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(19) **United States**(12) **Patent Application Publication****Liu et al.**(10) **Pub. No.: US 2007/0264194 A1**(43) **Pub. Date: Nov. 15, 2007**(54) **PEPTIDES THAT BIND TO
ATHEROSCLEROTIC LESIONS****Publication Classification**(75) Inventors: **Cheng Liu**, Carlsbad, CA (US);
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(2), (4) Date: **Dec. 15, 2006****Related U.S. Application Data**(60) Provisional application No. 60/311,507, filed on Aug.
10, 2001.(57) **ABSTRACT**

The present invention provides peptides that selectively bind to mammalian atherosclerotic lesions. The present invention also provides methods for in vivo identification of peptides capable of binding to biomolecules as well as methods for identifying the targets of such binding moieties. Methods to diagnose or treat pathologic conditions that involve atherosclerotic lesions are also provided by the invention that involve administering to a mammal a peptide attached to a reporter molecule or a therapeutic agent, respectively.

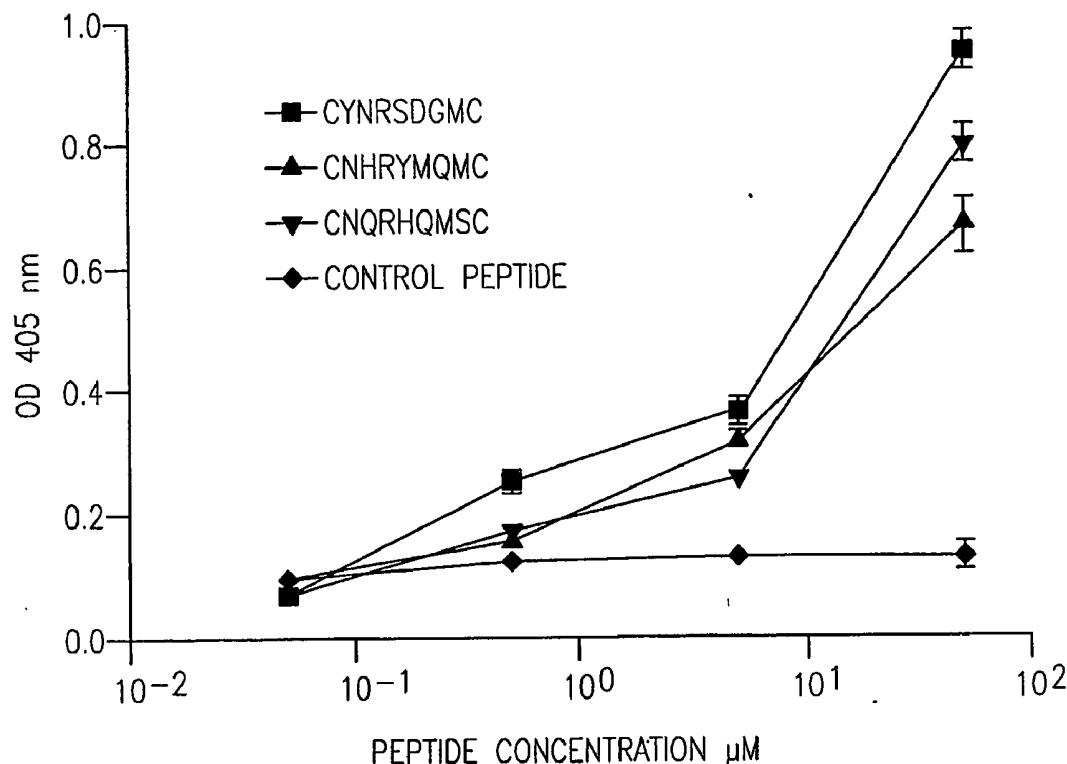




FIG. 1A



FIG. 1B



FIG. 1C



FIG. 1D



FIG. 2A

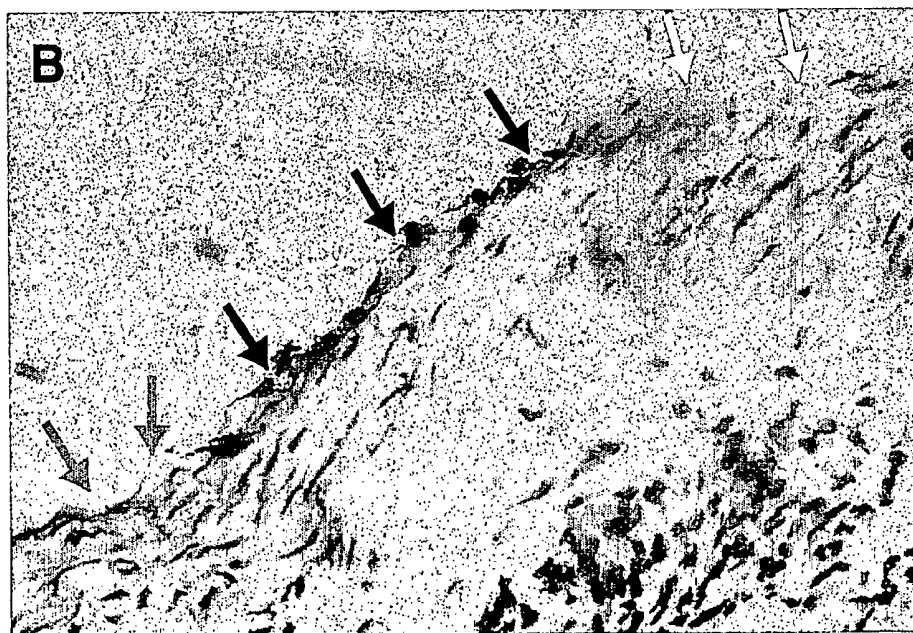


FIG. 2B

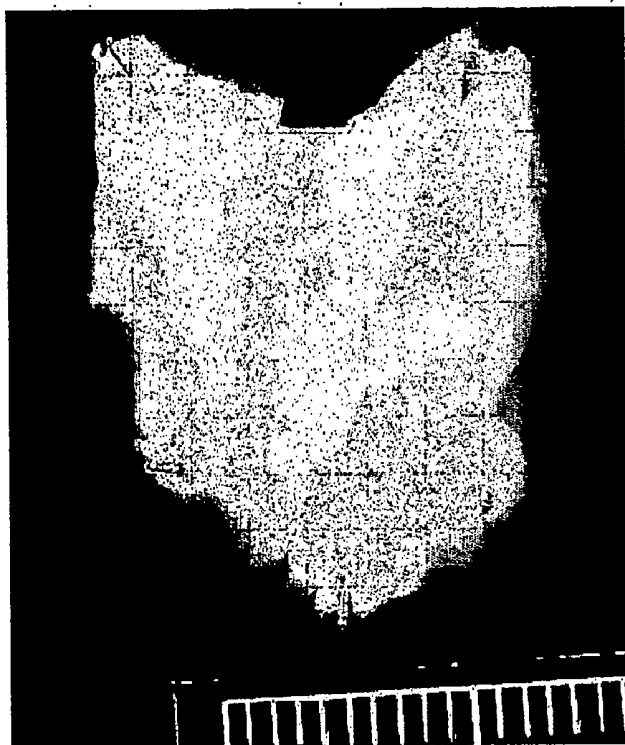


FIG. 3A

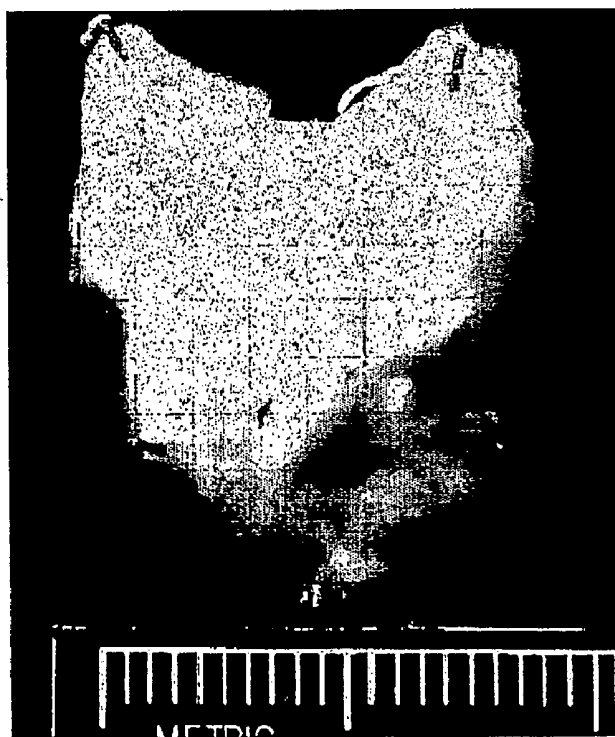


FIG. 3B

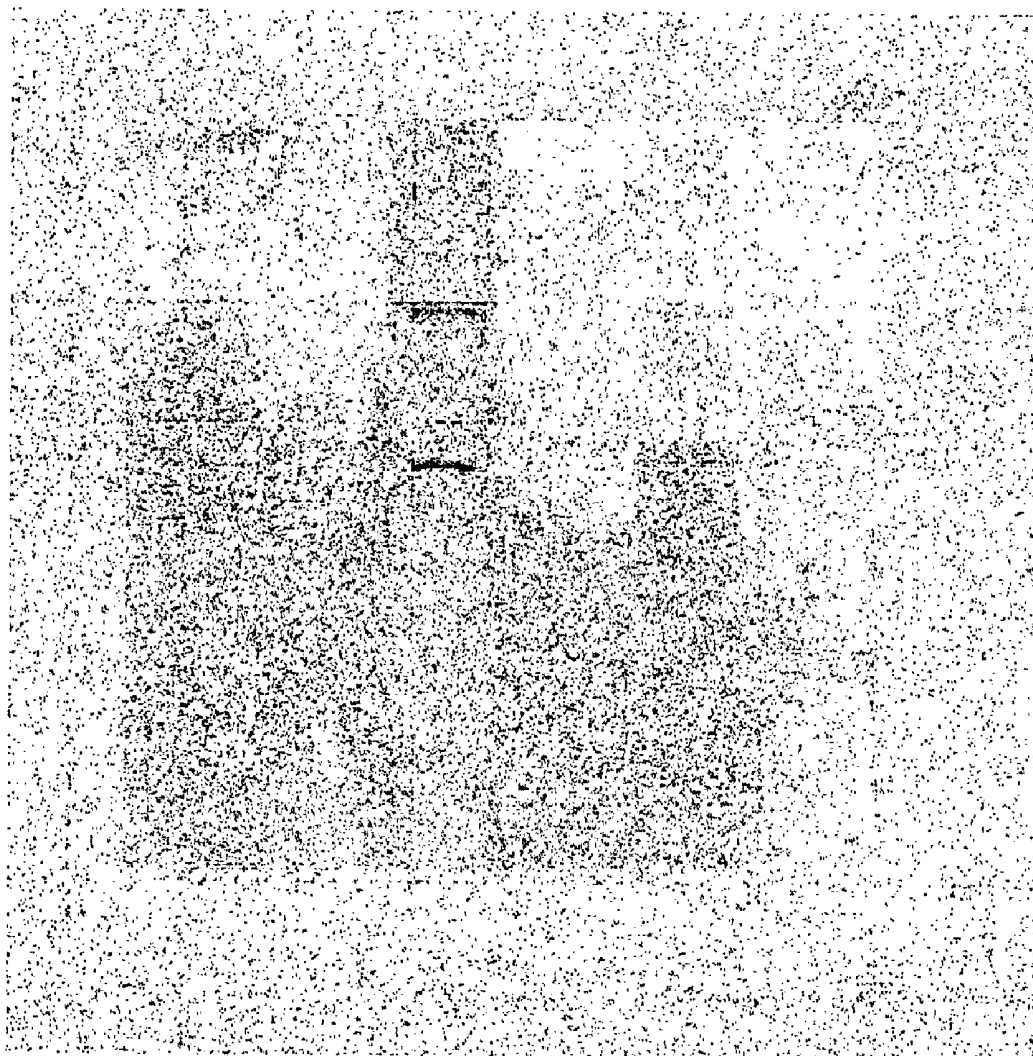


FIG. 4

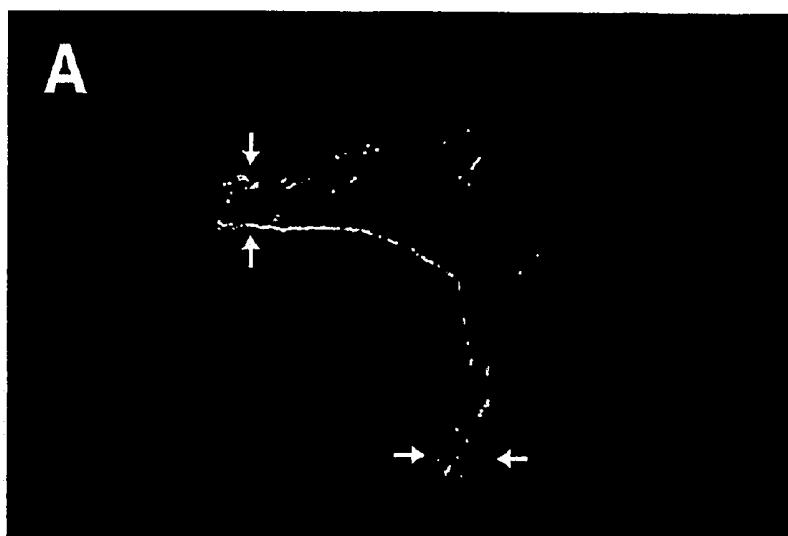


