embodiments, the peptides can be characterized by Formula I, below:

$$X^1\text{-}X^2\text{-}X^3{}_n\text{-}X^4 \qquad \text{I}$$

where, n is 0 or 1, X^1 is a hydrophobic amino acid and/or bears a hydrophobic protecting group, X^4 is a hydrophobic amino acid and/or bears a hydrophobic protecting group; and when n is 0 X^2 is an acidic or a basic amino acid; when n is 1: X^2 and X^3 are independently an acidic amino acid, a basic amino acid, an aliphatic amino acid, or an aromatic amino acid such that when X^2 is an acidic amino acid; X^3 is a basic amino acid, an aliphatic amino acid, or an aromatic amino acid; when X^2 is a basic amino acid; X^3 is an acidic amino acid, an aliphatic amino acid, or an aromatic amino acid; and when X^2 is an aliphatic or aromatic amino acid, X^3 is an acidic amino acid, or a basic amino acid.

[0139] Longer peptides (*e.g.*, up to 10, 11, or 15 amino acids) are also contemplated within the scope of this invention. Typically where the shorter peptides (*e.g.*, peptides according to formula I) are characterized by an acidic, basic, aliphatic, or aromatic amino acid, the longer peptides are characterized by acidic, basic, aliphatic, or aromatic domains comprising two or more amino acids of that type.

1) Functional properties of active small peptides.

[0140] It was a surprising finding of this invention that a number of physical properties predict the ability of small peptides (*e.g.*, less than 10 amino acids, preferably less than 8 amino acids, more preferably from about 3 to about 5 or 6 amino acids) of this invention to render HDL more anti-inflammatory and to mitigate atherosclerosis and/or other pathologies characterized by an inflammatory response in a mammal. The physical properties include high solubility in ethyl acetate (*e.g.*, greater than about 4 mg/mL), and solubility in aqueous buffer at pH 7.0. Upon contacting phospholipids such as 1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), in an aqueous environment, the particularly effective small peptides induce or participate in the formation of particles with a diameter of approximately 7.5 nm (± 0.1 nm), and/or induce or participate in the

formation of stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm, and/or also induce or participate in the formation of vesicular structures of approximately 38 nm). In certain preferred embodiments, the small peptides have a molecular weight of less than about 900 Da.

[0141] Thus, in certain embodiments, this invention contemplates small peptides that ameliorate one or more symptoms of an indication/pathology described herein, *e.g.*, an inflammatory condition, where the peptide(s): ranges in length from about 3 to about 8 amino acids, preferably from about 3 to about 6, or 7 amino acids, and more preferably from about 3 to about 5 amino acids; are soluble in ethyl acetate at a concentration greater than about 4mg/mL; are soluble in aqueous buffer at pH 7.0; when contacted with a phospholipid in an aqueous environment, form particles with a diameter of approximately 7.5 nm and/or form stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm; have a molecular weight less than about 900 daltons; convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory; and do not have the amino acid sequence Lys-Arg-Asp-Ser (SEQ ID NO:801), especially in which Lys-Arg-Asp and Ser are all L amino acids. In certain embodiments, these small peptides protect a phospholipid against oxidation by an oxidizing agent.

[0142] While these small peptides need not be so limited, in certain embodiments, these small peptides can include the small peptides described below.

2) Tripeptides.

[0143] It was discovered that certain tripeptides (3 amino acid peptides) can be synthesized that show desirable properties as described herein (*e.g.*, the ability to convert pro-inflammatory HDL to anti-inflammatory HDL, the ability to decrease LDL-induced monocyte chemotactic activity generated by artery wall cells, the ability to increase pre-beta HDL, *etc.*). In certain embodiments, the peptides are characterized by formula I, wherein N is zero, shown below as Formula II:

$$X^1\text{-}X^2\text{-}X^4 \qquad \text{II}$$

where the end amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or

more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). In certain embodiments, the X^2 amino acid is either acidic (*e.g.*, aspartic acid, glutamic acid, *etc.*) or basic (*e.g.*, histidine, arginine, lysine, *etc.*). The peptide can be all L- amino acids or include one or more or all D-amino acids.

[0144] Certain tripeptides of this invention include, but are not limited to the peptides shown in Table 7.

[0145] Table 7. Examples of certain preferred tripeptides bearing hydrophobic blocking groups and acidic, basic, or histidine central amino acids.

X^1	X^2	X^3	X^4	SEQ ID NO
Boc-Lys(εBoc)	Arg		Ser(*t*Bu)-O*t*Bu	672
Boc-Lys(εBoc)	Arg		Thr(*t*Bu)-O*t*Bu	673
Boc-Trp	Arg		Ile-O*t*Bu	674
Boc-Trp	Arg		Leu-O*t*Bu	675
Boc-Phe	Arg		Ile –O*t*Bu	676
Boc-Phe	Arg		Leu-O*t*Bu	677
Boc-Lys(εBoc)	Glu		Ser(*t*Bu)-O*t*Bu	678
Boc-Lys(εBoc)	Glu		Thr(*t*Bu)-O*t*Bu	679
Boc-Lys(εBoc)	Asp		Ser(*t*Bu)-O*t*Bu	680
Boc-Lys(εBoc)	Asp		Thr(*t*Bu)-O*t*Bu	681
Boc-Lys(εBoc)	Arg		Ser(*t*Bu)-O*t*Bu	682
Boc-Lys(εBoc)	Arg		Thr(*t*Bu)-O*t*Bu	683
Boc-Leu	Glu		Ser(*t*Bu)-O*t*Bu	684
Boc-Leu	Glu		Thr(*t*Bu)-O*t*Bu	685
Fmoc-Trp	Arg		Ser(*t*Bu)-O*t*Bu	686
Fmoc-Trp	Asp		Ser(*t*Bu)-O*t*Bu	687
Fmoc-Trp	Glu		Ser(*t*Bu)-O*t*Bu	688
Fmoc-Trp	Arg		Ser(*t*Bu)-O*t*Bu	689
Boc-Lys(εBoc)	Glu		Leu-*Ot*Bu	690
Fmoc-Leu	Arg		Ser(*t*Bu)-O*t*Bu	691
Fmoc-Leu	Asp		Ser(*t*Bu)-O*t*Bu	692
Fmoc-Leu	Glu		Ser(*t*Bu)-O*t*Bu	693
Fmoc-Leu	Arg		Ser(*t*Bu)-O*t*Bu	694
Fmoc-Leu	Arg		Thr(*t*Bu)-O*t*Bu	695
Boc-Glu	Asp		Tyr(*t*Bu)-O*t*Bu	696
Fmoc-Lys(εFmoc)	Arg		Ser(*t*Bu)-O*t*Bu	697
Fmoc-Trp	Arg		Ile-O*t*Bu	698
Fmoc-Trp	Arg		Leu-O*t*Bu	699
Fmoc-Phe	Arg		Ile-O*t*Bu	700

Fmoc-Phe	Arg	Leu-O*t*Bu	701
Boc-Trp	Arg	Phe-O*t*Bu	702
Boc-Trp	Arg	Tyr-O*t*Bu	703
Fmoc-Trp	Arg	Phe-O*t*Bu	704
Fmoc-Trp	Arg	Tyr-O*t*Bu	705
Boc-Orn(δBoc)	Arg	Ser(*t*Bu)-O*t*Bu	706
Nicotinyl Lys(εBoc)	Arg	Ser(*t*Bu)-O*t*Bu	707
Nicotinyl Lys(εBoc)	Arg	Thr(*t*Bu)-O*t*Bu	708
Fmoc-Leu	Asp	Thr(*t*Bu)-OtBu	709
Fmoc-Leu	Glu	Thr(*t*Bu)-OtBu	710
Fmoc-Leu	Arg	Thr(*t*Bu)-OtBu	711
Fmoc-norLeu	Arg	Ser(*t*Bu)-OtBu	712
Fmoc-norLeu	Asp	Ser(*t*Bu)-OtBu	713
Fmoc-norLeu	Glu	Ser(*t*Bu)-OtBu	714
Fmoc-Lys(εBoc)	Arg	Ser(*t*Bu)-OtBu	715
Fmoc-Lys(εBoc)	Arg	Thr(*t*Bu)-OtBu	716
Fmoc-Lys(εBoc)	Glu	Ser(*t*Bu)-OtBu	717
Fmoc-Lys(εBoc)	Glu	Thr(*t*Bu)-OtBu	718
Fmoc-Lys(εBoc)	Asp	Ser(*t*Bu)-OtBu	719
Fmoc-Lys(εBoc)	Asp	Thr(*t*Bu)-OtBu	720
Fmoc-Lys(εBoc)	Glu	Leu-*OtBu*	721
Fmoc-Lys(εBoc)	Arg	Leu-*OtBu*	722
Fmoc-Lys(εFmoc)	Arg	Thr(*t*Bu)-OtBu	723
Fmoc- Lys(εFmoc)	Glu	Ser(*t*Bu)-OtBu	724
Fmoc- Lys(εFmoc)	Glu	Thr(*t*Bu)-OtBu	725
Fmoc- Lys(εFmoc)	Asp	Ser(*t*Bu)-OtBu	726
Fmoc- Lys(εFmoc)	Asp	Thr(*t*Bu)-OtBu	727
Fmoc- Lys(εFmoc)	Arg	Ser(*t*Bu)-OtBu	728
Fmoc- Lys(εFmoc))	Glu	Leu-*OtBu*	729
Boc-Lys(εFmoc)	Asp	Ser(*t*Bu)-OtBu	730
Boc-Lys(εFmoc)	Asp	Thr(*t*Bu)-OtBu	731
Boc-Lys(εFmoc)	Arg	Thr(*t*Bu)-OtBu	732
Boc-Lys(εFmoc)	Glu	Leu-*OtBu*	733
Boc-Orn(δFmoc)	Glu	Ser(*t*Bu)-OtBu	734
Boc-Orn(δFmoc)	Asp	Ser(*t*Bu)-OtBu	735
Boc-Orn(δFmoc)	Asp	Thr(*t*Bu)-OtBu	736
Boc-Orn(δFmoc)	Arg	Thr(*t*Bu)-OtBu	737
Boc-Orn(δFmoc)	Glu	Thr(*t*Bu)-OtBu	738
Fmoc-Trp	Asp	Ile-OtBu	739
Fmoc-Trp	Arg	Ile-OtBu	740
Fmoc-Trp	Glu	Ile-OtBu	741
Fmoc-Trp	Asp	Leu-OtBu	742

Fmoc-Trp	Glu	Leu-OtBu	743
Fmoc-Phe	Asp	Ile-OtBu	744
Fmoc-Phe	Asp	Leu-OtBu	745
Fmoc-Phe	Glu	Leu-OtBu	746
Fmoc-Trp	Arg	Phe-OtBu	747
Fmoc-Trp	Glu	Phe-OtBu	748
Fmoc-Trp	Asp	Phe-OtBu	749
Fmoc-Trp	Asp	Tyr-OtBu	750
Fmoc-Trp	Arg	Tyr-OtBu	751
Fmoc-Trp	Glu	Tyr-OtBu	752
Fmoc-Trp	Arg	Thr(*t*Bu)-OtBu	753
Fmoc-Trp	Asp	Thr(*t*Bu)-OtBu	754
Fmoc-Trp	Glu	Thr(*t*Bu)-OtBu	755
Boc-Phe	Arg	norLeu-OtBu	756
Boc-Phe	Glu	norLeu-OtBu	757
Fmoc-Phe	Asp	norLeu-OtBu	758
Boc-Glu	His	Tyr(*t*Bu)-O*t*Bu	759
Boc-Leu	His	Ser(*t*Bu)-O*t*Bu	760
Boc-Leu	His	Thr(*t*Bu)-O*t*Bu	761
Boc-Lys(εBoc)	His	Ser(*t*Bu)-O*t*Bu	762
Boc-Lys(εBoc)	His	Thr(*t*Bu)-O*t*Bu	763
Boc-Lys(εBoc)	His	Leu-*OtBu*	764
Boc-Lys(εFmoc)	His	Ser(*t*Bu)-OtBu	765
Boc-Lys(εFmoc)	His	Thr(*t*Bu)-OtBu	766
Boc-Lys(εFmoc)	His	Leu-*OtBu*	767
Boc-Orn(δBoc)	His	Ser(*t*Bu)-O*t*Bu	768
Boc-Orn(δFmoc)	His	Thr(*t*Bu)-OtBu	769
Boc-Phe	His	Ile –O*t*Bu	770
Boc-Phe	His	Leu-O*t*Bu	771
Boc-Phe	His	norLeu-OtBu	772
Boc-Phe	Lys	Leu-O*t*Bu	773
Boc-Trp	His	Ile-O*t*Bu	774
Boc-Trp	His	Leu-O*t*Bu	775
Boc-Trp	His	Phe-O*t*Bu	776
Boc-Trp	His	Tyr-O*t*Bu	777
Boc-Phe	Lys	Leu-O*t*Bu	778
Fmoc- Lys(εFmoc)	His	Ser(*t*Bu)-OtBu	779

Fmoc- Lys(εFmoc)	His	Thr(*t*Bu)-OtBu	780
Fmoc- Lys(εFmoc)	His	Leu-O*t*Bu	781
Fmoc-Leu	His	Ser(*t*Bu)-O*t*Bu	782
Fmoc-Leu	His	Thr(*t*Bu)-OtBu	783
Fmoc-Lys(εBoc)	His	Ser(*t*Bu)-OtBu	784
Fmoc-Lys(εBoc)	His	Thr(*t*Bu)-OtBu	785
Fmoc-Lys(εBoc)	His	Leu-*OtBu*	786
Fmoc-Lys(εFmoc)	His	Ser(*t*Bu)-O*t*Bu	787
Fmoc-Lys(εFmoc)	His	Thr(*t*Bu)-OtBu	788
Fmoc-norLeu	His	Ser(*t*Bu)-OtBu	789
Fmoc-Phe	His	Ile-O*t*Bu	790
Fmoc-Phe	His	Leu-O*t*Bu	791
Fmoc-Phe	His	norLeu-OtBu	792
Fmoc-Trp	His	Ser(*t*Bu)-O*t*Bu	793
Fmoc-Trp	His	Ile-O*t*Bu	794
Fmoc-Trp	His	Leu-O*t*Bu	795
Fmoc-Trp	His	Phe-O*t*Bu	796
Fmoc-Trp	His	Tyr-O*t*Bu	797
Fmoc-Trp	His	Thr(*t*Bu)-OtBu	798
Nicotinyl Lys(εBoc)	His	Ser(*t*Bu)-O*t*Bu	799
Nicotinyl Lys(εBoc)	His	Thr(*t*Bu)-O*t*Bu	800

[0146] While the peptides of Table 7 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

3) Small peptides with central acidic and basic amino acids.

[0147] In certain embodiments, the peptides of this invention range from four amino acids to about ten amino acids. The terminal amino acids are typically hydrophobic either because of a hydrophobic side chain or because the terminal amino acids bear one or more hydrophobic protecting groups end amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is

blocked with Boc-, Fmoc-, Nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). Typically, the central portion of the peptide comprises a basic amino acid and an acidic amino acid (*e.g.*, in a 4 mer) or a basic domain and/or an acidic domain in a longer molecule.

[0148] These four-mers can be represented by Formula I in which X^1 and X^4 are hydrophobic and/or bear hydrophobic protecting group(s) as described herein and X^2 is acidic while X^3 is basic or X^2 is basic while X^3 is acidic. The peptide can be all L- amino acids or include one or more or all D-amino acids.

[0149] Certain preferred of this invention include, but are not limited to the peptides shown in Table 8.

[0150] Table 8. Illustrative examples of small peptides with central acidic and basic amino acids.

X^1	X^2	X^3	X^4	SEQ ID NO
Boc-Lys(εBoc)	Arg	Asp	Ser(*t*Bu)-O*t*Bu	801
Boc-Lys(εBoc)	Arg	Asp	Thr(*t*Bu)-O*t*Bu	802
Boc-Trp	Arg	Asp	Ile-O*t*Bu	803
Boc-Trp	Arg	Asp	Leu-O*t*Bu	804
Boc-Phe	Arg	Asp	Leu-O*t*Bu	805
Boc-Phe	Arg	Asp	Ile-O*t*Bu	806
Boc-Phe	Arg	Asp	norLeu-O*t*Bu	807
Boc-Phe	Arg	Glu	norLeu-O*t*Bu	808
Boc-Phe	Arg	Glu	Ile-*Ot*Bu	809
Boc-Phe	Asp	Arg	Ile-O*t*Bu	810
Boc-Phe	Glu	Arg	Ile-O*t*Bu	811
Boc-Phe	Asp	Arg	Leu-O*t*Bu	812
Boc-Phe	Arg	Glu	Leu-O*t*Bu	813
Boc-Phe	Glu	Arg	Leu-O*t*Bu	814
Boc-Phe	Asp	Arg	norLeu-O*t*Bu	815
Boc-Phe	Glu	Arg	norLeu-O*t*Bu	816
Boc-Lys(εBoc)	Glu	Arg	Ser(*t*Bu)-O*t*Bu	817
Boc-Lys(εBoc)	Glu	Arg	Thr(*t*Bu)-O*t*Bu	818
Boc-Lys(εBoc)	Asp	Arg	Ser(*t*Bu)-O*t*Bu	819
Boc-Lys(εBoc)	Asp	Arg	Thr(*t*Bu)-O*t*Bu	820
Boc-Lys(εBoc)	Arg	Glu	Ser(*t*Bu)-O*t*Bu	821
Boc-Lys(εBoc)	Arg	Glu	Thr(*t*Bu)-O*t*Bu	822
Boc-Leu	Glu	Arg	Ser(*t*Bu)-O*t*Bu	823