FIG. 5A

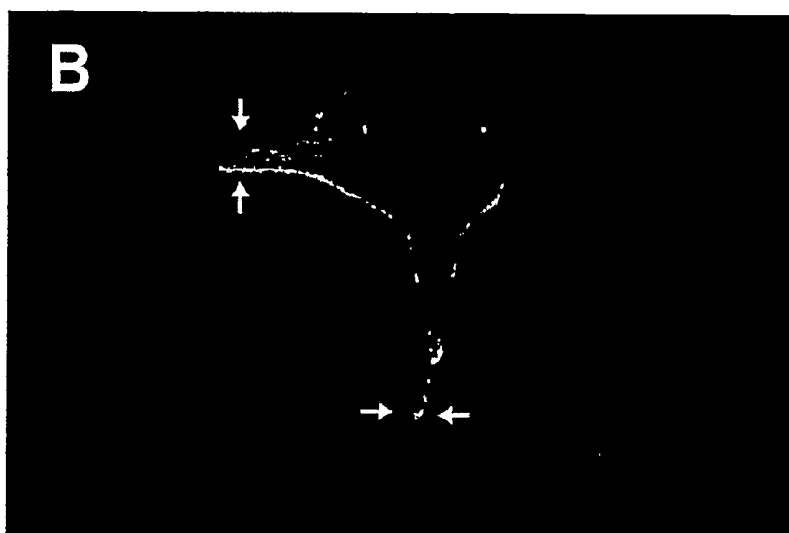


FIG. 5B



FIG. 5C

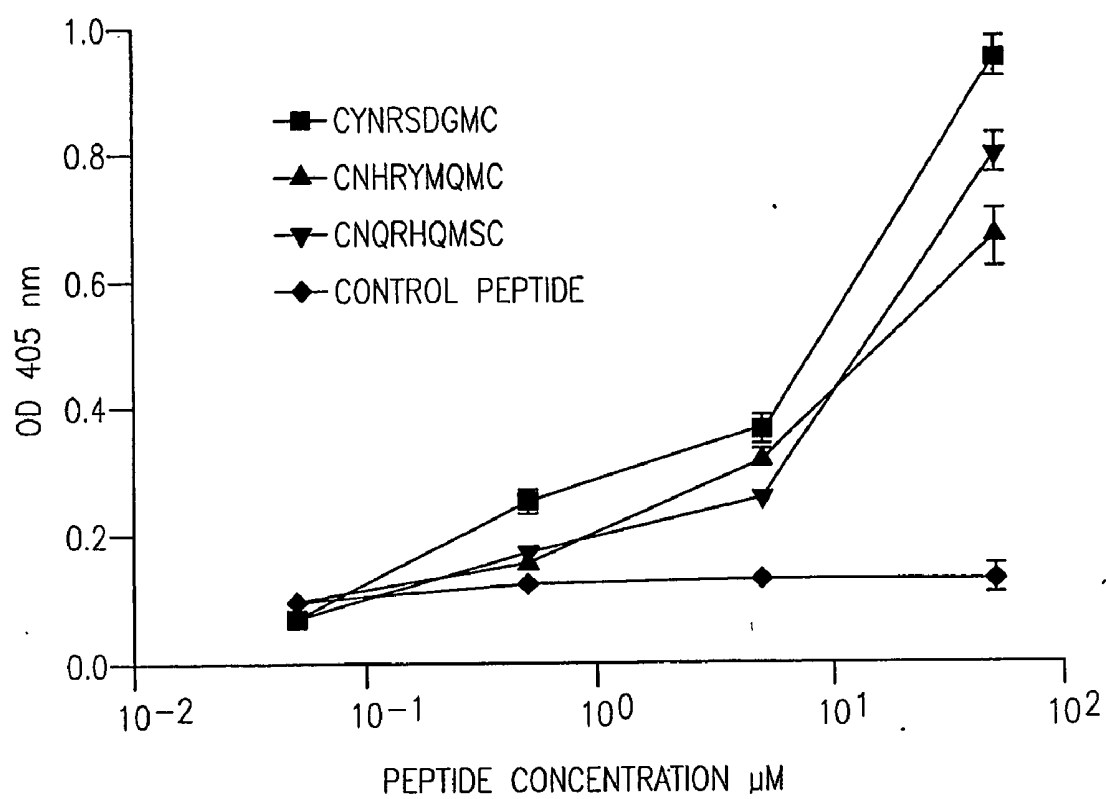


FIG. 6A

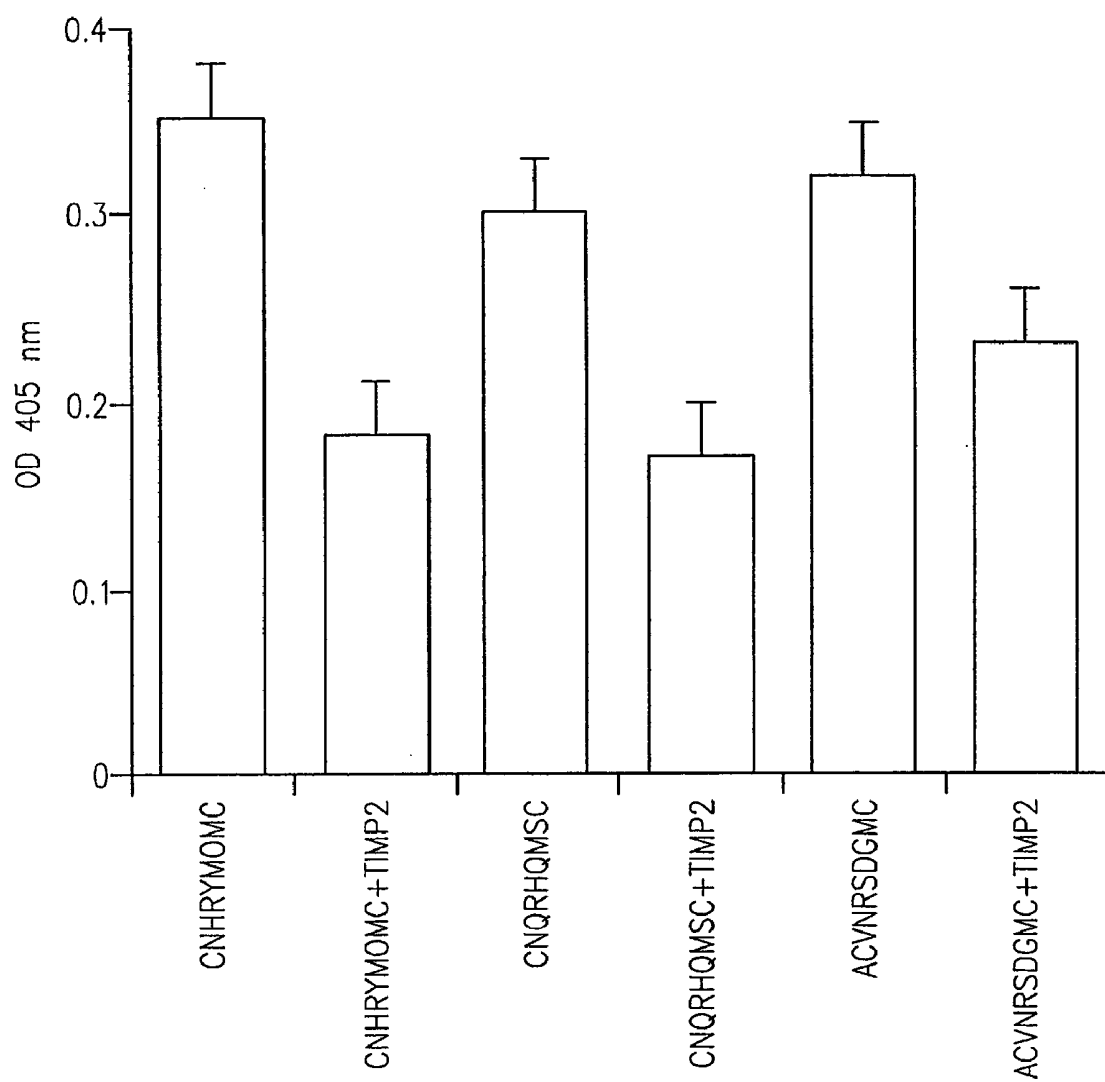


FIG. 6B

PEPTIDES THAT BIND TO ATHEROSCLEROTIC LESIONS

FIELD OF THE INVENTION

[0001] The present invention relates to detecting and treating vascular problems. In one embodiment, the invention provides peptides that selectively bind and home to atherosclerotic lesions in vivo. Methods to select such peptides by in vivo assays using phage display libraries are also provided, as well as methods to identify the target biomolecule bound by those peptides. The invention also provides methods to diagnose or treat pathologic conditions of endothelial tissues, for example, atherosclerotic lesions, by administering a peptide conjugated to a reporter molecule or to a therapeutic agent.

BACKGROUND TO THE INVENTION

[0002] Atherosclerosis is the pathologic process that principally contributes to the pathogenesis of myocardial and cerebral infarction. A whole range of pathological changes occurs during progression of atherosclerotic disease. While some of these changes can be described, the underlying molecular mechanisms and the exact sequence of events are not sufficiently well defined to accurately predict when a patient may suffer myocardial or cerebral infarction.

[0003] One of the characteristic early changes in the intima of a developing atherosclerotic plaque is the accumulation of lipid-laden foam cells, derived from blood-derived monocytes. An injury that causes endothelium dysfunction and localized inflammatory responses likely contributes to atherosclerotic lesion formation. The endothelial dysfunction is manifested, most notably at branch points in the arterial tree, by accumulation of lipoprotein and derived lipids in arterial wall and the appearance of specific glycoproteins (such as E-selectin) on the surface of the endothelial cells. These surface changes increase the attachment and migration of monocytes and T lymphocytes, probably through the influence of growth regulatory molecules released by the altered endothelium, the adherent leukocytes, and the underlying smooth muscle cells. As the process continues, the monocytes differentiate to become macrophages, which accumulate lipid and become foam cells. Together with the accompanying lymphocytes, they are believed to be the basis of fatty streak formation.

[0004] Further development of atherosclerotic lesions involves the proliferation of smooth muscle cells and the formation of connective tissue by smooth muscle cells. A matrix of connective tissue can form that comprises elastic fibre proteins, collagen and proteoglycans, cell death (apoptosis) and the accumulation of lipid in the surrounding matrix. The atherosclerotic process is a recurring one. Cell influx and proliferation leads to increases in size of advanced lesions. Progression of atherosclerosis is marked by the accumulation of smooth muscle cells and lipid-laden macrophages with an overlying fibrous cap, the disruptions or dissolution of which is proposed to be a frequent cause of the acute thrombosis that occurs in the vulnerable plaque and extends into the lumen of the blood vessel leading to occlusion and infarction of the local tissue (see, e.g., Libby, P. (2000). Changing concepts of atherogenesis. *J. Internal Medicine* 247: 349-58).

[0005] Central to the initiation and progression of atherosclerotic lesions are the associated dysfunctional changes in

the endothelium. Early lesions develop at sites of morphologically intact endothelium. Several classes of adhesive cell surface glycoproteins, such as VCAM-1, are implicated in atherogenesis, but many changes in gene expression within endothelial cells during atherogenesis are not well understood.

[0006] Some of the cellular events that occur during the progression of atherosclerosis in humans are similar to those observed in hypercholesterolemia animal models. Apo E is a cholesterol-rich plasma lipoprotein that is found in humans and hypercholesterolemic mice. Apo E appears to participate in the binding of VLDL and chylomicrons lipoproteins to hepatic LDL receptors and to the LDL R-related proteins. When mice with an inactivated Apo E gene ("knockout" mice) are fed a high fat diet, they display severe hypercholesterolemia with elevated cholesterol levels, including elevated VLDL, IDL, and to a lesser degree, LDL levels. The presence of high levels of Apo E is accompanied by low levels of HDL cholesterol. Much of the Apo E expressed in mice is truncated and lacks the LDL-R binding domain. Apo E knockout mice develop early fatty streak lesions within a few months of birth that progress into moderate atherosclerotic lesions with time.

[0007] While the general course of atherosclerosis is understood, the location and progression of potentially problematic atherosclerotic lesions are difficult to identify in vivo. Moreover, most therapeutic agents currently administered to a patient are not targeted to a particular site, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. Although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the epithelial barrier, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, new methods and targeting agents are needed for specifically delivering reporter molecules and therapeutic agents to cells and tissues that may benefit from detection and treatment of disease conditions or injuries. Such methods and targeting agents can avoid the general physiological effects of inappropriate delivery of such agents to other cells and tissues.