Boc-Leu	Glu	Arg	Thr(*t*Bu)-O*t*Bu	824
Fmoc-Trp	Arg	Asp	Ser(*t*Bu)-O*t*Bu	825
Fmoc-Trp	Asp	Arg	Ser(*t*Bu)-O*t*Bu	826
Fmoc-Trp	Glu	Arg	Ser(*t*Bu)-O*t*Bu	827
Fmoc-Trp	Arg	Glu	Ser(*t*Bu)-O*t*Bu	828
Boc-Lys(εBoc)	Glu	Arg	Leu-*Ot*Bu	829
Fmoc-Leu	Arg	Asp	Ser(*t*Bu)-O*t*Bu	830
Fmoc-Leu	Asp	Arg	Ser(*t*Bu)-O*t*Bu	831
Fmoc-Leu	Glu	Arg	Ser(*t*Bu)-O*t*Bu	832
Fmoc-Leu	Arg	Glu	Ser(*t*Bu)-O*t*Bu	833
Fmoc-Leu	Arg	Asp	Thr(*t*Bu)-O*t*Bu	834
Boc-Glu	Asp	Arg	Tyr(*t*Bu)-O*t*Bu	835
Fmoc-Lys(εFmoc)	Arg	Asp	Ser(*t*Bu)-O*t*Bu	836
Fmoc-Trp	Arg	Asp	Ile-O*t*Bu	837
Fmoc-Trp	Arg	Asp	Leu-O*t*Bu	838
Fmoc-Phe	Arg	Asp	Ile-O*t*Bu	839
Fmoc-Phe	Arg	Asp	Leu-O*t*Bu	840
Boc-Trp	Arg	Asp	Phe-O*t*Bu	841
Boc-Trp	Arg	Asp	Tyr-O*t*Bu	842
Fmoc-Trp	Arg	Asp	Phe-O*t*Bu	843
Fmoc-Trp	Arg	Asp	Tyr-O*t*Bu	844
Boc-Orn(δBoc)	Arg	Glu	Ser(*t*Bu)-O*t*Bu	845
Nicotinyl Lys(εBoc)	Arg	Asp	Ser(*t*Bu)-O*t*Bu	846
Nicotinyl Lys(εBoc)	Arg	Asp	Thr(*t*Bu)-O*t*Bu	847
Fmoc-Leu	Asp	Arg	Thr(*t*Bu)-OtBu	848
Fmoc-Leu	Glu	Arg	Thr(*t*Bu)-OtBu	849
Fmoc-Leu	Arg	Glu	Thr(*t*Bu)-OtBu	850
Fmoc-norLeu	Arg	Asp	Ser(*t*Bu)-OtBu	851
Fmoc-norLeu	Asp	Arg	Ser(*t*Bu)-OtBu	852
Fmoc-norLeu	Glu	Arg	Ser(*t*Bu)-OtBu	853
Fmoc-norLeu	Arg	Glu	Ser(*t*Bu)-OtBu	854
Fmoc-Lys(εBoc)	Arg	Asp	Ser(*t*Bu)-OtBu	855
Fmoc-Lys(εBoc)	Arg	Asp	Thr(*t*Bu)-OtBu	856
Fmoc-Lys(εBoc)	Glu	Arg	Ser(*t*Bu)-OtBu	857
Fmoc-Lys(εBoc)	Glu	Arg	Thr(*t*Bu)-OtBu	858
Fmoc-Lys(εBoc)	Asp	Arg	Ser(*t*Bu)-OtBu	859
Fmoc-Lys(εBoc)	Asp	Arg	Thr(*t*Bu)-OtBu	860
Fmoc-Lys(εBoc)	Arg	Glu	Ser(*t*Bu)-OtBu	861
Fmoc-Lys(εBoc)	Arg	Glu	Thr(*t*Bu)-OtBu	862
Fmoc-Lys(εBoc)	Glu	Arg	Leu-*OtBu*	863

Fmoc-Lys(εBoc)	Arg	Glu	Leu-*OtBu*	864
Fmoc-Lys(εFmoc)	Arg	Asp	Thr(*t*Bu)-OtBu	865
Fmoc- Lys(εFmoc)	Glu	Arg	Ser(*t*Bu)-OtBu	866
Fmoc- Lys(εFmoc)	Glu	Arg	Thr(*t*Bu)-OtBu	867
Fmoc- Lys(εFmoc)	Asp	Arg	Ser(*t*Bu)-OtBu	868
Fmoc- Lys(εFmoc)	Asp	Arg	Thr(*t*Bu)-OtBu	869
Fmoc- Lys(εFmoc)	Arg	Glu	Ser(*t*Bu)-OtBu	870
Fmoc- Lys(εFmoc)	Arg	Glu	Thr(*t*Bu)-OtBu	871
Fmoc- Lys(εFmoc))	Glu	Arg	Leu-*OtBu*	872
Boc-Lys(εFmoc)	Arg	Asp	Ser(*t*Bu)-OtBu	873
Boc-Lys(εFmoc)	Arg	Asp	Thr(*t*Bu)-OtBu	874
Boc-Lys(εFmoc)	Glu	Arg	Ser(*t*Bu)-OtBu	875
Boc-Lys(εFmoc)	Glu	Arg	Thr(*t*Bu)-OtBu	876
Boc-Lys(εFmoc)	Asp	Arg	Ser(*t*Bu)-OtBu	877
Boc-Lys(εFmoc)	Asp	Arg	Thr(*t*Bu)-OtBu	878
Boc-Lys(εFmoc)	Arg	Glu	Ser(*t*Bu)-OtBu	879
Boc-Lys(εFmoc)	Arg	Glu	Thr(*t*Bu)-OtBu	880
Boc-Lys(εFmoc)	Glu	Arg	Leu-*OtBu*	881
Boc-Orn(δFmoc)	Arg	Glu	Ser(*t*Bu)-OtBu	882
Boc-Orn(δFmoc)	Glu	Arg	Ser(*t*Bu)-OtBu	883
Boc-Orn(δFmoc)	Arg	Asp	Ser(*t*Bu)-OtBu	884
Boc-Orn(δFmoc)	Asp	Arg	Ser(*t*Bu)-OtBu	885
Boc-Orn(δFmoc)	Asp	Arg	Thr(*t*Bu)-OtBu	886
Boc-Orn(δFmoc)	Arg	Asp	Thr(*t*Bu)-OtBu	887
Boc-Orn(δFmoc)	Glu	Arg	Thr(*t*Bu)-OtBu	888
Boc-Orn(δFmoc)	Arg	Glu	Thr(*t*Bu)-OtBu	889
Fmoc-Trp	Asp	Arg	Ile-OtBu	890
Fmoc-Trp	Arg	Glu	Ile-OtBu	891
Fmoc-Trp	Glu	Arg	Ile-OtBu	892
Fmoc-Trp	Asp	Arg	Leu-OtBu	893
Fmoc-Trp	Arg	Glu	Leu-OtBu	894
Fmoc-Trp	Glu	Arg	Leu-OtBu	895
Fmoc-Phe	Asp	Arg	Ile-OtBu	896
Fmoc-Phe	Arg	Glu	Ile-OtBu	897
Fmoc-Phe	Glu	Arg	Ile-OtBu	898
Fmoc-Phe	Asp	Arg	Leu-OtBu	899
Fmoc-Phe	Arg	Glu	Leu-OtBu	900
Fmoc-Phe	Glu	Arg	Leu-OtBu	901
Fmoc-Trp	Arg	Asp	Phe-OtBu	902
Fmoc-Trp	Arg	Glu	Phe-OtBu	903

Fmoc-Trp	Glu	Arg	Phe-OtBu	904
Fmoc-Trp	Asp	Arg	Tyr-OtBu	905
Fmoc-Trp	Arg	Glu	Tyr-OtBu	906
Fmoc-Trp	Glu	Arg	Tyr-OtBu	907
Fmoc-Trp	Arg	Asp	Thr(*t*Bu)-OtBu	908
Fmoc-Trp	Asp	Arg	Thr(*t*Bu)-OtBu	909
Fmoc-Trp	Arg	Glu	Thr(*t*Bu)-OtBu	910
Fmoc-Trp	Glu	Arg	Thr(*t*Bu)-OtBu	911
Fmoc-Phe	Arg	Asp	norLeu-OtBu	912
Fmoc-Phe	Arg	Glu	norLeu-OtBu	913
Boc-Phe	Lys	Asp	Leu-OtBu	914
Boc-Phe	Asp	Lys	Leu-OtBu	915
Boc-Phe	Lys	Glu	Leu-OtBu	916
Boc-Phe	Glu	Lys	Leu-OtBu	917
Boc-Phe	Lys	Asp	Ile-OtBu	918
Boc-Phe	Asp	Lys	Ile-OtBu	919
Boc-Phe	Lys	Glu	Ile-OtBu	920
Boc-Phe	Glu	Lys	Ile-OtBu	921
Boc-Phe	Lys	Asp	norLeu-OtBu	922
Boc-Phe	Asp	Lys	norLeu-OtBu	923
Boc-Phe	Lys	Glu	norLeu-OtBu	924
Boc-Phe	Glu	Lys	norLeu-OtBu	925
Boc-Phe	His	Asp	Leu-OtBu	926
Boc-Phe	Asp	His	Leu-OtBu	927
Boc-Phe	His	Glu	Leu-OtBu	928
Boc-Phe	Glu	His	Leu-OtBu	929
Boc-Phe	His	Asp	Ile-OtBu	930
Boc-Phe	Asp	His	Ile-OtBu	931
Boc-Phe	His	Glu	Ile-OtBu	932
Boc-Phe	Glu	His	Ile-OtBu	933
Boc-Phe	His	Asp	norLeu-OtBu	934
Boc-Phe	Asp	His	norLeu-OtBu	935
Boc-Phe	His	Glu	norLeu-OtBu	936
Boc-Phe	Glu	His	norLeu-OtBu	937
Boc-Lys(εBoc)	Lys	Asp	Ser(*t*Bu)-OtBu	938
Boc-Lys(εBoc)	Asp	Lys	Ser(*t*Bu)-OtBu	939
Boc-Lys(εBoc)	Lys	Glu	Ser(*t*Bu)-OtBu	940
Boc-Lys(εBoc)	Glu	Lys	Ser(*t*Bu)-OtBu	941
Boc-Lys(εBoc)	His	Asp	Ser(*t*Bu)-OtBu	942
Boc-Lys(εBoc)	Asp	His	Ser(*t*Bu)-OtBu	943
Boc-Lys(εBoc)	His	Glu	Ser(*t*Bu)-OtBu	944

Boc-Lys(εBoc)	Glu	His	Ser(*t*Bu)-OtBu	945

[0151] While the peptides of Table 8 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

4) Small peptides having either an acidic or basic amino acid in the center together with a central aliphatic amino acid.

[0152] In certain embodiments, the peptides of this invention range from four amino acids to about ten amino acids. The terminal amino acids are typically hydrophobic either because of a hydrophobic side chain or because the terminal amino acids bear one or more hydrophobic protecting groups. End amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, Nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). Typically, the central portion of the peptide comprises a basic or acidic amino acid and an aliphatic amino acid (*e.g.*, in a 4 mer) or a basic domain or an acidic domain and an aliphatic domain in a longer molecule.

[0153] These four-mers can be represented by Formula I in which X^1 and X^4 are hydrophobic and/or bear hydrophobic protecting group(s) as described herein and X^2 is acidic or basic while X^3 is aliphatic or X^2 is aliphatic while X^3 is acidic or basic. The peptide can be all L- amino acids or include one, or more, or all D-amino acids.

[0154] Certain preferred peptides of this invention include, but are not limited to the peptides shown in Table 9.

[0155] Table 9. Examples of certain preferred peptides having either an acidic or basic amino acid in the center together with a central aliphatic amino acid.

X^1	X^2	X^3	X^4	SEQ ID NO
Fmoc-Lys(εBoc)	Leu	Arg	Ser(*t*Bu)-OtBu	946
Fmoc-Lys(εBoc)	Arg	Leu	Ser(*t*Bu)-OtBu	947
Fmoc-Lys(εBoc)	Leu	Arg	Thr(*t*Bu)-OtBu	948
Fmoc-Lys(εBoc)	Arg	Leu	Thr(*t*Bu)-OtBu	949

Fmoc-Lys(εBoc)	Glu	Leu	Ser(*t*Bu)-OtBu	950
Fmoc-Lys(εBoc)	Leu	Glu	Ser(*t*Bu)-OtBu	951
Fmoc-Lys(εBoc)	Glu	Leu	Thr(*t*Bu)-OtBu	952
Fmoc-Lys(εBoc)	Leu	Glu	Thr(*t*Bu)-OtBu	953
Fmoc- Lys(εFmoc)	Leu	Arg	Ser(*t*Bu)-OtBu	954
Fmoc- Lys(εFmoc)	Leu	Arg	Thr(*t*Bu)-OtBu	955
Fmoc- Lys(εFmoc)	Glu	Leu	Ser(*t*Bu)-OtBu	956
Fmoc- Lys(εFmoc)	Glu	Leu	Thr(*t*Bu)-OtBu	957
Boc-Lys(Fmoc)	Glu	Ile	Thr(*t*Bu)-OtBu	958
Boc-Lys(εFmoc)	Leu	Arg	Ser(*t*Bu)-OtBu	959
Boc-Lys(εFmoc)	Leu	Arg	Thr(*t*Bu)-OtBu	960
Boc-Lys(εFmoc)	Glu	Leu	Ser(*t*Bu)-OtBu	961
Boc-Lys(εFmoc)	Glu	Leu	Thr(*t*Bu)-OtBu	962
Boc-Lys(εBoc)	Leu	Arg	Ser(*t*Bu)-OtBu	963
Boc-Lys(εBoc)	Arg	Phe	Thr(*t*Bu)-OtBu	964
Boc-Lys(εBoc)	Leu	Arg	Thr(*t*Bu)-OtBu	965
Boc-Lys(εBoc)	Glu	Ile	Thr(*t*Bu)	966
Boc-Lys(εBoc)	Glu	Val	Thr(*t*Bu)	967
Boc-Lys(εBoc)	Glu	Ala	Thr(*t*Bu)	968
Boc-Lys(εBoc)	Glu	Gly	Thr(*t*Bu)	969
Boc--Lys(εBoc)	Glu	Leu	Ser(*t*Bu)-OtBu	970
Boc-Lys(εBoc)	Glu	Leu	Thr(*t*Bu)-OtBu	971

[0156] While the peptides of Table 9 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

5) Small peptides having either an acidic or basic amino acid in the center together with a central aromatic amino acid.

[0157] In certain embodiments, the "small" peptides of this invention range from four amino acids to about ten amino acids. The terminal amino acids are typically hydrophobic either because of a hydrophobic side chain or because the terminal amino acids bear one or more hydrophobic protecting groups end amino acids (X^1 and X^4) are hydrophobic either because of a hydrophobic side chain or because the side chain or the C and/or N terminus is blocked with one or more hydrophobic protecting group(s) (*e.g.*, the N-terminus is blocked with Boc-, Fmoc-, Nicotinyl-, *etc.*, and the C-terminus blocked with (*t*Bu)-O*t*Bu, *etc.*). Typically, the central portion of the peptide comprises a basic or acidic

amino acid and an aromatic amino acid (*e.g.*, in a 4 mer) or a basic domain or an acidic domain and an aromatic domain in a longer molecule.

[0158] These four-mers can be represented by Formula I in which X^1 and X^4 are hydrophobic and/or bear hydrophobic protecting group(s) as described herein and X^2 is acidic or basic while X^3 is aromatic or X^2 is aromatic while X^3 is acidic or basic. The peptide can be all L- amino acids or include one, or more, or all D-amino acids. Five-mers can be represented by a minor modification of Formula I in which X^5 is inserted as shown in Table 10 and in which X^5 is typically an aromatic amino acid.

[0159] Certain preferred peptides of this invention include, but are not limited to the peptides shown in Table 10.

[0160] Table 10. Examples of certain preferred peptides having either an acidic or basic amino acid in the center together with a central aromatic amino acid.

X^1	X^2	X^3	X^5	X^4	SEQ ID NO
Fmoc-Lys(εBoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	972
Fmoc-Lys(εBoc)	Trp	Arg		Tyr(*t*Bu)-OtBu	973
Fmoc-Lys(εBoc)	Arg	Tyr		Trp-OtBu	974
Fmoc-Lys(εBoc)	Tyr	Arg		Trp-OtBu	975
Fmoc-Lys(εBoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	976
Fmoc-Lys(εBoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	977
Fmoc-Lys(εBoc)	Arg	Trp		Thr(*t*Bu)-OtBu	978
Fmoc- Lys(εFmoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	979
Fmoc- Lys(εFmoc)	Arg	Tyr		Trp-OtBu	980
Fmoc- Lys(εFmoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	981
Fmoc- Lys(εFmoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	982
Fmoc- Lys(εFmoc)	Arg	Trp		Thr(*t*Bu)-OtBu	983
Boc-Lys(εFmoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	984
Boc-Lys(εFmoc)	Arg	Tyr		Trp-OtBu	985
Boc-Lys(εFmoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	986
Boc-Lys(εFmoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	987
Boc-Lys(εFmoc)	Arg	Trp		Thr(*t*Bu)-OtBu	988
Boc-Glu	Lys(εFmoc)	Arg		Tyr(*t*Bu)-OtBu	989
Boc-Lys(εBoc)	Arg	Trp		Tyr(*t*Bu)-OtBu	990
Boc-Lys(εBoc)	Arg	Tyr		Trp-OtBu	991
Boc-Lys(εBoc)	Arg	Tyr	Trp	Thr(*t*Bu)-OtBu	992
Boc-Lys(εBoc)	Arg	Tyr		Thr(*t*Bu)-OtBu	993
Boc-Lys(εBoc)	Arg	Phe		Thr(*t*Bu)-OtBu	994

Boc-Lys(εBoc)	Arg	Trp	Thr(*t*Bu)-OtBu	995

[0161] While the peptides of Table 10 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

6) Small peptides having aromatic amino acids or aromatic amino acids separated by histidine(s) at the center.

[0162] In certain embodiments, the peptides of this invention are characterized by π electrons that are exposed in the center of the molecule which allow hydration of the particle and that allow the peptide particles to trap pro-inflammatory oxidized lipids such as fatty acid hydroperoxides and phospholipids that contain an oxidation product of arachidonic acid at the sn-2 position.

[0163] In certain embodiments, these peptides consist of a minimum of 4 amino acids and a maximum of about 10 amino acids, preferentially (but not necessarily) with one or more of the amino acids being the D-sterioisomer of the amino acid, with the end amino acids being hydrophobic either because of a hydrophobic side chain or because the terminal amino acid(s) bear one or more hydrophobic blocking group(s), (*e.g.*, an N-terminus blocked with Boc-, Fmoc-, Nicotinyl-, and the like, and a C-terminus blocked with (*t*Bu)-O*t*Bu groups and the like). Instead of having an acidic or basic amino acid in the center, these peptides generally have an aromatic amino acid at the center or have aromatic amino acids separated by histidine in the center of the peptide.

[0164] Certain preferred peptides of this invention include, but are not limited to the peptides shown in Table 11.

[0165] Table 11. Examples of peptides having aromatic amino acids in the center or aromatic amino acids or aromatic domains separated by one or more histidines.