[0008] One commonly used method for identifying new molecules involves screening collections of natural materials, such as fermentation broths of plant extracts, or libraries of synthesized molecules. Assays that range in complexity from simple binding assays to elaborate physiological tests are utilized. Such screening methods can provide leads on possible active molecules, but such molecules often require extensive testing or design modifications before a truly useful molecule is identified. Moreover, such testing and design modifications are time-consuming and costly.

[0009] Libraries of peptides or polynucleotides have been utilized to identify molecules useful for a variety of purposes. The methods were originally developed to speed up the determination of epitopes recognized by monoclonal antibodies. For example, one standard method involves in parallel synthesis of large arrays of peptides and progressive serial screening with acceptor molecules labeled with fluo-

rescent or other reporter groups. The sequence of an effective peptide can be decoded from its address in the array. See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA*, 81: 3998-4002 (1984); Maeji et al., *J. Immunol. Methods*, 146: 83-90 (1992); and Fodor et al., *Science*, 251: 767-775 (1991).

[0010] In another approach, Lam et al., *Nature*, 354: 82-84 (1991) describe combinatorial libraries of peptides that are synthesized on resin beads such that each resin bead contains about 20 pmoles of the same peptide. The beads are screened with labeled acceptor molecules and those with bound acceptor are searched for by visual inspection, physically removed, and the peptide identified by direct sequence analysis. This method requires, however, sensitive methods for sequence determination.

[0011] A different approach for identification in a combinatorial peptide library is used by Houghten et al., *Nature*, 354: 84-86 (1991). For hexapeptides of the twenty natural amino acids, four hundred separate libraries are synthesized, each with the first two amino acids fixed and the remaining four positions occupied by all possible combinations. An assay, based on competition for binding or other activity, is then used to find the library with an active peptide. Then twenty new libraries are synthesized and assayed to determine the effective amino acid in the third position, and the process is repeated until all six positions in the peptide were identified.

[0012] More recently, Houghten (Abstract, European Peptide Society 1992 symposium, Interlaken, Switzerland) suggested a different approach. Starting with twenty amino acids, a total of $20 \times 6 = 120$ peptide mixtures are synthesized. In twenty mixtures, position 6 contains a unique amino acid, and positions 1-5 contain a mixture of all natural amino acids. In another twenty mixtures, position 5 contains a unique amino acid and all other positions contain a mixture of all twenty amino acids, etc. Once synthesized, all of the 120 peptide mixtures are tested simultaneously and the most active of each of the twenty mixtures representing each position is identified.

[0013] Another approach involves presentation of peptides on the surface of a bacteriophage. A library of peptides can be displayed, where each phage contains a DNA sequence that codes for an individual peptide. The library is made by synthesizing a large number of random oligonucleotides to generate all combinations of peptide sequences. Useful peptides can be selected by finding those that bind to the particular target. This method is known as biopanning. Phage recovered by such binding assays can be amplified and selection for binding can be repeated to eliminate phage that bind non-specifically. The sequences of peptides that bind specifically to a target are identified by DNA sequencing. See, for example, Cwirla et al., *Proc. Natl. Acad. Sci. USA*, 87: 6378-6382 (1990); Scott et al., *Science*, 249: 386-390 (1990); and Devlin et al., *Science*, 249: 404-406 (1990); Felici et al., *Gene*, 128: 21-27 (1993).

[0014] One such peptide library was made by O'Neil et al. (*Proteins: Structure, Function and Genetics*, 14: 509-515 (1992)). These authors have constructed a random circular hexapeptide sequence inserted in the pIII phage protein. The library was used to select ligands to the receptor glycoprotein IIb/IIIa, a member of the integrin family of cell adhesion molecules that mediate platelet aggregation through the

binding of fibrinogen and von Willebrand factor. However, all of this work was done in vitro.

[0015] If methods could be found to directly search for peptides that bind biomolecules and tissues in vivo, one of skill in the art could move more quickly toward identification of peptides useful for in vivo imaging and in vivo therapeutic purposes.

SUMMARY OF THE INVENTION

[0016] The invention provides isolated peptides of any one of formulae I-IV:

Xaa ₁ -Xaa ₂ -Xaa ₃ -Xaa ₄ -Xaa ₅ -Xaa ₆	I
Xaa ₁ -Xaa ₂ -Xaa ₃ -Xaa ₄ -Xaa ₅ -Xaa ₆ -Xaa _a	II
Xaa _a -Xaa ₁ -Xaa ₂ -Xaa ₃ -Xaa ₄ -Xaa ₅ -Xaa ₆	III
Xaa _a -Xaa ₁ -Xaa ₂ -Xaa ₃ -Xaa ₄ -Xaa ₅ -Xaa ₆ -Xaa _a	IV

[0017] wherein Xaa₁ is an aliphatic amino acid;

[0018] wherein Xaa₂, Xaa₃ and Xaa₄ are separately apolar amino acids;

[0019] wherein Xaa₅ and Xaa₆ are separately polar amino acids;

[0020] wherein Xaa₆ is a basic amino acid;

[0021] wherein Xaa_a is a cysteine-like amino acid; and

[0022] wherein the peptides can bind to a biomolecule or tissue in vivo.