X^1	X^2	X^3	X^4	X^5	SEQ ID NO
Boc-Lys(εBoc)	Phe	Trp	Phe	Ser(*t*Bu)-OtBu	996
Boc-Lys(εBoc)	Phe	Trp	Phe	Thr(*t*Bu)-OtBu	997
Boc-Lys(εBoc)	Phe	Tyr	Phe	Ser(*t*Bu)-OtBu	998
Boc-Lys(εBoc)	Phe	Tyr	Phe	Thr(*t*Bu)-OtBu	999
Boc-Lys(εBoc)	Phe	His	Phe	Ser(*t*Bu)-OtBu	1000

Boc-Lys(εBoc)	Phe	His	Phe	Thr(*t*Bu)-OtBu	1001
Boc-Lys(εBoc)	Val	Phe	Phe-Tyr	Ser(*t*Bu)-OtBu	1002
Nicotinyl-Lys(εBoc)	Phe	Trp	Phe	Ser(*t*Bu)-OtBu	1003
Nicotinyl-Lys(εBoc)	Phe	Trp	Phe	Thr(*t*Bu)-OtBu	1004
Nicotinyl-Lys(εBoc)	Phe	Tyr	Phe	Ser(*t*Bu)-OtBu	1005
Nicotinyl-Lys(εBoc)	Phe	Tyr	Phe	Thr(*t*Bu)-OtBu	1006
Nicotinyl-Lys(εBoc)	Phe	His	Phe	Ser(*t*Bu)-OtBu	1007
Nicotinyl-Lys(εBoc)	Phe	His	Phe	Thr(*t*Bu)-OtBu	1008
Boc-Leu	Phe	Trp	Phe	Thr(*t*Bu)-OtBu	1009
Boc-Leu	Phe	Trp	Phe	Ser(*t*Bu)-OtBu	1010

[0166] While the peptides of Table 11 are illustrated with particular protecting groups, it is noted that these groups may be substituted with other protecting groups as described herein and/or one or more of the shown protecting group can be eliminated.

7) Summary of tripeptides and tetrapeptides.

[0167] For the sake of clarity, a number of tripeptides and tetrapeptides of this invention are generally summarized below in Table 12.

[0168] Table 12. General structure of certain peptides of this invention.

X^1	X^2	X^3	X^4
hydrophobic side chain or hydrophobic protecting group(s)	Acidic or Basic	----	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Basic	Acidic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Acidic	Basic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Acidic or Basic	Aliphatic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Aliphatic	Acidic or Basic	hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Acidic or Basic	Aromatic	hydrophobic side chain or hydrophobic

				protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Aromatic	Acidic or Basic		hydrophobic side chain or hydrophobic protecting group(s)
hydrophobic side chain or hydrophobic protecting group(s)	Aromatic	His	Aromatic	hydrophobic side chain or hydrophobic protecting group(s)

[0169] Where longer peptides are desired, X^2 and X^3 can represent domains (*e.g.*, regions of two or more amino acids of the specified type) rather than individual amino acids. Table 12 is intended to be illustrative and not limiting. Using the teaching provided herein, other suitable peptides can readily be identified.

8) Paired amino acids and dipeptides.

[0170] In certain embodiments, this invention pertains to the discovery that certain pairs of amino acids, administered in conjunction with each other or linked to form a dipeptide have one or more of the properties described herein. Thus, without being bound to a particular theory, it is believed that when the pairs of amino acids are administered in conjunction with each other, as described herein, they are capable participating in or inducing the formation of micelles *in vivo*.

[0171] Similar to the other small peptides described herein, it is believed that the pairs of peptides will associate *in vivo*, and demonstrate physical properties including high solubility in ethyl acetate (*e.g.*, greater than about 4 mg/mL), solubility in aqueous buffer at pH 7.0. Upon contacting phospholipids such as 1,2-Dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), in an aqueous environment, it is believed the pairs of amino acids induce or participate in the formation of particles with a diameter of approximately 7.5 nm (± 0.1 nm), and/or induce or participate in the formation of stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm, and/or also induce or participate in the formation of vesicular structures of approximately 38 nm).

[0172] Moreover, it is further believed that the pairs of amino acids can display one or more of the following physiologically relevant properties:

[0173] 1. They convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory;

[0174] 2. They decrease LDL-induced monocyte chemotactic activity generated by artery wall cells;

[0175] 3. They stimulate the formation and cycling of pre-β HDL;

[0176] 4. They raise HDL cholesterol; and/or

[0177] 5. They increase HDL paraoxonase activity.

[0178] The pairs of amino acids can be administered as separate amino acids (administered sequentially or simultaneously, *e.g.* in a combined formulation) or they can be covalently coupled directly or through a linker (*e.g.* a PEG linker, a carbon linker, a branched linker, a straight chain linker, a heterocyclic linker, a linker formed of derivatized lipid, *etc.*). In certain embodiments, the pairs of amino acids are covalently linked through a peptide bond to form a dipeptide. In various embodiments while the dipeptides will typically comprise two amino acids each bearing an attached protecting group, this invention also contemplates dipeptides wherein only one of the amino acids bears one or more protecting groups.

[0179] The pairs of amino acids typically comprise amino acids where each amino acid is attached to at least one protecting group (*e.g.*, a hydrophobic protecting group as described herein). The amino acids can be in the D or the L form. In certain embodiments, where the amino acids comprising the pairs are not attached to each other, each amino acid bears two protecting groups (*e.g.*, such as molecules 1 and 2 in Table 13).

[0180] Table 13. Illustrative amino acid pairs of this invention.

	Amino Acid Pair/dipeptide
1.	Boc-Arg-OtBu*
2.	Boc-Glu-OtBu*
3.	Boc-Phe-Arg-OtBu**
4.	Boc-Glu-Leu-OtBu**
5.	Boc-Arg-Glu-OtBu***

*This would typically be administered in conjunction with a second amino acid.

**In certain embodiments, these dipeptides would be administered in conjunction with each other.

*** In certain embodiments, this peptide would be administered either alone or in combination with one of the other peptides described herein..

[0181] Suitable pairs of amino acids can readily be identified by providing the pair of protected amino acids and/or a dipeptide and then screening the pair of amino acids/dipeptide for one or more of the physical and/or physiological properties described above. In certain embodiments, this invention excludes pairs of amino acids and/or dipeptides comprising aspartic acid and phenylalanine. In certain embodiments, this invention excludes pairs of amino acids and/or dipeptides in which one amino acid is (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine (nateglinide).

[0182] In certain embodiments, the amino acids comprising the pair are independently selected from the group consisting of an acidic amino acid (*e.g.*, aspartic acid, glutamic acid, *etc.*), a basic amino acid (*e.g.*, lysine, arginine, histidine, *etc.*), and a non-polar amino acid (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, *etc.*). In certain embodiments, where the first amino acid is acidic or basic, the second amino acid is non-polar and where the second amino acid is acidic or basic, the first amino acid is non-polar. In certain embodiments, where the first amino acid is acidic, the second amino acid is basic, and vice versa. (*see, e.g.,* Table 14).

[0183] Similar combinations can be obtained by administering pairs of dipeptides. Thus, for example in certain embodiments, molecules 3 and 4 in Table 13 would be administered in conjunction with each other.

Table 14. Certain generalized amino acid pairs/dipeptides.

	First Amino acid	Second Amino acid
1.	Acidic	Basic
2.	Basic	Acidic
3.	Acidic	Non-polar
4.	Non-polar	Acidic
5.	Basic	Non-polar
6.	Non-polar	Basic

[0184] It is noted that these amino acid pairs/dipeptides are intended to be illustrative and not limiting. Using the teaching provided herein other suitable amino acid pairs/dipeptides can readily be determined.

E) Apo-J (G* peptides).

[0185] In certain It was a discovery of this invention that peptides that mimicking the amphipathic helical domains of apo J are capable of mitigating one or more symptoms of atherosclerosis and/or other pathologies described herein. Apolipoprotein J possesses ~~a~~ wide nonpolar face termed globular protein-like, or G* amphipathic helical domains. The class G amphipathic helix is found in globular proteins, and thus, the name class G. This class of amphipathic helix is characterized by a random distribution of positively charged and negatively charged residues on the polar face with a narrow nonpolar face. Because of the narrow nonpolar face this class does not readily associate with phospholipids. The G* of amphipathic helix possesses similar, but not identical, characteristics to the G amphipathic helix. Similar to the class G amphipathic helix, the G* class peptides possesses a random distribution of positively and negatively charged residues on the polar face. However, in contrast to the class G amphipathic helix which has a narrow nonpolar face, this class has a wide nonpolar face that allows this class to readily bind phospholipid and the class is termed G* to differentiate it from the G class of amphipathic helix.

[0186] A number of suitable G* amphipathic peptides are described in copending applications USSN 10/120,508, filed April 5, 2002, USSN 10/520,207, filed April 1, 2003, and PCT Application PCT/US03/09988, filed April 1, 2003. In addition, a variety of suitable peptides of this invention that are related to G* amphipathic helical domains of apo J are illustrated in Table 15.

[0187] Table 15. Certain peptides for use in this invention related to G* amphipathic helical domains of apo J.

Amino Acid Sequence	SEQ ID NO
LLEQLNEQFNWVSRLANLTQGE	1011
LLEQLNEQFNWVSRLANL	1012
NELQEMSNQGSKYVNKEIQNAVNGV	1013
IQNAVNGVKQIKTLIEKTNEE	1014
RKTLLSNLEEAKKKKEDALNETRESETKLKEL	1015
PGVCNETMMALWEECK	1016
PCLKQTCMKFYARVCR	1017
ECKPCLKQTCMKFYARVCR	1018
LVGRQLEEFL	1019
MNGDRIDSLLEN	1020
QQTHMLDVMQD	1021
FSRASSIIDELFQD	1022

PFLEMIHEAQQAMDI	1023
PTEFIREGDDD	1024
RMKDQCDKCREILSV	1025
PSQAKLRRELDESLQVAERLTRKYNELLKSYQ	1026
LLEQLNEQFNWVSRLANLTEGE	1027
DQYYLRVTTVA	1028
PSGVTEVVVKLFDS	1029
PKFMETVAEKALQEYRKKHRE	1030

[0188] The peptides of this invention, however, are not limited to G* variants of apo J. Generally speaking G* domains from essentially any other protein preferably apo proteins are also suitable. The particular suitability of such proteins can readily be determined using assays for protective activity (*e.g.*, protecting LDL from oxidation, and the like), *e.g.* as illustrated herein in the Examples. Some particularly preferred proteins include G* amphipathic helical domains or variants thereof (*e.g.*, conservative substitutions, and the like) of proteins including, but not limited to apo AI, apo AIV, apo E, apo CII, apo CIII, and the like.

[0189] Certain preferred peptides for related to G* amphipathic helical domains related to apoproteins other than apo J are illustrated in Table 16.

[0190] Table 16. Certain peptides for use in this invention related to G* amphipathic helical domains related to apoproteins other than apo J.

Amino Acid Sequence	SEQ ID NO
WDRVKDLATVYVDVLKDSGRDYVSQF (Related to the 8 to 33 region of apo AI)	1031
VATVMWDYFSQLSNNAKEAVEHLQK (Related to the 7 to 31 region of apo AIV)	1032
RWELALGRFWDYLRWVQTLSEQVQEEL (Related to the 25 to 51 region of apo E)	1033
LSSQVTQELRALMDETMKELKELKAYKSELEEQLT (Related to the 52 to 83 region of apo E)	1034
ARLSKELQAAQARLGADMEDVCGRLV (Related to the 91 to 116 region of apo E)	1035
VRLASHLRKLRKRLLRDADDLQKRLA (Related to the135 to 160 region of apo E)	1036
PLVEDMQRQWAGLVEKVQA (267 to 285 of apo E.27)	1037

MSTYTGIFTDQVLSVLK	1038
(Related to the 60 to 76 region of apo CII)	
LLSFMQGYMKHATKTAKDALSS	1039
(Related to the 8 to 29 region of apo CIII)	

[0191] Additional illustrative G* peptides are shown in Table 17.

[0192] Table 17. Additional illustrative G* peptides.

Peptide	SEQ ID NO
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1040
Ac-Lys-Trp-Phe-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1041
Ac-Lys-Trp-Leu-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1042
Ac-Lys-Trp-Val-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1043
Ac-Lys-Tyr-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1044
Ac-Lys-Trp-Ile-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1045
Ac-Lys-Trp-Phe-Tyr-His-Ile-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1046
Ac-Lys-Trp-Leu-Tyr-His-Val-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1047
Ac-Lys-Trp-Val-Tyr-His-Tyr-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1048
Ac-Lys-Tyr-Ile-Trp-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1049
Ac-Lys-Tyr-Ile-Trp-His-Ile-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1050
Ac-Lys-Tyr-Ile-Trp-His-Val-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1051
Ac-Lys-Tyr-Ile-Trp-His-Tyr-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1052
Ac-Lys-Phe-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1053
Ac-Lys-Leu-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1054
Ac-Lys-Ile-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1055
Ac-Lys-Tyr-Ile-Trp-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1056
Ac-Lys-Trp-Ile-Tyr-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1057
Ac-Lys-Trp-Ile-Tyr-Leu-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1058
Ac-Lys-Trp-Ile-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1059
Ac-Lys-Trp-Ile-Tyr-His-Tyr-Thr-Glu-Gly-Ser-Thr-	1060

Asp-Leu-Arg-Thr-Glu-Gly-NH_2	
Ac-Lys-Trp-Ile-Tyr-His-Ile-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1061
Ac-Lys-Trp-Ile-Tyr-His-Leu-Ser-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1062
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Asp-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1063
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Thr-Ser-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1064
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Glu-Leu-Arg-Thr-Glu-Gly-NH_2	1065
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1066
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Tyr-Arg-Thr-Glu-Gly-NH_2	1067
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1068
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Val-Arg-Thr-Glu-Gly-NH_2	1069
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Lys-Thr-Glu-Gly-NH_2	1070
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Ser-Glu-Gly-NH_2	1071
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Asp-Gly-NH_2	1072
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Thr-Glu-Gly-NH_2	1073
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Ser-Glu-Gly-NH_2	1074
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Ser-Glu-Gly-NH_2	1075
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Ser-Asp-Gly-NH_2	1076
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1077
Ac-Arg-Tyr-Ile-Trp-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1078
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Asp-Gly-NH_2	1079
Ac-Arg-Trp-Ile-Phe-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1080
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Lys-Thr-Glu-Gly-NH_2	1081
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Asp-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1082
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Asp-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1083
Ac-Arg-Trp-Ile-Tyr-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1084
Ac-Arg-Trp-Ile-Tyr-Phe-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1085
Ac-Lys-Trp-Phe-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1086
Ac-Arg-Trp-Phe-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-	1087

Asp-Leu-Arg-Thr-Glu-Gly-NH_2	
Ac-Lys-Trp-Ile-Phe-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Asp-Gly-NH_2	1088
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Asp-Gly-NH_2	1089
Ac-Arg-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Asp-Gly-NH_2	1090
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Thr-Glu-Gly-NH_2	1091
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Lys-Thr-Asp-Gly-NH_2	1092
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Lys-Thr-Glu-Gly-NH_2	1093
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Tyr-Lys-Thr-Glu-Gly-NH_2	1094
Ac-Lys-Trp-Ile-Tyr-His-Leu-Thr-Glu-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1095
Ac-Lys-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1096
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1097
Ac-Lys-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1098
Ac-Lys-Trp-Phe-Tyr-His-Phe-Thr-Asp-Gly-Ser-Thr-Asp-Ile-Arg-Thr-Glu-Gly-NH_2	1099
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Leu-Arg-Thr-Glu-Gly-NH_2	1100
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Glu-Gly-NH_2	1101
Ac-Arg-Trp-Phe-Tyr-His-Phe-Thr-Glu-Gly-Ser-Thr-Asp-Phe-Arg-Thr-Asp-Gly-NH_2	1102
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1103
Ac-Asp-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1104
Ac-Glu-Lys-Cys-Val-Asp-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1105
Ac-Glu-Lys-Cys-Val-Glu-Asp-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1106
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1107
Ac-Asp-Lys-Cys-Val-Asp-Asp-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1108
Ac-Asp-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1109
Ac-Glu-Arg-Cys-Val-Asp-Asp-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1110
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1111
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Ile-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1112
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Val-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1113
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-	1114

Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1115
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Ile-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1116
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Val-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1117
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1118
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Thr-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1119
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Ile-Ser-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1120
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Val-Ser-Thr-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1121
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1122
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Thr-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1123
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Ser-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1124
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1125
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1126
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1127
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1128
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1129
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Glu-Ser-Lys-Ala-Phe-NH_2	1130
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Ile-Asp-Ser-Lys-Ala-Phe-NH_2	1131
Ac-Glu-Lys-Cys-Val-Glu-Glu-Leu-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1132
Ac-Asp-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1133
Ac-Asp-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1134
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1135
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1136
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1137
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Ser-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1138
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Gln-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1139
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Gln-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1140
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Gln-Phe-Thr-	1141

Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Gln-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1142
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Gln-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1143
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Gln-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1144
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Ala-Phe-NH_2	1145
Ac-Glu-Arg-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1146
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Ala-Phe-NH_2	1147
Ac-Glu-Arg-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Glu-Ser-Lys-Ala-Phe-NH_2	1148
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Leu-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1149
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Asp-Ser-Lys-Phe-Phe-NH_2	1150
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1151
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Glu-Ser-Lys-Phe-Phe-NH_2	1152
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Leu-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1153
Ac-Glu-Arg-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1154
Ac-Glu-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1155
Ac-Asp-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1156
Ac-Glu-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Ala-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1157
Ac-Asp-Lys-Ala-Val-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Ala-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1158
Ac-Asp-Arg-Ala-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1159
Ac-Asp-Arg-Ala-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Ala-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1160
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Phe-Glu-Ser-Lys-Phe-Phe-NH_2	1161
Ac-Glu-Lys-Cys-Tyr-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1162
Ac-Asp-Lys-Cys-Trp-Glu-Glu-Phe-Lys-Ser-Phe-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1163
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Tyr-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1164
Ac-Glu-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Trp-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Phe-Phe-NH_2	1165
Ac-Glu-Lys-Cys-Val-Glu-Glu-Phe-Lys-Ser-Trp-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1166
Ac-Asp-Lys-Cys-Phe-Glu-Glu-Phe-Lys-Ser-Trp-Thr-Ser-Cys-Leu-Asp-Ser-Lys-Ala-Phe-NH_2	1167

[0193] Other suitable peptides include, but are not limited to the peptides of Table 18.

[0194] Table 18. Illustrative peptides having an improved hydrophobic phase.

Name	Sequence	SEQ ID NO
V2W3A5F1017-D-4F	Ac-Asp-Val-Trp-Lys-Ala-Ala-Tyr-Asp-Lys-Phe-Ala-Glu-Lys-Phe-Lys-Glu-Phe-Phe-NH2	1168
V2W3F10-D-4F	Ac-Asp-Val-Trp-Lys-Ala-Phe-Tyr-Asp-Lys-Phe-Ala-Glu-Lys-Phe-Lys-Glu-Ala-Phe-NH2	1169
W3-D-4F	Ac-Asp-Phe-Trp-Lys-Ala-Phe-Tyr-Asp-Lys-Val-Ala-Glu-Lys-Phe-Lys-Glu-Ala-Phe-NH2	1170

[0195] The peptides described here (V2W3A5F10,17-D-4F; V2W3F10-D-4F; W3-D-4F) may be more potent than the original D-4F.

[0196] Still other suitable peptides include, but are not limited to: P^1-Dimethyltyrosine-D-Arg-Phe-Lys-P^2 (SEQ ID NO:1171) and P^1-Dimethyltyrosine-Arg-Glu-Leu-P^2 where P1 and P2 are protecting groups as described herein. In certain embodiments, these peptides include, but are not limited to BocDimethyltyrosine-D-Arg-Phe-Lys(OtBu) and BocDimethyltyrosine-Arg-Glu-Leu(OtBu).

[0197] In certain embodiments, the peptides of this invention include peptides comprising or consisting of the amino acid sequence LAEYHAK (SEQ ID NO:1172) comprising at least one D amino acid and/or at least one or two terminal protecting groups. In certain embodiments, this invention includes a peptide that ameliorates one or more symptoms of an inflammatory condition, wherein the peptide: ranges in length from about 3 to about 10 amino acids; comprises an amino acid sequence where the sequence comprises acidic or basic amino acids alternating with aromatic or hydrophobic amino acids; comprises hydrophobic terminal amino acids or terminal amino acids bearing a hydrophobic protecting group; is not the sequence LAEYHAK (SEQ ID NO:1173) comprising all L amino acids; where the peptide converts pro-inflammatory HDL to anti-inflammatory HDL and/or makes anti-inflammatory HDL more anti-inflammatory.

[0198] It is also noted that the peptides listed in the Tables herein are not fully inclusive. Using the teaching provided herein, other suitable peptides can routinely be produced (*e.g.* by conservative or semi-conservative substitutions (*e.g.* D replaced by E),

extensions, deletions, and the like). Thus, for example, one embodiment utilizes truncations of any one or more of peptides identified by SEQ ID Nos:1011-1039.

[0199] Longer peptides are also suitable. Such longer peptides may entirely form a class G or G* amphipathic helix, or the G amphipathic helix (helices) can form one or more domains of the peptide. In addition, this invention contemplates multimeric versions of the peptides. Thus, for example, the peptides illustrated in the tables herein can be coupled together (directly or through a linker (*e.g.* a carbon linker, or one or more amino acids) with one or more intervening amino acids). Suitable linkers include, but are not limited to Proline (-Pro-), Gly_4Ser_3 (SEQ ID NO: 1174), and the like. Thus, one illustrative multimeric peptide according to this invention is (D-J336)-P-(D-J336) (*i.e.* Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T- Q-G-E-**P-**L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-NH_2, SEQ ID NO: 1175).

[0200] This invention also contemplates the use of "hybrid" peptides comprising a one or more G or G* amphipathic helical domains and one or more class A amphipathic helices. Suitable class A amphipathic helical peptides are described in PCT publication WO 02/15923. Thus, by way of illustration, one such "hybrid" peptide is (D-J336)-Pro-(4F) (*i.e.* Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-**P-**D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2, SEQ ID NO: 1176), and the like.

[0201] Using the teaching provided herein, one of skill can routinely modify the illustrated amphipathic helical peptides to produce other suitable apo J variants and/or amphipathic G and/or A helical peptides of this invention. For example, routine conservative or semi-conservative substitutions (*e.g.*, E for D) can be made of the existing amino acids. The effect of various substitutions on lipid affinity of the resulting peptide can be predicted using the computational method described by Palgunachari *et al.* (1996) *Arteriosclerosis, Thrombosis, & Vascular Biology* 16: 328-338. The peptides can be lengthened or shortened as long as the class helix structure(s) are preserved. In addition, substitutions can be made to render the resulting peptide more similar to peptide(s) endogenously produced by the subject species.

[0202] While, in preferred embodiments, the peptides of this invention utilize naturally-occurring amino acids or D forms of naturally occurring amino acids, substitutions with non-naturally occurring amino acids (*e.g.*, methionine sulfoxide, methionine methylsulfonium, norleucine, episilon-aminocaproic acid, 4-aminobutanoic

acid, tetrahydroisoquinoline-3-carboxylic acid, 8-aminocaprylic acid, 4-aminobutyric acid, Lys(N(epsilon)-trifluoroacetyl), α-aminoisobutyric acid, and the like) are also contemplated.

[0203] New peptides can be designed and/or evaluated using computational methods. Computer programs to identify and classify amphipathic helical domains are well known to those of skill in the art and many have been described by Jones *et al.*(1992) *J. Lipid Res.* 33: 287-296). Such programs include, but are not limited to the helical wheel program (WHEEL or WHEEL/SNORKEL), helical net program (HELNET, HELNET/SNORKEL, HELNET/Angle), program for addition of helical wheels (COMBO or COMBO/SNORKEL), program for addition of helical nets (COMNET, COMNET/SNORKEL, COMBO/SELECT, COMBO/NET), consensus wheel program (CONSENSUS, CONSENSUS/SNORKEL), and the like.

F) Blocking groups and D residues.

[0204] While the various peptides and/or amino acid pairs described herein may be shown with no protecting groups, in certain embodiments (*e.g.* particularly for oral administration), they can bear one, two, three, four, or more protecting groups. The protecting groups can be coupled to the C- and/or N-terminus of the peptide(s) and/or to one or more internal residues comprising the peptide(s) (*e.g.*, one or more R-groups on the constituent amino acids can be blocked). Thus, for example, in certain embodiments, any of the peptides described herein can bear, *e.g.* an acetyl group protecting the amino terminus and/or an amide group protecting the carboxyl terminus. One example of such a "dual protected peptide is Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-NH_2 (SEQ ID NO:1011 with blocking groups), either or both of these protecting groups can be eliminated and/or substituted with another protecting group as described herein.

[0205] Without being bound by a particular theory, it was a discovery of this invention that blockage, particularly of the amino and/or carboxyl termini of the subject peptides of this invention greatly improves oral delivery and significantly increases serum half-life.

[0206] A wide number of protecting groups are suitable for this purpose. Such groups include, but are not limited to acetyl, amide, and alkyl groups with acetyl and alkyl groups being particularly preferred for N-terminal protection and amide groups being preferred for carboxyl terminal protection. In certain particularly preferred embodiments,

the protecting groups include, but are not limited to alkyl chains as in fatty acids, propeonyl, formyl, and others. Particularly preferred carboxyl protecting groups include amides, esters, and ether-forming protecting groups. In one preferred embodiment, an acetyl group is used to protect the amino terminus and an amide group is used to protect the carboxyl terminus. These blocking groups enhance the helix-forming tendencies of the peptides. Certain particularly preferred blocking groups include alkyl groups of various lengths, *e.g.* groups having the formula: CH_3-$(CH_2)_n$-CO- where n ranges from about 1 to about 20, preferably from about 1 to about 16 or 18, more preferably from about 3 to about 13, and most preferably from about 3 to about 10.

[0207] In certain particularly preferred embodiments, the protecting groups include, but are not limited to alkyl chains as in fatty acids, propeonyl, formyl, and others. Particularly preferred carboxyl protecting groups include amides, esters, and ether-forming protecting groups. In one preferred embodiment, an acetyl group is used to protect the amino terminus and an amide group is used to protect the carboxyl terminus. These blocking groups enhance the helix-forming tendencies of the peptides. Certain particularly preferred blocking groups include alkyl groups of various lengths, *e.g.* groups having the formula: CH_3-$(CH_2)_n$-CO- where n ranges from about 3 to about 20, preferably from about 3 to about 16, more preferably from about 3 to about 13, and most preferably from about 3 to about 10.

[0208] Other protecting groups include, but are not limited to Fmoc, t-butoxycarbonyl (*t*-BOC), 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

[0209] Protecting/blocking groups are well known to those of skill as are methods of coupling such groups to the appropriate residue(s) comprising the peptides of this

invention (*see, e.g.*, Greene *et al.*, (1991) *Protective Groups in Organic Synthesis, 2nd ed.*, John Wiley & Sons, Inc. Somerset, N.J.). In one preferred embodiment, for example, acetylation is accomplished during the synthesis when the peptide is on the resin using acetic anhydride. Amide protection can be achieved by the selection of a proper resin for the synthesis. During the synthesis of the peptides described herein in the examples, rink amide resin was used. After the completion of the synthesis, the semipermanent protecting groups on acidic bifunctional amino acids such as Asp and Glu and basic amino acid Lys, hydroxyl of Tyr are all simultaneously removed. The peptides released from such a resin using acidic treatment comes out with the n-terminal protected as acetyl and the carboxyl protected as NH_2 and with the simultaneous removal of all of the other protecting groups.

[0210] In certain particularly preferred embodiments, the peptides comprise one or more D-form (dextro rather than levo) amino acids as described herein. In certain embodiments at least two enantiomeric amino acids, more preferably at least 4 enantiomeric amino acids and most preferably at least 8 or 10 enantiomeric amino acids are "D" form amino acids. In certain embodiments every other, ore even every amino acid (*e.g.* every enantiomeric amino acid) of the peptides described herein is a D-form amino acid.

[0211] In certain embodiments at least 50% of the enantiomeric amino acids are "D" form, more preferably at least 80% of the enantiomeric amino acids are "D" form, and most preferably at least 90% or even all of the enantiomeric amino acids are "D" form amino acids.

G) Peptide Mimetics.

[0212] In addition to the peptides described herein, peptidomimetics are also contemplated. Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics" (Fauchere (1986) *Adv. Drug Res.* 15: 29; Veber and Freidinger (1985) *TINS* p.392; and Evans *et al.* (1987) *J. Med. Chem.* 30: 1229) and are usually developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect.

[0213] Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*e.g.* SEQ ID NO:5 shown in Table 1), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: $-CH_2NH-$, $-CH_2S-$, $-CH_2-CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, *etc.* by methods known in the art and further described in the following references: Spatola (1983) p. 267 in *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*, B. Weinstein, eds., Marcel Dekker, New York,; Spatola (1983) *Vega Data* 1(3) *Peptide Backbone Modifications.* (general review); Morley (1980) *Trends Pharm Sci* pp. 463-468 (general review); Hudson *et al.* (1979) *Int J Pept Prot Res* 14:177-185 ($-CH_2NH-$, CH_2CH_2-); Spatola et al. (1986) *Life Sci* 38:1243-1249 ($-CH_2-S$); Hann, (1982) *J Chem Soc Perkin Trans* I 307-314 (-CH-CH-, cis and trans); Almquist *et al.* (1980) *J Med Chem.* 23:1392-1398 ($-COCH_2-$); Jennings-White *et al.* (1982) *Tetrahedron Lett.* 23:2533 ($-COCH_2-$); Szelke et al., European Appln. EP 45665 (1982) CA: 97:39405 (1982) (-CH(OH)CH2-); Holladay *et al.* (1983) *Tetrahedron Lett* 24:4401-4404 ($-C(OH)CH_2-$); and Hruby (1982) *Life Sci.,* 31:189-199 ($-CH_2-S-$)).

[0214] One particularly preferred non-peptide linkage is $-CH_2NH-$. Such peptide mimetics may have significant advantages over polypeptide embodiments, including, for example: more economical production, greater chemical stability, enhanced pharmacological properties (half-life, absorption, potency, efficacy, *etc.*), reduced antigenicity, and others.

[0215] In addition, circularly permutations of the peptides described herein or constrained peptides (including cyclized peptides) comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch (1992) *Ann. Rev. Biochem.* 61: 387); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

H) Small organic molecules.

[0216] In certain embodiments, the active agents of this invention include small organic molecules, *e.g.* as described in copending application USSN 60/600,925, filed August 11, 2004. In various embodiments the small organic molecules are similar to, and in certain cases, mimetics of the tetra- and penta-peptides described in copending

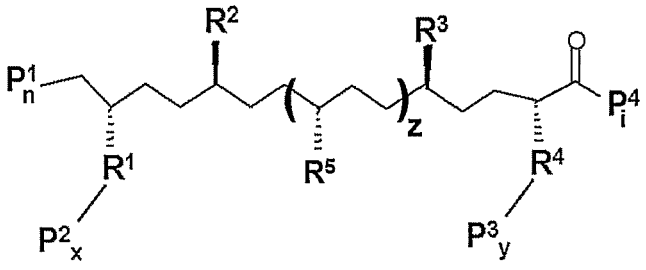
application USSN 10/649,378, filed on August 26, 2003 and USSN 60/494,449, filed on August 11.

[0217] The small organic molecules of this invention typically have molecular weights less than about 900 Daltons. Typically the molecules are highly soluble in ethyl acetate (*e.g.*, at concentrations equal to or greater than 4 mg/mL), and also are soluble in aqueous buffer at pH 7.0.

[0218] Contacting phospholipids such as 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), with the small organic molecules of this invention in an aqueous environment typically results in the formation of particles with a diameter of approximately 7.5 nm (± 0.1 nm). In addition, stacked bilayers are often formed with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm. Vesicular structures of approximately 38 nm are also often formed. Moreover, when the molecules of this invention are administered to a mammal they render HDL more anti-inflammatory and mitigate one or more symptoms of atherosclerosis and/or other conditions characterized by an inflammatory response.

[0219] Thus, in certain embodiments, the small organic molecule is one that ameliorates one or more symptoms of a pathology characterized by an inflammatory response in a mammal (*e.g.* atherosclerosis), where the small molecule is soluble in ethyl acetate at a concentration greater than 4mg/mL, is soluble in aqueous buffer at pH 7.0, and, when contacted with a phospholipid in an aqueous environment, forms particles with a diameter of approximately 7.5 nm and forms stacked bilayers with a bilayer dimension on the order of 3.4 to 4.1 nm with spacing between the bilayers in the stack of approximately 2 nm, and has a molecular weight les than 900 daltons.

[0220] In certain embodiment, the molecule has the formula:



I.

where P^1, P^2, P^3, and P^4 are independently selected hydrophobic protecting groups; R^1 and $R^4$are independently selected amino acid R groups; n, i, x, y, and z are independently zero or 1 such that when n and x are both zero, R^1 is a hydrophobic group and when y and i are both zero, R^4 is a hydrophobic group; R^2 and R^3 are acidic or basic groups at pH 7.0 such that when R^2 is acidic, R^3 is basic and when R^2 is basic, R^3 is acidic; and R^5, when present is selected from the group consisting of an aromatic group, an aliphatic group, a positively charged group, or a negatively charged group. In certain embodiments, R^2 or R^3 is -(CH_2)j-COOH where j=1, 2, 3, or 4 and/or -(CH_2)j-NH_2 where j = 1, 2, 3, 4, or 5, or -(CH_2)j-NH-C(=NH)-NH_2 where n= 1, 2, 3 or 4. In certain embodiments, R^2, R^3, and R^5, when present, are amino acid R groups. Thus, for example, In various embodiments R^2 and R^3 are independently an aspartic acid R group, a glutamic acid R group, a lysine R group, a histidine R group, or an arginine R group (*e.g.*, as illustrated in Table 1).

[0221] In certain embodiments, R^1 is selected from the group consisting of a Lys R group, a Trp R group, a Phe R group, a Leu R group, an Orn R group, pr a norLeu R group. In certain embodiments, R^4 is selected from the group consisting of a Ser R group, a Thr R group, an Ile R group, a Leu R group, a norLeu R group, a Phe R group, or a Tyr R group.

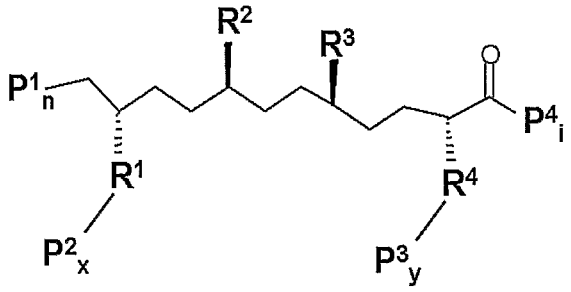
[0222] In various embodiments x is 1, and R^5 is an aromatic group (*e.g.*, a Trp R group).

[0223] In various embodiments at least one of n, x, y, and i is 1 and P^1, P^2, P^3, and P^4 when present, are independently selected from the group consisting of polyethylene glycol (PEG), an acetyl, amide, a 3 to 20 carbon alkyl group, fmoc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-fluorenecarboxylic, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts),-4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), benzyloxy (BzlO), benzyl (Bzl), benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), a propyl group, a butyl group, a pentyl group, a hexyl group, and trifluoroacetyl (TFA). In certain embodiments, P^1 when present and/or

P^2 when present are independently selected from the group consisting of Boc-, Fmoc-, and Nicotinyl- and/or P^3 when present and/or P^4 when present are independently selected from the group consisting of *t*Bu, and O*t*Bu.

[0224] While a number of protecting groups (P^1, P^2, P^3, P^4) are illustrated above, this list is intended to be illustrative and not limiting. In view of the teachings provided herein, a number of other protecting/blocking groups will also be known to one of skill in the art. Such blocking groups can be selected to minimize digestion (*e.g.*, for oral pharmaceutical delivery), and/or to increase uptake/bioavailability (*e.g.*, through mucosal surfaces in nasal delivery, inhalation therapy, rectal administration), and/or to increase serum/plasma half-life. In certain embodiments, the protecting groups can be provided as an excipient or as a component of an excipient.

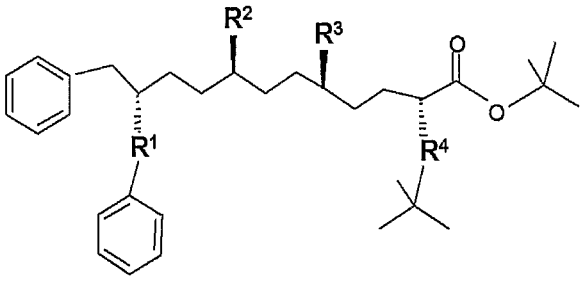
[0225] In certain embodiments, z is zero and the molecule has the formula:



II.

where P^1, P^2, P^3, P^4, R^1, R^2, R^3, R^4, n, x, y, and i are as described above.

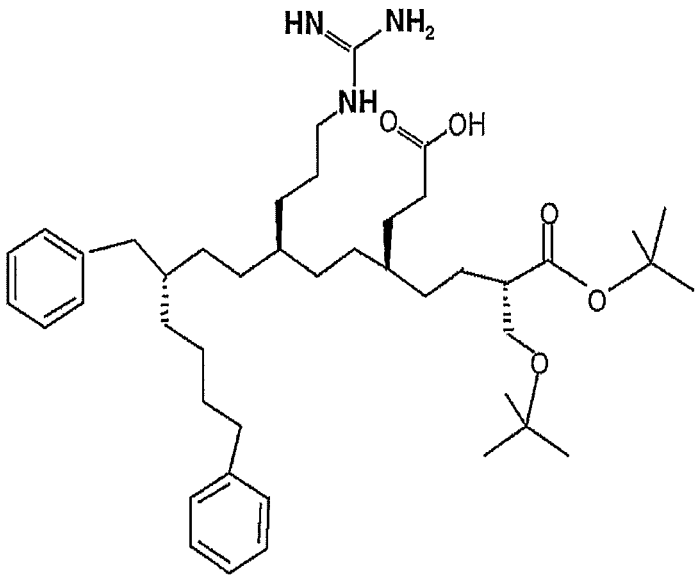
[0226] In certain embodiments, z is zero and the molecule has the formula:



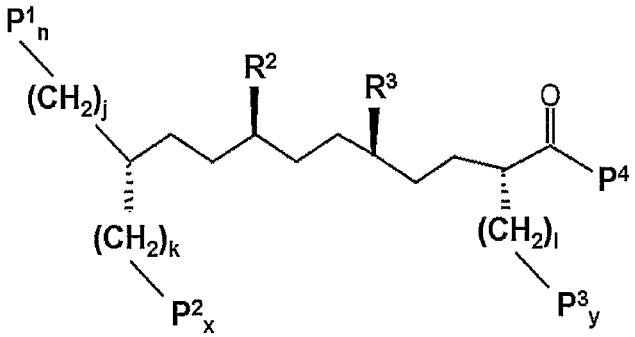
III.

where R^1, R^2, R^3, and R^4 are as described above .