Specific peptides provided by the invention have even-numbered SEQ ID NOs, including SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, SEQ ID NO:178, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:188, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID

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[0023] The invention is also directed to isolated peptide variants that include peptides with sequences identical at four of the amino acid positions of any of the even-numbered SEQ ID NOs and that can bind to an atherosclerotic lesion. In a preferred embodiment, the invention provides isolated peptide variants that include peptides with sequences identical at five, more preferably six, of the amino acid positions of any of the even-numbered SEQ ID NOs and that can bind to an atherosclerotic lesion. Preferred peptide variants have sequences similar to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 and/or SEQ ID NO:464.

[0024] The invention is further directed to an isolated nucleic acid encoding a peptide with any of the even-numbered SEQ ID NOs provided herein. For example, such isolated nucleic acids can have any of the odd-numbered SEQ ID NOs provided herein. In another embodiment, the invention provides an isolated nucleic acid capable of hybridizing under stringent conditions to a DNA having either strand of the odd-numbered SEQ ID NOs provided herein. In one embodiment, such stringent hybridization conditions include hybridization in 6×SSC and at 55° C.

[0025] The invention still further provides a method of identifying a peptide capable of binding to mammalian vascular tissues that includes, circulating a phage display library through the vascular tissues of a mammal; isolating a phage that selectively adheres to the vascular tissues of the mammal; and identifying a peptide displayed on the phage, wherein the peptide is capable of binding to the vascular tissues of the mammal. Such a method can also include minimally amplifying the isolated phage isolated to provide a population of phage that selectively adhere to the vascular tissues of the mammal; circulating the population of phage through the vascular tissues of a mammal; isolating a second selected phage that selectively adheres to the vascular tissues of the mammal; and identifying a peptide displayed on the second selected phage, wherein the peptide is capable of binding to the vascular tissues of the mammal.

[0026] The invention also provides a method of identifying a protein bound by a peptide that is capable of binding to the vascular tissues of a mammal that includes, separating a mixture of proteins prepared from the vascular tissues of a mammal; contacting the mixture of proteins with a peptide that is capable of binding to the vascular tissues of the mammal; and identifying a protein that binds the peptide.

[0027] The invention further provides a method of identifying a peptide capable of binding to an atherosclerotic lesion in a mammal that includes, circulating a phage display library through the vascular tissues of a mammal; isolating a phage that selectively adheres to an atherosclerotic lesion in the mammal; and identifying a peptide displayed on the phage, wherein the peptide is capable of binding to an atherosclerotic lesion of the mammal. The isolated phage can also be minimally amplified to provide a population of phage that selectively adhere to an atherosclerotic lesion in the mammal. That population of phage can be circulated through the vascular tissues of a mammal and a second selected phage that selectively adheres to an atherosclerotic lesion in the mammal can be isolated. A peptide displayed on the second selected phage can be isolated that is capable of binding to an atherosclerotic lesion in the mammal.

[0028] The invention still further provides a method of identifying a protein bound by a peptide that is capable of binding to an atherosclerotic lesion of a mammal that includes separating a mixture of proteins prepared from atherosclerotic lesions from a mammal, contacting the separated mixture of proteins with a peptide that is capable of binding to an atherosclerotic lesion of the mammal, and identifying a protein that binds the peptide.

[0029] The invention also provides a method of identifying the location of atherosclerotic lesions in a mammal that includes, administering a peptide conjugated to a reporter molecule to the vascular system of a mammal and observing the location of the reporter molecule. The peptide used is

conjugated to the reporter molecule can bind to an atherosclerotic lesion in a mammal.

[0030] The invention further provides a method of identifying the severity of an atherosclerotic lesion in a mammal that includes administering a peptide conjugated to a reporter molecule to the vascular system of a mammal and observing the amount, localization, shape, density, or relative distribution of reporter molecules on an atherosclerotic lesion in the mammal. The peptide conjugated to the reporter molecule can bind to an atherosclerotic lesion in a mammal through a specific target biomolecule. Such binding permits visualization not only of the atherosclerotic lesion, but also of the amount, localization, shape, density, or relative distribution of target biomolecules on the atherosclerotic lesion.

[0031] The invention is also directed to methods of treating diseases such as stroke, atherosclerosis, acute coronary syndromes including unstable angina, thrombosis and myocardial infarction, plaque rupture, both primary and secondary (in-stent) restenosis in coronary or peripheral arteries, transplantation-induced sclerosis, peripheral limb disease, intermittent claudication and diabetic complications (including ischemic heart disease, peripheral artery disease, congestive heart failure, retinopathy, neuropathy and nephropathy), or thrombosis. These methods involve administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent, wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can beneficially treat any of these diseases. For example, the therapeutic agent may be able to reduce or control the size of an atherosclerotic lesion.

[0032] In one embodiment, the invention also provides a method of treating atherosclerosis in a mammal that includes administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent, wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can beneficially treat atherosclerosis. Such therapeutic agents include, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, anti-inflammatory agents or liposomes that contain thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, or anti-inflammatory agents.

[0033] The invention further provides a method of preventing heart attack in a mammal that includes administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent, wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can help prevent heart attack. Such therapeutic agents include, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, anti-inflammatory agents or liposomes that contain thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue

factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, or anti-inflammatory agents. The therapeutic agent can also be an enzyme capable of converting a prodrug into an active drug. Hence the peptides of the invention can deliver catalysts to atherosclerotic lesions where the catalyst can promote formation of an agent useful for treating or preventing atherosclerosis, vascular diseases and/or heart disease.