[0227] In one embodiment, the molecule has the formula:



[0228] In certain embodiments, this invention contemplates small molecules having one or more of the physical and/or functional properties described herein and having the formula:



where P^1, P^2, P^3, and P^4 are independently selected hydrophobic protecting groups as described above, n, x, and y are independently zero or 1; j, k, and l are independently zero, 1, 2, 3, 4, or 5; and R^2 and R^3 are acidic or basic groups at pH 7.0 such that when R^2 is acidic, R^3 is basic and when R^2 is basic, R^3 is acidic. In certain preferred embodiments, the small molecule is soluble in water; and the small molecule has a molecular weight less than about 900 Daltons. In certain embodiments, n, x, y, j, and l are 1; and k is 4.

[0229] In certain embodiments, P^1 and/or P^2 are aromatic protecting groups. In certain embodiments, R^2 and R^3 are amino acid R groups, *e.g.,* as described above. In various embodiments least one of n, x, and y, is 1 and P^1, P^2, P^3 and P^4 when present, are independently protecting groups, *e.g.* as described above. In certain embodiments the protecting groups, when present, are independently selected from the group consisting of polyethylene glycol (PEG), an acetyl, amide, 3 to 20 carbon alkyl groups, Fmoc, 9-

fluoreneacetyl group, 1-fluorenecarboxylic group, 9-fluorenecarboxylic, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts),-4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-penta

III. Functional assays of active agents.

[0230] Certain active agents for use in the methods of this invention are described herein by various formulas (*e.g.*, Formula I, above) and/or by particular sequences. In certain embodiments, preferred active agents of this invention are characterized by one or more of the following functional properties:

1. They convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory;
2. They decrease LDL-induced monocyte chemotactic activity generated by artery wall cells;
3. They stimulate the formation and cycling of pre-β HDL;
4. They raise HDL cholesterol; and/or
5. They increase HDL paraoxonase activity.

[0231] The specific agents disclosed herein, and/or agents corresponding to the various formulas described herein can readily be tested for one or more of these activities as desired.

[0232] Methods of screening for each of these functional properties are well known to those of skill in the art. In particular, it is noted that assays for monocyte chemotactic activity, HDL cholesterol, and HDL HDL paraoxonase activity are illustrated in PCT/US01/26497 (WO 2002/15923).

IV. Peptide preparation.

[0233] The peptides used in this invention can be chemically synthesized using standard chemical peptide synthesis techniques or, particularly where the peptide does not comprise "D" amino acid residues, can be recombinantly expressed. In certain embodiments, even peptides comprising "D" amino acid residues are recombinantly expressed. Where the polypeptides are recombinantly expressed, a host organism (*e.g.*

bacteria, plant, fungal cells, *etc.*) in cultured in an environment where one or more of the amino acids is provided to the organism exclusively in a D form. Recombinantly expressed peptides in such a system then incorporate those D amino acids.

[0234] In preferred embodiments the peptides are chemically synthesized by any of a number of fluid or solid phase peptide synthesis techniques known to those of skill in the art. Solid phase synthesis in which the C-terminal amino acid of the sequence is attached to an insoluble support followed by sequential addition of the remaining amino acids in the sequence is a preferred method for the chemical synthesis of the polypeptides of this invention. Techniques for solid phase synthesis are well known to those of skill in the art and are described, for example, by Barany and Merrifield (1963) *Solid-Phase Peptide Synthesis;* pp. 3-284 *in The Peptides: Analysis, Synthesis, Biology. Vol. 2: Special Methods in Peptide Synthesis, Part A.*; Merrifield *et al.* (1963) *J. Am. Chem. Soc.,* 85: 2149-2156, and Stewart et al. (1984) *Solid Phase Peptide Synthesis,* 2nd ed. Pierce Chem. Co., Rockford, Ill.

[0235] In certain embodiments, the peptides are synthesized by the solid phase peptide synthesis procedure using a benzhyderylamine resin (Beckman Bioproducts, 0.59 mmol of NH_2/g of resin) as the solid support. The COOH terminal amino acid (*e.g.*, *t*-butylcarbonyl-Phe) is attached to the solid support through a 4-(oxymethyl)phenacetyl group. This is a more stable linkage than the conventional benzyl ester linkage, yet the finished peptide can still be cleaved by hydrogenation. Transfer hydrogenation using formic acid as the hydrogen donor is used for this purpose. Detailed protocols used for peptide synthesis and analysis of synthesized peptides are described in a miniprint supplement accompanying Anantharamaiah *et al.* (1985) *J. Biol. Chem.,* 260(16): 10248-10255.

[0236] It is noted that in the chemical synthesis of peptides, particularly peptides comprising D amino acids, the synthesis usually produces a number of truncated peptides in addition to the desired full-length product. The purification process (*e.g.* HPLC) typically results in the loss of a significant amount of the full-length product.

[0237] It was a discovery of this invention that, in the synthesis of a D peptide (*e.g.* D-4), in order to prevent loss in purifying the longest form one can dialyze and use the mixture and thereby eliminate the last HPLC purification. Such a mixture loses about

50% of the potency of the highly purified product (*e.g.* per wt of protein product), but the mixture contains about 6 times more peptide and thus greater total activity.

V. Pharmaceutical formulations and devices.

A) Pharmaceutical formulations.

[0238] In order to carry out the methods of the invention, one or more active agents of this invention are administered, *e.g.* to an individual diagnosed as having one or more symptoms of atherosclerosis, or as being at risk for atherosclerosis and or the various other pathologies described herein. The active agent(s) can be administered in the "native" form or, if desired, in the form of salts, esters, amides, prodrugs, derivatives, and the like, provided the salt, ester, amide, prodrug or derivative is suitable pharmacologically, *i.e.*, effective in the present method. Salts, esters, amides, prodrugs and other derivatives of the active agents can be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by March (1992) *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th Ed. N.Y. Wiley-Interscience.

[0239] For example, acid addition salts are prepared from the free base using conventional methodology, that typically involves reaction with a suitable acid. Generally, the base form of the drug is dissolved in a polar organic solvent such as methanol or ethanol and the acid is added thereto. The resulting salt either precipitates or can be brought out of solution by addition of a less polar solvent. Suitable acids for preparing acid addition salts include both organic acids, *e.g.*, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Particularly preferred acid addition salts of the active agents herein are halide salts, such as may be prepared using hydrochloric or hydrobromic acids. Conversely, preparation of basic salts of the active agents of this invention are prepared in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide,

trimethylamine, or the like. Particularly preferred basic salts include alkali metal salts, *e.g.*, the sodium salt, and copper salts.

[0240] Preparation of esters typically involves functionalization of hydroxyl and/or carboxyl groups which may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, *i.e.*, moieties that are derived from carboxylic acids of the formula RCOOH where R is alky, and preferably is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures.

[0241] Amides and prodrugs can also be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs are typically prepared by covalent attachment of a moiety that results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

[0242] The active agents identified herein are useful for parenteral, topical, oral, nasal (or otherwise inhaled), rectal, or local administration, such as by aerosol or transdermally, for prophylactic and/or therapeutic treatment of one or more of the pathologies/indications described herein (*e.g.*, atherosclerosis and/or symptoms thereof). The pharmaceutical compositions can be administered in a variety of unit dosage forms depending upon the method of administration. Suitable unit dosage forms, include, but are not limited to powders, tablets, pills, capsules, lozenges, suppositories, patches, nasal sprays, injectibles, implantable sustained-release formulations, lipid complexes, *etc.*

[0243] The active agents of this invention are typically combined with a pharmaceutically acceptable carrier (excipient) to form a pharmacological composition. Pharmaceutically acceptable carriers can contain one or more physiologically acceptable compound(s) that act, for example, to stabilize the composition or to increase or decrease the absorption of the active agent(s). Physiologically acceptable compounds can include, for example, carbohydrates, such as glucose, sucrose, or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins, protection and uptake enhancers such as lipids, compositions that reduce the clearance or hydrolysis of the active agents, or excipients or other stabilizers and/or buffers.

[0244] Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid. One skilled in the art would appreciate that the choice of pharmaceutically acceptable carrier(s), including a physiologically acceptable compound depends, for example, on the route of administration of the active agent(s) and on the particular physio-chemical characteristics of the active agent(s).

[0245] The excipients are preferably sterile and generally free of undesirable matter. These compositions may be sterilized by conventional, well-known sterilization techniques.

[0246] In therapeutic applications, the compositions of this invention are administered to a patient suffering from one or more symptoms of the one or more pathologies described herein, or at risk for one or more of the pathologies described herein in an amount sufficient to prevent and/or cure and/or or at least partially prevent or arrest the disease and/or its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose." Amounts effective for this use will depend upon the severity of the disease and the general state of the patient's health. Single or multiple administrations of the compositions may be administered depending on the dosage and frequency as required and tolerated by the patient. In any event, the composition should provide a sufficient quantity of the active agents of the formulations of this invention to effectively treat (ameliorate one or more symptoms) the patient.

[0247] The concentration of active agent(s) can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Concentrations, however, will typically be selected to provide dosages ranging from about 0.1 or 1 mg/kg/day to about 50 mg/kg/day and sometimes higher. Typical dosages range from about 3 mg/kg/day to about 3.5 mg/kg/day, preferably from about 3.5 mg/kg/day to about 7.2 mg/kg/day, more preferably from about 7.2 mg/kg/day to about 11.0 mg/kg/day, and most preferably from about 11.0 mg/kg/day to about 15.0 mg/kg/day. In certain preferred embodiments, dosages range from about 10 mg/kg/day to about 50 mg/kg/day. In certain embodiments, dosages range from about 20 mg to about 50 mg given orally twice daily. It

will be appreciated that such dosages may be varied to optimize a therapeutic regimen in a particular subject or group of subjects.

[0248] In certain preferred embodiments, the active agents of this invention are administered orally (*e.g.* via a tablet) or as an injectable in accordance with standard methods well known to those of skill in the art. In other preferred embodiments, the peptides, may also be delivered through the skin using conventional transdermal drug delivery systems, *i.e.*, transdermal "patches" wherein the active agent(s) are typically contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is typically contained in a layer, or "reservoir," underlying an upper backing layer. It will be appreciated that the term "reservoir" in this context refers to a quantity of "active ingredient(s)" that is ultimately available for delivery to the surface of the skin. Thus, for example, the "reservoir" may include the active ingredient(s) in an adhesive on a backing layer of the patch, or in any of a variety of different matrix formulations known to those of skill in the art. The patch may contain a single reservoir, or it may contain multiple reservoirs.

[0249] In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. The backing layer in these laminates, which serves as the upper surface of the device, preferably functions as a primary structural element of the "patch" and provides the device with much of its flexibility. The material selected for the backing layer is preferably substantially impermeable to the active agent(s) and any other materials that are present.

[0250] Other preferred formulations for topical drug delivery include, but are not limited to, ointments and creams. Ointments are semisolid preparations which are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent, are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the

"internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. The specific ointment or cream base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing.

[0251] Unlike typical peptide formulations, the peptides of this invention comprising D-form amino acids can be administered, even orally, without protection against proteolysis by stomach acid, *etc.* Nevertheless, in certain embodiments, peptide delivery can be enhanced by the use of protective excipients. This is typically accomplished either by complexing the polypeptide with a composition to render it resistant to acidic and enzymatic hydrolysis or by packaging the polypeptide in an appropriately resistant carrier such as a liposome. Means of protecting polypeptides for oral delivery are well known in the art (see, *e.g.*, U.S. Patent 5,391,377 describing lipid compositions for oral delivery of therapeutic agents).

[0252] Elevated serum half-life can be maintained by the use of sustained-release protein "packaging" systems. Such sustained release systems are well known to those of skill in the art. In one preferred embodiment, the ProLease biodegradable microsphere delivery system for proteins and peptides (Tracy (1998) *Biotechnol. Prog.*, 14: 108; Johnson *et al.* (1996) *Nature Med.* 2: 795; Herbert *et al.* (1998), *Pharmaceut. Res.* 15, 357) a dry powder composed of biodegradable polymeric microspheres containing the active agent in a polymer matrix that can be compounded as a dry formulation with or without other agents.

[0253] The ProLease microsphere fabrication process was specifically designed to achieve a high encapsulation efficiency while maintaining integrity of the active agent. The process consists of (i) preparation of freeze-dried drug particles from bulk by spray freeze-drying the drug solution with stabilizing excipients, (ii) preparation of a drug-polymer suspension followed by sonication or homogenization to reduce the drug particle size, (iii) production of frozen drug-polymer microspheres by atomization into liquid nitrogen, (iv) extraction of the polymer solvent with ethanol, and (v) filtration and vacuum drying to produce the final dry-powder product. The resulting powder contains the solid form of the active agents, which is homogeneously and rigidly dispersed within porous

polymer particles. The polymer most commonly used in the process, poly(lactide-co-glycolide) (PLG), is both biocompatible and biodegradable.

[0254] Encapsulation can be achieved at low temperatures (*e.g.*, -40°C). During encapsulation, the protein is maintained in the solid state in the absence of water, thus minimizing water-induced conformational mobility of the protein, preventing protein degradation reactions that include water as a reactant, and avoiding organic-aqueous interfaces where proteins may undergo denaturation. A preferred process uses solvents in which most proteins are insoluble, thus yielding high encapsulation efficiencies (*e.g.*, greater than 95%).

[0255] In another embodiment, one or more components of the solution can be provided as a "concentrate", *e.g.*, in a storage container (*e.g.*, in a premeasured volume) ready for dilution, or in a soluble capsule ready for addition to a volume of water.

[0256] The foregoing formulations and administration methods are intended to be illustrative and not limiting. It will be appreciated that, using the teaching provided herein, other suitable formulations and modes of administration can be readily devised.

B) Lipid-based formulations.

[0257] In certain embodiments, the active agents of this invention are administered in conjunction with one or more lipids. The lipids can be formulated as an excipient to protect and/or enhance transport/uptake of the active agents or they can be administered separately.

[0258] Without being bound by a particular theory, it was discovered of this invention that administration (*e.g.* oral administration) of certain phospholipids can significantly increase HDL/LDL ratios. In addition, it is believed that certain medium-length phospholipids are transported by a process different than that involved in general lipid transport. Thus, co-administration of certain medium-length phospholipids with the active agents of this invention confer a number of advantages: They protect the active agents from digestion or hydrolysis, they improve uptake, and they improve HDL/LDL ratios.

[0259] The lipids can be formed into liposomes that encapsulate the active agents of this invention and/or they can be complexed/admixed with the active agents and/or they can be covalently coupled to the active agents. Methods of making liposomes and

encapsulating reagents are well known to those of skill in the art (*see, e.g.,* Martin and Papahadjopoulos (1982) *J. Biol. Chem.*, 257: 286-288; Papahadjopoulos *et al.* (1991) *Proc. Natl. Acad. Sci. USA*, 88: 11460-11464; Huang *et al.* (1992) *Cancer Res.*, 52:6774-6781; Lasic *et al.* (1992) *FEBS Lett.*, 312: 255-258., and the like).

[0260] Preferred phospholipids for use in these methods have fatty acids ranging from about 4 carbons to about 24 carbons in the sn-1 and sn-2 positions. In certain preferred embodiments, the fatty acids are saturated. In other preferred embodiments, the fatty acids can be unsaturated. Various preferred fatty acids are illustrated in Table 19.

[0261] **Table 19.** Preferred fatty acids in the sn-1 and/or sn-2 position of the preferred phospholipids for administration of active agents described herein.

Carbon No.	Common Name	IUPAC Name
3:0	Propionoyl	Trianoic
4:0	Butanoyl	Tetranoic
5:0	Pentanoyl	Pentanoic
6:0	Caproyl	Hexanoic
7:0	Heptanoyl	Heptanoic
8:0	Capryloyl	Octanoic
9:0	Nonanoyl	Nonanoic
10:0	Capryl	Decanoic
11:0	Undcanoyl	Undecanoic
12:0	Lauroyl	Dodecanoic
13:0	Tridecanoyl	Tridecanoic
14:0	Myristoyl	Tetradecanoic
15:0	Pentadecanoyl	Pentadecanoic
16:0	Palmitoyl	Hexadecanoic
17:0	Heptadecanoyl	Heptadecanoic
18:0	Stearoyl	Octadecanoic
19:0	Nonadecanoyl	Nonadecanoic
20:0	Arachidoyl	Eicosanoic
21:0	Heniecosanoyl	Heniecosanoic
22:0	Behenoyl	Docosanoic
23:0	Trucisanoyl	Trocosanoic
24:0	Lignoceroyl	Tetracosanoic
14:1	Myristoleoyl (9-cis)	
14:1	Myristelaidoyl (9-trans)	
16:1	Palmitoleoyl (9-cis)	
16:1	Palmitelaidoyl (9-trans)	

The fatty acids in these positions can be the same or different. Particularly preferred phospholipids have phosphorylcholine at the sn-3 position.

C) Specialized delivery/devices.

1. Drug-eluting stents.

[0262] Restenosis, the reclosure of a previously stenosed and subsequently dilated peripheral or coronary vessel occurs at a significant rate (*e.g.*, 20-50% for these procedures) and is dependent on a number of clinical and morphological variables. Restenosis may begin shortly following an angioplasty procedure, but usually ceases at the end of approximately six (6) months.

[0263] A recent technology that has been developed to address the problem of restenosis in intravascular stents. Stents are typically devices that are permanently implanted (expanded) in coronary and peripheral vessels. The goal of these stents is to provide a long-term "scaffolding" or support for the diseased (stenosed) vessels. The theory being, if the vessel is supported from the inside, it will not close down or restenose.

[0264] Known stent designs include, but are not limited to monofilament wire coil stents (*see, e.g.*, U.S. Patent 4,969,458); welded metal cages (*see, e.g.*, U.S. Patents 4,733,665 and 4,776,337), thin-walled metal cylinders with axial slots formed around the circumference (*see, e.g.*, U.S. Patents 4,733,665, 4,739,762, 4,776,337, and the like). Known construction materials for use in stents include, but are not limited to polymers, organic fabrics and biocompatible metals, such as, stainless steel, gold, silver, tantalum, titanium, and shape memory alloys such as Nitinol.

[0265] To further prevent restenosis, stents can be covered and/or impregnated with one or more pharmaceutical, *e.g.*, in controlled release formulations to inhibit cell proliferation associated with rest enosis. Most commonly such "drug-eluting" stents are designed to deliver various cancer drugs (cytotoxins).

[0266] However, because of their activity in mitigating inflammatory responses, reducing and/or eliminated oxidized lipids and/or other oxidized species, inhibiting macrophage chemotactic activity and the like, the active agents described herein are well suited to prevent restenosis. Thus, in certain embodiments, this invention contemplates stents having one or more of the active agents described herein coated on the surface and/or retained within cavities or microcavities in the surface of the stent.

[0267] In certain embodiments the active agents are contained within biocompatible matrices (*e.g.* biocompatible polymers such as urethane, silicone, and the like). Suitable biocompatible materials are described, for example, in U.S. Patent Publications 20050084515, 200500791991, 20050070996, and the like. In various embodiments the polymers include, but are not limited to silicone-urethane copolymer, a polyurethane, a phenoxy, ethylene vinyl acetate, polycaprolactone, poly(lactide-co-glycolide), polylactide, polysulfone, elastin, fibrin, collagen, chondroitin sulfate, a biocompatible polymer, a biostable polymer, a biodegradable polymer

[0268] Thus, in certain embodiments this invention provides a stent for delivering drugs to a vessel in a body. The stent typically comprises stent framework including a plurality of reservoirs formed therein. The reservoirs typically include an active agent and/or active agent-containing polymer positioned in the reservoir and/or coated on the surface of the stent. In various embodiments the stent is a metallic base or a polymeric base. Certain preferred stent materials include, but are not limited to stainless steel, nitinol, tantalum, MP35N alloy, platinum, titanium, a suitable biocompatible alloy, a suitable biocompatible polymer, and/or a combination thereof.

[0269] In various embodiments where the stent comprises pores (*e.g.* reservoirs), the pores can include micropores (*e.g.*, having a diameter that ranges from about 10 to about 50 μm, preferably about 20 μm or less). In various embodiments the micropores have a depth in the range of about 10 μm to about 50 μm. In various embodiments the micropores extend through the stent framework having an opening on an interior surface of the stent and an opening on an exterior surface of the stent. In certain embodiments the stent can, optionally comprise a cap layer disposed on the interior surface of the stent framework, the cap layer covering at least a portion of the through-holes and providing a barrier characteristic to control an elution rate of the active agent(s) in the polymer from the interior surface of the stent framework. In various embodiments the reservoirs comprise channels along an exterior surface of the stent framework. The stent can optionally have multiple layers of polymer where different layers of polymer carry different active agent(s) and/or other drugs.

[0270] In certain embodiments the stent comprises: an adhesion layer positioned between the stent framework and the polymer. Suitable adhesion layers include, but are not limited to a polyurethane, a phenoxy, poly(lactide-co-glycolide)- , polylactide, polysulfone, polycaprolactone, an adhesion promoter, and/or a combination thereof.

[0271] In addition to stents, the active agents can be coated on or contained within essentially any implantable medical device configured for implantation in a extravascular and/or intravascular location.

[0272] Also provided are methods of manufacturing a drug-polymer stent, comprising. The methods involve providing a stent framework; cutting a plurality of reservoirs in the stent framework, *e.g.,* using a high power laser; applying one or more of the active agents and/or a drug polymer to at least one reservoir; drying the drug polymer; applying a polymer layer to the dried drug polymer; and drying the polymer layer. The active agent(s) and/or polymer(s) can be applied by any convenient method including but not limited to spraying, dipping, painting, brushing and dispensing.

[0273] Also provided are methods of treating a vascular condition and/or a condition characterized by an inflammatory response and/or a condition characterized by the formation of oxidized reactive species. The methods typically involve positioning a stent or other implantable device as described above within the body (*e.g.* within a vessel of a body) and eluting at least active agent from at least one surface of the implant.

2. Impregnated grafts and transplants.

[0274] Vascular grafts can be classified as either biological or synthetic. There are two commonly used types of biological grafts. An autograft is one taken from another site in the patient. In peripheral vascular surgery by far the most commonly used such graft is the long saphenous vein. This can be used *in situ* with the valves surgically destroyed with an intraluminal cutting valvutome.

[0275] Alternatively, the vein can be removed and reversed but this typically produces a discrepancy between the anastomotic size of the artery and vein. In thoracic surgery the use of internal mammary artery for coronary artery bypass surgery is another example of an autograft. An allograft is one taken from another animal of the same species. Externally supported umbilical vein is rarely used but is an example of such a graft.

[0276] Synthetic grafts are most commonly made from Dacron or polytetrafluroethylene (PTFE). Dacron grafts are frequently used in aortic and aorto-iliac surgery. Below the inguinal ligament the results of all synthetic grafts are inferior to those obtained with the use of vein grafts. Suitable vein is not always available and in this

situation PTFE is typically used. It can be used in conjunction with vein as a composite graft. Neointimal hyperplasia at the distal anastomosis can be reduced by the incorporation of a segment of vein as either a Millar Cuff or Taylor Patch to improve the long-term patency of the grafts.

[0277] The commonest complications associated with the use of vascular grafts include Graft occlusion, Graft infection, true and false aneurysms at the site of anastomosis, distal embolization, and erosion in to adjacent structures - *e.g.* Aorto-enteric fistulae. Many of these conditions are associated with an inflammatory response, macrophage migration into the site, and/or the formation of reactive oxygen species (*e.g.*, oxidized lipids). To reduce such complications, the graft (synthetic or biological can be soaked, or otherwise coated, with one or more of the active agents described herein.

[0278] In addition, it is contemplated that other implantable tissues or materials can similarly be impregnated or coated with one or more active agents of this invention. Thus, for example, in certain embodiments this invention contemplates the use of impregnated sutures to minimize inflammation and/or infection and/or tissue rejection.

3. Subcutaneous matrices.

[0279] In certain embodiments, one or more active agents described herein are administered alone or in combination with other therapeutics as described herein in implantable (*e.g.*, subcutaneous) matrices.

[0280] A major problem with standard drug dosing is that typical delivery of drugs results in a quick burst of medication at the time of dosing, followed by a rapid loss of the drug from the body. Most of the side effects of a drug occur during the burst phase of its release into the bloodstream. Secondly, the time the drug is in the bloodstream at therapeutic levels is very short, most is used and cleared during the short burst.

[0281] Drugs (*e.g.*, the active agents described herein) imbedded in various matrix materials for sustained release provides some solution to these problems. Drugs embedded, for example, in polymer beads or in polymer wafers have several advantages. First, most systems allow slow release of the drug, thus creating a continuous dosing of the body with small levels of drug. This typically prevents side effects associated with high burst levels of normal injected or pill based drugs. Secondly, since these polymers can be made to release over hours to months, the therapeutic span of the drug is markedly

increased. Often, by mixing different ratios of the same polymer components, polymers of different degradation rates can be made, allowing remarkable flexibility depending on the agent being used. A long rate of drug release is beneficial for people who might have trouble staying on regular dosage, such as the elderly, but is also an ease of use improvement that everyone can appreciate. Most polymers can be made to degrade and be cleared by the body over time, so they will not remain in the body after the therapeutic interval.

[0282] Another advantage of polymer based drug delivery is that the polymers often can stabilize or solubilize proteins, peptides, and other large molecules that would otherwise be unusable as medications. Finally, many drug/polymer mixes can be placed directly in the disease area, allowing specific targeting of the medication where it is needed without losing drug to the "first pass" effect. This is certainly effective for treating the brain, which is often deprived of medicines that can't penetrate the blood/brain barrier.

[0283] A number of implantable matrix (sustained release) systems are know to those of skill and can readily be adapted for use with one or more of the active agents described herein. Suitable sustained release systems include, but are not limited to Re-Gel®, SQ2Gel®, and Oligosphere® by MacroMed, ProLease® and Medisorb® by Alkermes, Paclimer® and Gliadel® Wafer by Guilford pharmaceuticals, the Duros implant by Alza, acoustic bioSpheres by Point Biomedical, the Intelsite capsule by Scintipharma, Inc., and the like.

4. Other "specialty delivery systems".

[0284] Other "specialty" delivery systems include, but are not limited to lipid based oral mist that allows absorption of drugs across the oral mucosa, developed by Generex Biotechnology, the oral transmucosal system (OTS™) by Anesta Corp., the inhalable dry powder and PulmoSpheres technology by Inhale Therapeutics, the AERx® Pulmonary Drug Delivery System by Aradigm, the AIR mechanism by Alkermes, and the like.

[0285] Another approach to delivery developed by Alkermes is a system targeted for elderly and pediatric use, two populations for which taking pills is often difficult is known as Drug Sipping Technology (DST). The medication is placed in a drinking straw device, prevented from falling out by filters on either end of it. The patient merely has to drink clear liquid (water, juice, soda) through the straw. The drug dissolves in the liquid as

it is pulled through and is ingested by the patient. The filter rises to the top of the straw when all of the medication is taken. This method has the advantage in that it is easy to use, the liquid often masks the medication's taste, and the drug is pre-dissolved for more efficient absorption.

[0286] It is noted that these uses and delivery systems are intended to be illustrative and not limiting. Using the teachings provided herein, other uses and delivery systems will be known to those of skill in the art.

VI. Additional pharmacologically active agents.

Combined active agents

[0287] In various embodiments, the use of combinations of two or more active agents described is contemplated in the treatment of the various pathologies/indications described herein. The use of combinations of active agents can alter pharmacological activity, bioavailability, and the like.

[0288] By way of illustration, it is noted that D-4F rapidly associates with pre-beta HDL and HDL and then is rapidly cleared from the circulation (it is essentially non-detectable 6 hours after an oral dose), while D-[113-122]apoJ slowly associates with pre-beta HDL and to a lesser extent with HDL but remains associated with these HDL fractions for at least 36 hours. FREL associates with HDL and only HDL but remains detectable in HDL for much longer than D-4F (*i.e.*, it is detectable in HDL 48 hours after a single oral dose in mice). In certain embodiments this invention thus contemplates combinations of, for example, these three peptides to reduce the amount to reduce production expense, and/or to optimize dosage regimen, therapeutic profile, and the like. In certain embodiments combinations of the active agents described herein can be simply coadministered and/or added together to form a single pharmaceutical formulation. In certain embodiments the various active agent(s) can be complexed together (*e.g.* via hydrogen bonding) to form active agent complexes that are more effective than the parent agents.

Use with additional pharmacologically active materials.

[0289] Additional pharmacologically active materials (*i.e.*, drugs) can be delivered in conjunction with one or more of the active agents described herein. In certain

embodiments, such agents include, but are not limited to agents that reduce the risk of atherosclerotic events and/or complications thereof. Such agents include, but are not limited to beta blockers, beta blockers and thiazide diuretic combinations, statins, aspirin, ace inhibitors, ace receptor inhibitors (ARBs), and the like.

[0290] It was discovered that, adding a low dosage active agent (*e.g.,* of D-4F) (1 μg/ml) to the drinking water of apoE null mice for 24 hours did not significantly improve HDL function (*see, e.g.,* related application USSN 10/423,830, filed on April 25, 2003, which is incorporated herein by reference). In addition, adding 0.05 mg/ml of atorvastatin or pravastatin alone to the drinking water of the apoE null mice for 24 hours did not improve HDL function. However, when D-4F 1 μg/ml was added to the drinking water together with 0.05 mg/ml of atorvastatin or pravastatin there was a significant improvement in HDL function). Indeed the pro-inflammatory apoE null HDL became as anti-inflammatory as 350 μg/ml of normal human HDL (h, HDL see, *e.g.*, related application USSN 10/423,830).

[0291] Thus, doses of D-4F alone, or statins alone, which by themselves had no effect on HDL function when given together acted synergistically. When D-4F and a statin were given together to apo E null mice, their pro-inflammatory HDL at 50 μg/ml of HDL-cholesterol became as effective as normal human HDL at 350 μg/ml of HDL-cholesterol in preventing the inflammatory response induced by the action of HPODE oxidizing PAPC in cocultures of human artery wall cells.

[0292] Thus, in certain embodiments this invention provides methods for enhancing the activity of statins. The methods generally involve administering one or more of the active agents described herein, as described herein in conjunction with one or more statins. The active agents achieve synergistic action between the statin and the agent(s) to ameliorate one or more symptoms of atherosclerosis. In this context statins can be administered at significantly lower dosages thereby avoiding various harmful side effects (*e.g.,* muscle wasting) associated with high dosage statin use and/or the anti-inflammatory properties of statins at any given dose are significantly enhanced.

[0293] Suitable statins include, but are not limited to pravastatin (Pravachol/Bristol-Myers Squibb), simvastatin (Zocor/Merck), lovastatin (Mevacor/Merck), and the like.

[0294] In various embodiments the active agent(s) described herein are administered in conjunction with one or more beta blockers. Suitable beta blockers include, but are not limited to cardioselective (selective beta 1 blockers), *e.g.,* acebutolol (Sectral™), atenolol (Tenormin™), betaxolol (Kerlone™), bisoprolol (Zebeta™), metoprolol (Lopressor™), and the like. Suitable non-selective blockers (block beta 1 and beta 2 equally) include, but are not limited to carteolol (Cartrol™), nadolol (Corgard™), penbutolol (Levatol™), pindolol (Visken™), propranolol (Inderal™), timolol (Blockadren™), labetalol (Normodyne™, Trandate™), and the like.

[0295] Suitable beta blocker thiazide diuretic combinations include, but are not limited to Lopressor HCT, ZIAC, Tenoretic, Corzide, Timolide, Inderal LA 40/25, Inderide, Normozide, and the like.

[0296] Suitable ace inhibitors include, but are not limited to captopril (*e.g.* Capoten™ by Squibb), benazepril (*e.g.,* Lotensin™ by Novartis), enalapril (*e.g.,* Vasotec™ by Merck), fosinopril (*e.g.,* Monopril™ by Bristol-Myers), lisinopril (*e.g.* Prinivil™ by Merck or Zestril™ by Astra-Zeneca), quinapril (*e.g.* Accupril™ by Parke-Davis), ramipril (*e.g.,* Altace™ by Hoechst Marion Roussel, King Pharmaceuticals), imidapril, perindopril erbumine (*e.g.,* Aceon™ by Rhone-Polenc Rorer), trandolapril (*e.g.,* Mavik™ by Knoll Pharmaceutical), and the like. Suitable ARBS (Ace Receptor Blockers) include but are not limited to losartan (*e.g.* Cozaar™ by Merck), irbesartan (*e.g.,* Avapro™ by Sanofi), candesartan (*e.g.,* Atacand™ by Astra Merck), valsartan (*e.g.,* Diovan™ by Novartis), and the like.

[0297] In various embodiments, one or more agents described herein are administered with one or more of the drugs identified below.

[0298] Thus, in certain embodiments one or more active agents are administered in conjunction with cholesteryl ester transfer protein (CETP) inhibitors (*e.g.,* torcetrapib, JTT-705. CP-529414) and/or acyl-CoA:cholesterol O-acyltransferase (ACAT) inhibitors (*e.g.,* Avasimibe (CI-1011), CP 113818, F-1394, and the like), and/or immunomodulators (*e.g.,* FTY720 (sphingosine-1-phosphate receptor agonist), Thalomid (thalidomide), Imuran (azathioprine), Copaxone (glatiramer acetate), Certican® (everolimus), Neoral® (cyclosporine), antd the like), and/or dipeptidyl-peptidase-4 (DPP4) inhibitors (*e.g.,* 2-Pyrrolidinecarbonitrile, 1-[[[2-[(5-cyano-2-pyridinyl) amino]ethyl]amino]acetyl], *see also* U.S. Patent Publication 2005-0070530), and/or calcium channel blockers (*e.g.,*

Adalat, Adalat CC, Calan, Calan SR, Cardene, Cardizem, Cardizem CD, Cardizem SR, Dilacor-XR, DynaCirc, Isoptin, Isoptin SR, Nimotop, Norvasc, Plendil, Procardia, Procardia XL, Vascor, Verelan), and/or peroxisome proliferator-activated receptor (PPAR) agonists for, *e.g.*, α, γ; δ receptors (*e.g.*, Azelaoyl PAF, 2-Bromohexadecanoic acid, Ciglitizone, Clofibrate, 15-Deoxy-$\delta^{12,14}$-prostaglandin J_2, Fenofibrate, Fmoc-Leu-OH, GW1929, GW7647, 8(S)-Hydroxy-(5Z,9E,11Z,14Z)-eicosatetraenoic acid (8(S)-HETE), Leukotriene B_4, LY-171,883 (Tomelukast), Prostaglandin A_2, Prostaglandin J_2, Tetradecylthioacetic acid (TTA), Troglitazone (CS-045), WY-14643 (Pirinixic acid)), and the like.

[0299] In certain embodiments one or more of the active agents are administered in conjunction with fibrates (*e.g.*, clofibrate (atromid), gemfibrozil (lopid), fenofibrate (tricor), *etc.*), bile acid sequestrants (*e.g.*, cholestyramine, colestipol, *etc.*), cholesterol absorption blockers (*e.g.*, ezetimibe (Zetia), *etc.*), Vytorin ((ezetimibe/simvastatin combination), and/or steroids, warfarin, and/or aspirin, and/or Bcr-Abl inhibitors/antagonists (*e.g.*, Gleevec (Imatinib Mesylate), AMN107, STI571 (CGP57148B), ON 012380, PLX225, and the like), and/or renin angiotensin pathway blockers (*e.g.*, Losartan (Cozaar®), Valsartan (Diovan®), Irbesartan (Avapro®), Candesartan (Atacand®), and the like), and/or angiotensin II receptor antagonists (*e.g,.* losartan (Cozaar), valsartan (Diovan), irbesartan (Avapro), candesartan (Atacand) and telmisartan (Micardis), *etc.*), and/or PKC inhibitors (*e.g.*, Calphostin C, Chelerythrine chloride, Chelerythrine . chloride, Copper bis-3,5-diisopropylsalicylate, Ebselen, EGF Receptor (human) (651-658) (N-Myristoylated), Gö 6976, H-7 . dihydrochloride, 1-O-Hexadecyl-2-O-methyl-*rac*-glycerol, Hexadecyl-phosphocholine ($C_{16:0}$); Miltefosine, Hypericin, Melittin (natural), Melittin (synthetic), ML-7 . hydrochloride, ML-9 . hydrochloride, Palmitoyl-DL-carnitine . hydrochloride, Protein Kinase C (19-31), Protein Kinase C (19-36), Quercetin . dihydrate, Quercetin . dihydrate, D-*erythro*-Sphingosine (isolated), D-*erythro*-Sphingosine (synthetic), Sphingosine, N,N-dimethyl, D-*erythro*-Sphingosine, Dihydro-, D-*erythro*-Sphingosine, N,N-Dimethyl-, D-*erythro*-Sphingosine chloride, N,N,N-Trimethyl-, Staurosporine, Bisindolylmaleimide I, G-6203, and the like).

[0300] In certain embodiments, one or more of the active agents are administered in conjunction with ApoAI, Apo A-I derivatives and/or agonists (*e.g.*, ApoAI milano, see, *e.g.*, U.S. Patent Publications 20050004082, 20040224011, 20040198662, 20040181034, 20040122091, 20040082548, 20040029807, 20030149094, 20030125559, 20030109442,

20030065195, 20030008827, and 20020071862, and U.S. Patents 6,831,105, 6,790,953, 6,773,719, 6,713,507, 6,703,422, 6,699,910, 6,680,203, 6,673,780, 6,646,170, 6,617,134, 6,559,284, 6,506,879, 6,506,799, 6,459,003, 6,423,830, 6,410,802, 6,376,464, 6,367,479, 6,329,341, 6,287,590, 6,090,921, 5,990,081, and the like), renin inhibitors (*e.g.*, SPP630 and SPP635, SPP100, Aliskiren, and the like), and/or MR antagonist (*e.g.*, spironolactone, aldosterone glucuronide, and the like), and/or aldosterone synthase inhibitors, and/or alpha-adrenergic antagonists (*e.g.*, Aldomet® (Methyldopa), Cardura® (Doxazosin), Catapres®; Catapres-TTS®; Duraclon™ (Clonidine), Dibenzyline® (Phenoxybenzamine), Hylorel® (Guanadrel), Hytrin® (Terazosin), Minipress® (Prazosin), Tenex® (Guanfacine), Guanabenz, Phentolamine, Reserpine, and the like), and/or liver X receptor (LXR) agonists (*e.g.*, T0901317, GW3965, ATI-829, acetyl-podocarpic dimer (APD), and the like), and/or farnesoid X receptor (FXR) agonists (*e.g.*, GW4064, 6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), T0901317, and the like), and/or plasminogen activator-1 (PAI-1) inhibitors (*see, e.g.*, oxime-based PAI-1 inhibitors, see also U.S. Patent 5,639,726, and the like), and/or low molecular weight heparin, and/or AGE inhibitors/breakers (*e.g.*, Benfotiamine, aminoguanidine, pyridoxamine, Tenilsetam, Pimagedine, and the like) and/or ADP receptor blockers (*e.g.*, Clopidigrel, AZD6140, and the like), and/or ABCA1 agonists, and/or scavenger receptor B1 agonists, and/or Adiponectic receptor agonist or adiponectin inducers, and/or stearoyl-CoA Desaturase I (SCD1) inhibitors, and/or Cholesterol synthesis inhibitors (non-statins), and/or Diacylglycerol Acyltransferase I (DGAT1) inhibitors, and/or Acetyl CoA Carboxylase 2 inhibitors, and/or LP-PLA2 inhibitors, and/or GLP-1, and/or glucokinase activator, and/or CB-1 agonists, and/or anti-thrombotic/coagulants, and/or Factor Xa inhibitors, and/or GPIIb/IIIa inhibitors, and/or Factor VIIa inhibitors, and/or Tissue factor inhibitors, and/or anti-inflammatory drugs, and/or Probucol and derivatives (*e.g.* AGI-1067, etc.), and/or CCR2 antagonists, and/or CX3CR1 antagonists, and/or IL-1 antagonists, and/or nitrates and NO donors, and/or phosphodiesterase inhibitors, and the like.

IX. Kits for the treatment of one or more indications.

[0301] In another embodiment this invention provides kits for amelioration of one or more symptoms of atherosclerosis or for the prophylactic treatment of a subject (human or animal) at risk for atherosclerosis and/or the treatment or prophylaxis of one or more of the conditions described herein. The kits preferably comprise a container containing one or more of the active agents described herein.. The active agent(s) can be provided in a

unit dosage formulation (*e.g.* suppository, tablet, caplet, patch, *etc.*) and/or may be optionally combined with one or more pharmaceutically acceptable excipients.

[0302] The kit can, optionally, further comprise one or more other agents used in the treatment of the condition/pathology of interest. Such agents include, but are not limited to, beta blockers, vasodilators, aspirin, statins, ace inhibitors or ace receptor inhibitors (ARBs) and the like, *e.g.* as described above.

[0303] In addition, the kits optionally include labeling and/or instructional materials providing directions (*i.e.*, protocols) for the practice of the methods or use of the "therapeutics" or "prophylactics" of this invention. Preferred instructional materials describe the use of one or more active agent(s) of this invention to mitigate one or more symptoms of atherosclerosis (or other pathologies described herein) and/or to prevent the onset or increase of one or more of such symptoms in an individual at risk for atherosclerosis (or other pathologies described herein). The instructional materials may also, optionally, teach preferred dosages/therapeutic regiment, counter indications and the like.

[0304] While the instructional materials typically comprise written or printed materials they are not limited to such. Any medium capable of storing such instructions and communicating them to an end user is contemplated by this invention. Such media include, but are not limited to electronic storage media (*e.g.*, magnetic discs, tapes, cartridges, chips), optical media (*e.g.*, CD ROM), and the like. Such media may include addresses to internet sites that provide such instructional materials.

EXAMPLES

[0305] The following examples are offered to illustrate, but not to limit the claimed invention.

Example 1

Use of ApoJ-Related Peptides to Mediate Symptoms of Atherosclerosis

Prevention of LDL-induced monocyte chemotactic activity

[0306] Figure 1 illustrates a comparison of the effect of D-4F (Anantharamaiah *et al.* (2002) *Circulation*, 105: 290-292) with the effect of an apoJ peptide made from D amino acids (D-J336, Ac-L-L-E-Q-L-N-E-Q-F-N-W-V-S-R-L-A-N-L-T-Q-G-E-NH_2,

SEQ ID NO:1177)) on the prevention of LDL-induced monocyte chemotactic activity *in vitro* in a co-incubation. Human aortic endothelial cells were incubated with medium alone (no addition), with control human LDL (200 μg protein/ml) or control human LDL + control human HDL (350 μg HDL protein/ml). D-J336 or D-4F was added to other wells in a concentration range as indicated plus control human LDL (200 μg protein/ml). Following overnight incubation, the supernatants were assayed for monocyte chemotactic activity. As shown in Figure 1, the *in vitro* concentration of the apoJ variant peptide that prevents LDL-induced monocyte chemotactic activity by human artery wall cells is 10 to 25 times less than the concentration required for the D-4F peptide.

Prevention of LDL-induced monocyte chemotactic activity by Pre-Treatment of artery wall cells with D-J336

[0307] Figure 2 illustrates a comparison of the effect of D-4F with the effect of D-J336 on the prevention of LDL induced monocyte chemotactic activity in a pre-incubation. Human aortic endothelial cells were pre- incubated with D-J336 or D-4F at 4, 2, and 1 μg/ml for DJ336 or 100, 50, 25, and 12.5 μg/ml for D-4F for 6 hrs. The cultures were then washed and were incubated with medium alone (no addition), or with control human LDL (200 μg protein/ml), or with control human LDL + control human HDL (350 μg HDL protein/ml) as assay controls. The wells that were pre-treated with peptides received the control human LDL at 200 μg protein/ml. Following overnight incubation, the supernatants were assayed for monocyte chemotactic activity.

[0308] As illustrated in Figure 2, the ApoJ variant peptide was 10-25 times more potent in preventing LDL oxidation by artery wall cells *in vitro.*

The effect of apo J peptide mimetics on HDL protective capacity in LDL receptor null mice.

[0309] D-4F designated as F, or the apoJ peptide made from D amino acids (D-J336, designated as J) was added to the drinking water of LDL receptor null mice (4 per group) at 0.25 or 0.5 mg per ml of drinking water. After 24- or 48-hrs blood was collected from the mice and their HDL was isolated and tested for its ability to protect against LDL-induced monocyte chemotactic activity. Assay controls included culture wells that received no lipoproteins (no addition), or control human LDL alone (designated as LDL, 200 μg cholesterol/ml), or control LDL + control human HDL (designated as + HDL, 350

μg HDL cholesterol). For testing the mouse HDL, the control LDL was added together with mouse HDL (+F HDL or +J HDL) to artery wall cell cultures. The mouse HDL was added at 100 μg cholesterol/ml respectively. After treatment with either D-4F or D-J336 the mouse HDL at 100 μg/ml was as active as 350 μg/ml of control human HDL in preventing the control LDL from inducing the artery wall cells to produce monocyte chemotactic activity. . The reason for the discrepancy between the relative doses required for the D-J336 peptide relative to D-4F *in vitro* and *in vivo* may be related to the solubility of the peptides in water and we believe that when measures are taken to achieve equal solubility the D-J peptides will be much more active *in vivo* as they are *in vitro*.

Protection against LDL–induced monocyte chemotactic activity by HDL from apo E null mice given oral peptides.

[0310] Figure 4 illustrates the effect of oral apoA-1 peptide mimetic and apoJ peptide on HDL protective capacity. ApoE null mice (4 per group) were provided with D-4F (designated as F) at 50, 30, 20, 10, 5 μg per ml of drinking water or apoJ peptide (designated as J) at 50, 30 or 20 μg per ml of drinking water. After 24 hrs blood was collected, plasma fractionated by FPLC and fractions containing LDL (designated as mLDL for murine LDL) and fractions containing HDL (designated as mHDL) were separately pooled and HDL protective capacity against LDL oxidation as determined by LDL-induced monocyte chemotactic activity was determined. For the assay controls the culture wells received no lipoproteins (no additions), mLDL alone (at 200 μg cholesterol/ml), or mLDL + standard normal human HDL (designated as Cont. h HDL, at 350 μg HDL cholesterol/ml).

[0311] For testing the murine HDL, mLDL together with murine HDL (+F mHDL or +J mHDL) were added to artery wall cell cultures. The HDL from the mice that did not receive any peptide in their drinking water is designated as no peptide mHDL. The murine HDL was used at 100 μg cholesterol/ml. After receiving D-4F or D-J336 the murine HDL at 100 μg/ml was as active as 350 μg/ml of normal human HDL. As shown in Figure 4, when added to the drinking water the D-J peptide was as potent as D-4F in enhancing HDL protective capacity in apo E null mice.

Ability of LDL obtained from apoE null mice given oral peptides to induce monocyte chemotactic activity.

[0312] Figure 5 illustrates the effect of oral apo A-1 peptide mimetic and apoJ peptide on LDL susceptibility to oxidation. ApoE null mice (4 per group) were provided, in their drinking water, with D-4F (designated as F) at 50, 30, 20, 10, 5 μg per ml of drinking water or the apoJ peptide (D-J336 made from D amino acids and designated as J) at 50, 30 or 20 μg per ml of drinking water. After 24 hrs blood was collected from the mice shown in Figure 4, plasma fractionated by FPLC and fractions containing LDL (designated as mLDL for murine LDL) were pooled and LDL susceptibility to oxidation as determined by induction of monocyte chemotactic activity was determined. For the assay controls the culture wells received no lipoproteins (no additions), mLDL alone (at 200 μg cholesterol/ml), or mLDL + standard normal human HDL (designated as Cont. h HDL, 350 μg HDL cholesterol).

[0313] Murine LDL, mLDL, from mice that received the D-4F (F mLDL) or those that received the apoJ peptide (J mLDL) were added to artery wall cell cultures. LDL from mice that did not receive any peptide in their drinking water is designated as No peptide LDL.

[0314] As shown in Figure 5, when added to the drinking water, D-J336 was slightly more potent than D-4F in rendering the LDL from apo E null mice resistant to oxidation by human artery wall cells as determined by the induction of monocyte chemotactic activity.

Protection against phospholipid oxidation and induction of monocyte chemotactic activity by HDL obtained from apo E null mice given oral peptides.

[0315] Figure 6 illustrates the effect of oral apoA-1 peptide mimetic and apoJ peptide on HDL protective capacity. ApoE null mice (4 per group) were provided with D-4F (designated as F) at 50, 30, 20, 10, 5 μg per ml of drinking water or apoJ peptide (D-J336 made from D amino acids and designated as J) at 50, 30 or 20 μg per ml of drinking water. After 24 hrs blood was collected, plasma fractionated by FPLC and fractions containing HDL (designated as mHDL) were pooled and HDL protective capacity against PAPC oxidation as determined by the induction of monocyte chemotactic activity was determined. For the assay controls the culture wells received no lipoproteins (no additions), the phospholipid PAPC at 20 μg /ml + HPODE, at 1.0 μg/ml, or

PAPC+HPODE plus standard normal human HDL (at 350 μg HDL cholesterol/ml and designated as +Cont. h HDL).

[0316] For testing the murine HDL, PAPC+HPODE together with murine HDL (+F mHDL or +J mHDL) were added to artery wall cell cultures. The HDL from mice that did not receive any peptide in their drinking water is designated as "no peptide mHDL". The murine HDL was used at 100 μg cholesterol/ml.

[0317] The data show in Figure 6 indicate that, when added to the drinking water, D-J336 was as potent as D-4F in causing HDL to inhibit the oxidation of a phospholipid PAPC by the oxidant HPODE in a human artery wall co-culture as measured by the generation of monocyte chemotactic activity

Effect of oral apoA-1 peptide mimetic and apoJ peptide on plasma paraoxonase activity in mice.

[0318] Figure 7 shows the effect of oral apoA-1 peptide mimetic and apoJ peptide on plasma paraoxonase activity in mice. ApoE null mice (4 per group) were provided with D-4F designated as F at 50, 10, 5 or 0 μg per ml of drinking water or apoJ peptide (D-J336 made from D amino acids and designated as J) at 50, 10 or 5 μg per ml of drinking water. After 24 hrs blood was collected and plasma was assayed for PON1 activity. These data demonstrate that, when added to the drinking water, D-J336 was at least as potent as D-4F in increasing the paraoxonase activity of apo E null mice.

Example 2

Oral G* Peptides Increase HDL Protective Capacity in Apo E Deficient Mice.

[0319] Female, 4 month old apoE deficient mice (n=4 per group) were treated with G* peptides having the following amino acid sequences. Peptide 113-122 = Ac-L V G R Q L E E F L-NH_2 (SEQ ID NO. 9), Peptide 336-357 = Ac-L L E Q L N E Q F N W V S R L A N L T Q G E-NH2 (SEQ ID NO. 17), and Peptide 377-390 = Ac-P S G V T E V V V K L F D S-NH_2 (SEQ ID NO. 19).

[0320] Each mouse received 200 μg of the peptide by stomach tube. Four hours later blood was obtained, plasma separated, lipoproteins fractionated and HDL (at 25 μg per ml) was assayed for protective capacity against the oxidation of LDL (at 100 μg per ml) in cultures of human artery wall cells. The data are shown in Figure 8. The peptide afforded significant HDL-protective capacity in the mice.

[0321] In another experiment, female, 4 month old apoE deficient mice (n=4 per group) were treated with the 11 amino acid G* peptide 146-156 with the sequence: Ac-Q Q T H M L D V M Q D-NH_2. (SEQ ID NO:11). The mice received the peptide in their drinking water at the indicated concentrations (*see* Figure 9). Following eighteen hrs, blood was obtained, plasma separated, lipoproteins fractionated and HDL (at 50 μg cholesterol per ml) was assayed for protective capacity against the oxidation of PAPC (at 25 μg per ml) + HPODE (at 1.0 μg per ml) in cultures of human artery wall cells. Assay controls included No additions, PAPC+ HPODE and PAPC + HPODE plus Control HDL (designated as +HDL). The data are mean+/- SD of the number of migrated monocytes in nine high power fields in triplicate cultures. Asterisks indicate significance at the level of $p<0.05$ vs. the water control (0 μg/ml).

Example 3

Solution Phase Chemistry for Peptide Synthesis

[0322] In certain embodiments, a solution-phase synthesis chemistry provides a more economical means of synthesizing peptides of this invention.

[0323] Prior to this invention synthesis was typically performed using an all-solid phase synthesis chemistry. The solid phase synthesis of peptides of less than 9 amino acids is much more economical than the solid phase synthesis of peptides of more than 9 amino acids. Synthesis of peptides of more than 9 amino acids results in a significant loss of material due to the physical dissociation of the elongating amino acid chain from the resin. The solid phase synthesis of peptides containing less than 9 amino acids is much more economical because the there is relatively little loss of the elongating chain from the resin.

[0324] In certain embodiments, the solution phase synthesis functions by converting the synthesis of the 18 amino acid apoA-I mimetic peptide, 4F (and other related peptides) from an all solid phase synthesis to either an all solution phase synthesis or to a combination of solid phase synthesis of three chains each containing, *e.g.,* 6 amino acids followed by the assembly of the three chains in solution. This provides a much more economical overall synthesis. This procedure is readily modified where the peptides are not 18 amino acids in length. Thus, for example, a 15 mer can be synthesized by solid phase synthesis of three 5 mers followed by assembly of the three chains in solution. A 14

mer can be synthesized by the solid phase synthesis of two 5 mers and one 4 mer followed by assembly of these chains in solution, and so forth.

A) Summary of synthesis protocol.

An scheme for the synthesis of the peptide D4F (Ac-D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F-NH_2, (SEQ ID NO:5) is illustrated in Table 20. (The scheme and yields for the synthesis are shown in Table 20.

[0325] Table 20. Illustrative solution phase synthesis scheme.

Methods Used for D4F Synthesis						
Synthesis	**Resin**	**Fmoc Amino Acid**	**Coupling Reagent**	**Final Wt. of Resin (gms)**	**Wt. of Crude Peptide (gms) Yield (%)**	**Wt. of Pure Peptide (mg) Yield ((%)**
Stepwise Solid Phase	Rink Amide (1 mmole) 1.8 gms	6 Equiv	HBTU/ HOBT	4	2.0 86	500 25
Stepwise Solid Phase	Rink Amide (1 mmole) 1.8 gms	2 Equiv	DIC/HOBT	3.9	2.0 86	450 22.5
Fragment coupling (6+6+6)	Rink Amide (1 mmole) 1.8 gms*		HBTU/ HOBT	3.3	1.0 43	100 10
Synthesis of D4F Fragments			Fragment 1 (2HN-KFKEAF (SEQ ID NO:1178) on rink amide resin (K and E are properly protected)			
Fragment 2 6 residues stepwise Solid Phase	Cl-TrT-Resin (5 mmol) 6.5 gms	6 Equiv	HBTU/ HOBT	11	2.2 crude protected 36	
			Fmoc-Y(But)-D(But)-K(Boc)-V-A-E(But)-COOH (SEQ ID NO:1179)			
Fragment 2 6 residues stepwise Solid Phase	Cl-TrT-Resin (5 mmol) 6.5 gms	6 Equiv	HBTU/ HOBT	10	1.8 crude protected 32	
			Ac-D(But)-W-F-K(Boc)-A-F-COOH (SEQ ID NO:1180)			

Synthesis by solution phase using fragments produced by the solid phase method.

Fragment 1. Wang resin. C-terminal hexapeptide (subjected to ammonolysis). Yield quantitative.
NH2-K(Boc)-F-K(Boc)-E(But)-A-F-Wang resin (SEQ ID NO:1181)

NH2-K(Boc)-F-K(Boc)-E(But)-A-F-CO-NH2
(SEQ ID NO:1182)

Fragment 2 from above was coupled to fragment 1 in DMF using DIC/HOBT.
Fmoc-Y(But)-D(But)-K(Bpc)-V-A-E(But)-K(Boc)-F-K(Boc)-E(But)-F-Co-NH2
(SEQ ID NO:1183) 12 residue peptide was characterized as free peptide after removing protecting groups. Yield was 50%

Fmoc from the above- 12 rtesidue was removed by piperidine in DMF (20%. After drying the peptide was copled to Fragment 3 using DCl/HOBT in DMF.
Ac-D(But)-W-F-K(Boc)-A-F-Y(But)-D(but)-K(Boc)-V-A-E(But)-K(Boc)-F-K(Boc)-E(But)-A-FCO-NH2 (SEQ ID NO:1184)
Protected peptide yield was quantitative.
Protecting groups removed using mixture of TFA (80%), phenol (5%), thioanisole (5%). water)5%), triisopropylsilane (TIS, 5%), stirred for 90 min.
Precipitated by ether and purified by C-4 HPLC column. Yield 25%

B) Details of synthesis protocol.

1. Fragment condensation procedure to synthesize D-4F

[0326] Fragments synthesized for fragment condensation on solid phase are:

Fragment 1: Ac-D(OBut)-W-F-K(εBoc)-A-F- COOH (SEQ ID NO:1185);

Fragment 2:Fmoc-Y(OBut)-D(OBut)-K(εBoc)-V-A-E(OBut)-COOH (SEQ ID NO:1186); and

Fragment 3 Fmoc-K(εBoc)F-K(εBoc)-E(OBut)-A-F- Rink amide resin (SEQ ID NO:1187).

[0327] Fragment 1 was left on the resin to obtain final peptide amide after TFA treatment.

[0328] To synthesize fragment 1: Fmoc-Phe (1.2 equivalents) was added to chlorotrityl resin (Nova Biochem, 1.3 mMol/g substitution, 5 mMol or 6.5 g was used) in presence of six equivalents of DIEA in DMF:dichloromethane (1:1)) and stirred for 4h. Excess of functionality on the resin was capped with methanol in presence of dichloromethane and DIEA. After the removal of Fmoc- Fmoc amino acid derivatives (2 equivalents) were added using HOBt/HBTU reagents as described above. Final Fmoc-D(OBut)-W-F-K(εBoc)-A-F Chlorotrityl resin was treated with Fmoc deblocking agent and acetylated with 6 equivalents of acetic anhydride in presence of diisoprolylethyl amine. The resulting Ac-D(OBut)-W-F-K(εBoc)-A-F –resin was treated with a mixture of triflouroethanol-acetic acid-dichloromethane (2:2:6, 10ml/g of resin) for 4h at room temperature. After removal of the resin by filtration, the solvent was removed by aziotropic distillation with n-hexane under vacuum. The residue (1.8g) was determined by mass spectral analysis to be Ac-D(OBut)-W-F-K(εBoc)-A-F -COOH (SEQ ID NO:1188).

[0329] Fragment 2, Fmoc-Y(OBut)-D(OBut)-K(εBoc)-V-A-E(OBut)-COOH (SEQ ID NO:1189), was obtained using the procedure described for Fragment 1. Final yield was 2.2g.

[0330] Fragment 3. 0.9g (0.5mmol) of Rink amide resin (Nova Biochem) was used to obtain fragment Rink amide resin was treated with 20% pipetidine in dichloromethane for 5 min once and 15 min the second time (Fmoc deblocking reagents). 1. 2equivalents of Fmoc-Phe was condensed using condensing agents HOBt/HBTU (2

equivalents in presence of few drops of diisopropylethyl amine) (amino acid condensation). Deblocking and condensation of the rest of the amino acids were continued to obtain the of Fmoc- K(εBoc)F-K(εBoc)-E(OBut)-A-F -rink amide resin (SEQ ID NO:1190). Fmoc was cleaved and the peptide resin K(εBoc)F-K(εBoc)-E(OBut)-A-F- rink amide resin (SEQ ID NO:1190) was used for fragment condensation as described below.

[0331] Fragment 2 in DMF was added to Fragment 3 (1.2 equivalents) using HOBt-HBTU procedure in presence of DIEA overnight. After washing the resin with DMF and deblocking Fmoc- Fragment 1 (1.2 equivalents) was added to the dodecapeptide resin using HOBt-HBTU procedure overnight.

[0332] The final peptide resin (3.3g) was treated with a mixture of TFA-Phenol-triisopropylsilane-thioanisole-water (80:5:5:5) for 1.5h (10 ml of the reagent/g of the resin). The resin was filtered off and the solution was diluted with10 volumes of ether. Precipitated peptide was isolated by centrifugation and washed twice with ether. 1g of the crude peptide was subjected to HPLC purification to obtain 100 mg of the peptide.

2. Characterization of peptide.

[0333] The peptide was identified by mass spectral and analytical HPLC methods.

[0334] As shown in Figure 14 the product of the solution phase synthesis scheme is very biologically active in producing HDL and pre-beta HDL that inhibit LDL-induced monocyte chemotaxis in apo E null mice. ApoE null mice were fed 5 micrograms of the D-4F synthesized as described above (Frgmnt) or the mice were given the same amount of mouse chow without D-4F (Chow). Twelve hours after the feeding was started, the mice were bled and their plasma was fractionated on FPLC. LDL (100 micrograms LDL-cholesterol) was added to cocultures of human artery wall cells alone (LDL) or with a control human HDL (Control HDL) or with HDL (50 micrograms HDL-cholesterol) or post-HDL (pHDL; prebeta HDL) from mice that did (Frgmnt) or did not (Chow) receive the D-4F and the monocyte chemotactic activity produced was determined

Example 4 Comparison of D-4F and Reverse (retro-) D-4F Activity.

[0335] As shown in Figure 16, the biological activities of D-4F and reverse RD-4F are not significantly different. Female apoE null mice were administered by stomach tube 0, 3, 6, 12, or 25 micrograms of D-4F or Reverse D-4F in 100 microliters of water. Blood

was obtained 7 hours later and the plasma was fractionated by FPLC. A standard control human LDL was added to human artery wall cells at a concentration of 100 micrograms of LDL-cholesterol/mL (LDL). The resulting monocyte chemotactic activity was normalized to 1.0. The same LDL at the same concentration was added to the human artery wall cells together with HDL at 50 micrograms HDL-cholesterol/mL from a normal human (hHDL) or from the apoE null mice that received the dose of D-4F or Reverse D-4F shown on the X-axis. The resulting monocyte chemotactic activity was normalized to that of the LDL added without HDL. The resulting value is the HDL Inflammatory Index. The results shown are the Mean ± S.D. for the data from three separate experiments.

[0336] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

What is claimed is:

1. A peptide that ameliorates a symptom of atherosclerosis, wherein said peptide comprises the amino acid sequence or the retro amino acid sequence of a peptide listed in peptide listed in Table 4, Table 5, or Table 6.

2. The peptide of claim 1, wherein said peptide further comprises a protecting group coupled to the amino or carboxyl terminus.

3. The peptide of claim 1, wherein said peptide further comprises a first protecting group coupled to the amino terminus and a second protecting group coupled to the carboxyl terminus.

4. The peptide of claim 2, wherein said protecting group is a protecting group selected from the group consisting of acetyl, amide, and 3 to 20 carbon alkyl groups, Fmoc, Tboc, 9-fluoreneacetyl group, 1-fluorenecarboxylic group, 9-florenecarboxylic group, 9-fluorenone-1-carboxylic group, benzyloxycarbonyl, Xanthyl (Xan), Trityl (Trt), 4-methyltrityl (Mtt), 4-methoxytrityl (Mmt), 4-methoxy-2,3,6-trimethyl-benzenesulphonyl (Mtr), Mesitylene-2-sulphonyl (Mts), 4,4-dimethoxybenzhydryl (Mbh),Tosyl (Tos), 2,2,5,7,8-pentamethyl chroman-6-sulphonyl (Pmc), 4-methylbenzyl (MeBzl), 4-methoxybenzyl (MeOBzl), Benzyloxy (BzlO), Benzyl (Bzl), Benzoyl (Bz), 3-nitro-2-pyridinesulphenyl (Npys), 1-(4,4-dimentyl-2,6-diaxocyclohexylidene)ethyl (Dde), 2,6-dichlorobenzyl (2,6-DiCl-Bzl), 2-chlorobenzyloxycarbonyl (2-Cl-Z), 2-bromobenzyloxycarbonyl (2-Br-Z), Benzyloxymethyl (Bom), t-butoxycarbonyl (Boc), cyclohexyloxy (cHxO),t-butoxymethyl (Bum), t-butoxy (tBuO), t-Butyl (tBu), Acetyl (Ac), and Trifluoroacetyl (TFA).

5. The peptide of claim 1, wherein one or more amino acids comprising said peptide are "D" amino acids.

6. The peptide of claim 1, wherein all amino acids comprising said peptide "D" amino acids.

7. The peptide of claim 1, wherein said peptide is mixed with a pharmacologically acceptable excipient.

8. The peptide of claim 1, wherein said peptide is mixed with a pharmacologically acceptable excipient suitable for oral administration to a mammal.

9. The peptide of claims 2-8, wherein said peptide comprises a protecting group coupled to the amino terminal and said amino terminal protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl.

10. The peptide of claim 9, wherein said peptide comprises a protecting group coupled to the carboxyl terminal and said carboxyl terminal protecting group is an amide.

11. The peptide of claim 9, wherein said peptide comprises:

a first protecting group coupled to the amino terminus wherein said protecting group is a protecting group selected from the group consisting of acetyl, propeonyl, and a 3 to 20 carbon alkyl; and

a second protecting group coupled to the carboxyl terminal and said carboxyl terminal protecting group is an amide.

12. A method of treating a vascular condition and/or a condition characterized by an inflammatory response and/or a condition characterized by the formation of oxidized reactive species in a mammal, said method comprising:

administering to a mammal in need thereof a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6 in an amount sufficient to amelioriate one or more symptoms of said condition.

13. The method of claim 12, wherein said administration is by a route selected from the group consisting of oral administration, nasal administration, rectal administration, intraperitoneal injection, and intravascular injection, subcutaneous injection, transcutaneous administration, and intramuscular injection.

14. The method of claim 12, wherein said active agent is administered in conjunction with a drug selected from the group consisting of CETP inhibitors, FTY720, Certican, DPP4 inhibitors, Calcium channel blockers, ApoA1 derivative or mimetic or agonist, PPAR agonists , Steroids, Gleevec, Cholesterol Absorption blockers (Zetia) , Vytorin, Any Renin Angiotensin pathway blockers, Angiotensi II receptor antagonist (Diovan etc), ACE inhibitors, Renin inhibitors, MR antagonist and Aldosterone synthase inhibitor, Beta-blockers, Alpha-adrenergic antagonists, LXR agonist, FXR agonist, Scavenger Receptor B1 agonist, ABCA1 agonist, Adiponectic receptor agonist or adiponectin inducers, Stearoyl-CoA Desaturase I (SCD1) inhibitor, Cholesterol synthesis inhibitors (non-statins), Diacylglycerol Acyltransferase I (DGAT1) inhibitor, Acetyl CoA Carboxylase 2 inhibitor, PAI-1 inhibitor, LP-PLA2 inhibitor, GLP-1, Glucokinase activator, CB-1 agonist, AGE inhibitor/breaker, PKC inhibitors, Anti-thrombotic/coagulants:, Aspirin, ADP receptor blockers e.g. Clopidigrel, Factor Xa inhibitor, GPIIb/IIIa inhibitor, Factor VIIa inhibitor, Warfarin, Low molecular weight heparin, Tissue factor inhibitor, Anti-inflammatory drugs:, Probucol and derivative e.g. AGI-1067 etc, CCR2 antagonist, CX3CR1 antagonist, IL-1 antagonist, Nitrates and NO donors, and Phosphodiesterase inhibitors.

15. The use of a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6 in the treatment of a condition selected from the group consisting of atherosclerotic plaque formation, atherosclerotic lesion formation, myocardial infarction, stroke, congestive heart failure, arteriole function, arteriolar disease, arteriolar disease associated with aging, arteriolar disease associated with Alzheimer's disease, arteriolar disease associated with chronic kidney disease, arteriolar disease associated with hypertension, arteriolar disease associated with multi-infarct dementia, arteriolar disease associated with subarachnoid hemorrhage, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), , emphysema, asthma, idiopathic pulmonary fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, osteoporosis, Paget's disease , coronary calcification, rheumatoid arthritis, polyarteritis nodosa, polymyalgia rheumatica, lupus erythematosus, multiple sclerosis , Wegener's granulomatosis, central nervous system vasculitis (CNSV), Sjögren's syndrome, scleroderma, polymyositis., AIDS inflammatory response, bacterial infection, fungal infection, viral infection, parasitic infection, influenza, avian flu, viral pneumonia, endotoxic shock syndrome, sepsis , sepsis syndrome , trauma/wound, organ transplant,

transplant atherosclerosis, transplant rejection , corneal ulcer, chronic/non-healing wound, ulcerative colitis, reperfusion injury (prevent and/or treat), ischemic reperfusion injury (prevent and/or treat), spinal cord injuries (mitigating effects) , cancers, myeloma/multiple myeloma, ovarian cancer, breast cancer, colon cancer, bone cancer, osteoarthritis, inflammatory bowel disease , allergic rhinitis, cachexia , diabetes , Alzheimer's disease , implanted prosthesis, biofilm formation, Crohns' disease, dermatitis, acute and chronic, eczema, psoriasis, contact dermatitis, scleroderma, Type I Diabetes, Type II Diabetes, juvenile onset diabetes, prevention of the onset of diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, erectile dysfunction, macular degeneration, multiple sclerosis, nephropathy, neuropathy, Parkinson's Disease, peripheral vascular disease, and meningitis.

16. The use of a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6 for the manufacture of a medicament for the treatment of a condition selected from the group consisting of atherosclerotic plaque formation, atherosclerotic lesion formation, myocardial infarction, stroke, congestive heart failure, arteriole function, arteriolar disease, arteriolar disease associated with aging, arteriolar disease associated with Alzheimer's disease, arteriolar disease associated with chronic kidney disease, arteriolar disease associated with hypertension, arteriolar disease associated with multi-infarct dementia, arteriolar disease associated with subarachnoid hemorrhage, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), , emphysema, asthma, idiopathic pulmonary fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, osteoporosis, Paget's disease , coronary calcification, rheumatoid arthritis, polyarteritis nodosa, polymyalgia rheumatica, lupus erythematosus, multiple sclerosis , Wegener's granulomatosis, central nervous system vasculitis (CNSV), Sjögren's syndrome, scleroderma, polymyositis., AIDS inflammatory response, bacterial infection, fungal infection, viral infection, parasitic infection, influenza, avian flu, viral pneumonia, endotoxic shock syndrome, sepsis , sepsis syndrome , trauma/wound, organ transplant, transplant atherosclerosis, transplant rejection , corneal ulcer, chronic/non-healing wound, ulcerative colitis, reperfusion injury (prevent and/or treat), ischemic reperfusion injury (prevent and/or treat), spinal cord injuries (mitigating effects) , cancers, myeloma/multiple myeloma, ovarian cancer, breast cancer, colon cancer, bone cancer, osteoarthritis, inflammatory bowel disease , allergic rhinitis, cachexia , diabetes , Alzheimer's disease ,

implanted prosthesis, biofilm formation, Crohns' disease, dermatitis, acute and chronic, eczema, psoriasis, contact dermatitis, scleroderma, Type I Diabetes, Type II Diabetes, juvenile onset diabetes, prevention of the onset of diabetes, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, erectile dysfunction, macular degeneration, multiple sclerosis, nephropathy, neuropathy, Parkinson's Disease, peripheral vascular disease, and meningitis.

17. A stent for delivering drugs to a vessel in a body comprising: a stent framework including a plurality of reservoirs formed therein, and a peptide comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6.

18. The stent of claim 17, wherein said active agent is contained within a polymer.

19. The stent of claim 17, wherein the stent framework comprises one of a metallic base or a polymeric base.

20. The stent of claim 17, wherein the stent framework base comprises a material selected from the group consisting of stainless steel, nitinol, tantalum, MP35N alloy, platinum, titanium, a suitable biocompatible alloy, a suitable biocompatible polymer, and a combination thereof.

21. The stent of claim 17, wherein the reservoirs comprise micropores.

22. The stent of claim 21, wherein the micropores have a diameter of about 20 microns or less.

23. The stent of claim 21, wherein the micropores have a diameter in the range of about 20 microns to about 50 microns.

24. The stent of claim 21, wherein the micropores have a depth in the range of about 10 to about 50 microns.

25. The stent of claim 21, wherein the micropores have a depth of about 50 microns.

26. The stent of claim 21, wherein the micropores extend through the stent framework having an opening on an interior surface of the stent and an opening on an exterior surface of the stent.

27. The stent of claim 21, wherein further comprising: a cap layer disposed on the interior surface of the stent framework, the cap layer covering at least a portion of the through-holes and providing a barrier characteristic to control an elution rate of a drug in the drug polymer from the interior surface of the stent framework.

28. The stent of claim 17, wherein the reservoirs comprise channels along an exterior surface of the stent framework.

29. The stent of claim 18, wherein the polymer comprises a first layer of a first drug polymer having a first pharmaceutical characteristic and the polymer layer comprises a second drug polymer having a second pharmaceutical characteristic.

30. The stent of claim 18, further comprising a barrier layer positioned between the polymer comprising the active agent,

31. The stent of claim 17, further comprising: a catheter coupled to the stent framework.

32. The stent of claim 31, wherein the catheter includes a balloon used to expand the stent.

33. The stent of claim 31, wherein the catheter includes a sheath that retracts to allow expansion of the stent.

34. A method of manufacturing a drug-polymer stent, comprising: providing a stent framework; cutting a plurality of reservoirs in the stent framework; applying a composition comprising one or more peptides comprising the amino acid sequence or the retro amino acid sequence of a peptide listed in Table 4, Table 5, or Table 6 to at least one reservoir; and drying the composition.

35. The method of claim 34, further comprising applying a polymer layer to the dried composition; and drying the polymer layer.

36. A method of treating a vascular condition, comprising:

positioning a stent according to claim 17 within a vessel of a body;

expanding the stent; and

eluting at least one active agent from at least a surface of the stent.

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