DESCRIPTION OF THE FIGURES

[0034] FIG. 1 provides images of aorta from mice injected with 10^{11} phage bearing CAPGPSKSC (SEQ ID NO:4) or control phage without this peptide sequence. Binding of phage to aorta was visualized with biotinylated anti-phage antibody and streptavidin-linked enzyme activation of DAB.

[0035] FIG. 1A shows a young non-atherosclerotic Apo E knockout mouse injected with CAPGPSKSC (SEQ ID NO:4) phage. In the aorta of these mice, atherosclerotic lesions have not yet developed, and no phage binding to the aorta is detectable. These results suggest that phage bearing the CAPGPSKSC (SEQ ID NO:4) peptide bind target molecules that are associated with atherosclerotic lesions and whose expression is not up-regulated by the deficiency of ApoE.

[0036] FIG. 1B shows a normal aorta from a Balb/C mouse. No association of phage with the aortic surface is observed suggesting the biomolecule that binds CAPGPSKSC (SEQ ID NO:4) phage is not present in detectable quantities on the surface of normal aorta endothelium.

[0037] FIG. 1C shows an aorta from an Apo B knockout mouse fed a high fat diet. Atherosclerotic lesions (white) are clearly visible. This mouse was injected with 10^{11} control phage. No detectable association of control phage with the lesions is observed.

[0038] FIG. 1D shows an aorta of an atherosclerotic Apo E knockout mouse fed a high fat diet. This mouse was injected with 10^{11} CAPGPSKSC (SEQ ID NO:4) phage. Phage binding to the lesions is specifically visualized as red-brown staining of the white atherosclerotic lesions.

[0039] FIG. 2A depicts an aorta from an atherosclerotic ApoE knockout mouse fed high fat diet and infused with biotinylated CAPGPSKSC (SEQ ID NO:4) peptide (visualized as red-brown staining). The staining pattern of the peptide is like that of phage displaying the peptide.

[0040] FIG. 2B shows a histologic section of a typical atherosclerotic lesion from the aorta of an atherosclerotic ApoE knockout mouse. The binding of this peptide is most intense in the endothelium overlying the atherosclerotic lesion (black arrows), and peptide positivity is diminished towards the adjacent apparently uninvolved endothelium (grey arrows). Binding of peptide is not observed in the center of the lesion where the endothelium is not present (white arrows), consistent with endothelial cell localization of the target molecule.

[0041] FIG. 3 provides two images of an atherosclerotic lesion in a human arterial specimen. FIG. 3A is an image of the specimen before application of a biotinylated CAPGPSKSC (SEQ ID NO:4) peptide of the invention.

Following application of the biotinylated CAPGPSKSC (SEQ ID NO:4) peptide to the luminal surface of the specimen, the specimen was washed and any peptide bound and was visualized by enzyme-linked avidin conversion of DAB substrate. Bound peptide is apparent in FIG. 3B against the white tissue as darker, brownish red staining. The association of CAPGPSKSC (SEQ ID NO:4) phage with the lesion, but not with non-atherosclerotic surfaces of arteries and veins, indicates that humans express the target biomolecule of this peptide in atherosclerotic lesions, and suggests that the peptide may be used for diagnostic and therapeutic purposes in humans.

[0042] FIG. 4 is a photograph of a Western blot identifying the target biomolecule of the CAPGPSKSC (SEQ ID NO:4) peptide in mouse endothelial cells (bEND.3). The total protein lysate (lane 1) and membrane preparations were separated on a SDS polyacrylamide gel and then transferred to a nitrocellulose membrane. The membrane was probed with biotinylated peptide CAPGPSKSC (SEQ ID NO:4). Two sharp bands were observed on a Western blot of a whole cell lysate of mouse endothelial cell line (bEND.3), using the biotinylated CAPGPSKSC (SEQ ID NO:4) peptide to detect target proteins. The sizes of the proteins bound by the CAPGPSKSC (SEQ ID NO:4) peptide were about 82 kilodaltons (P82) and about 120 kilodaltons (P120). The sharpness of the detected bands suggests that these target proteins are not glycoproteins. The P82 protein was also detected in membrane fractions partially purified by Triton X114 extraction. These data suggest that the P82 protein is a membrane protein.

[0043] FIG. 5 provides images of phage binding to aortic valves from ApoE knockout mice with atherosclerotic lesions. The mice were infused with 10^{11} pfu of phage carrying the CNQRHQMSC (SEQ ID NO:336) sequence. FIG. 5A depicts a section of aortic valve from an atherosclerotic ApoE knockout mouse. Note the aortic valve is thickened by the presence of atherosclerotic lesions as indicated by white arrows. The endothelial cells report red with biotinylated rat anti mouse CD 31 antibody, and the associated phage report green with anti-phage antibody.

[0044] FIG. 5B provides a photograph of an aortic valve from a non-atherosclerotic ApoE knockout mouse fed normal chow fed. Note the normal thin aortic valve leafs in contrast to that of the atherosclerotic mouse in panel A. Association of phage with endothelial surfaces was also reported (green) with anti-phage antibody.

[0045] FIG. 5C provides a photograph of vascular tissue exposed to a control phage. No phage association was evident. These data indicate that the CNQRHQMSC (SEQ ID NO:336) peptide associates with a molecule present on both atherosclerotic and normal endothelial surfaces.

[0046] FIG. 6A illustrates that three synthetic peptides with homology to TIMP-2 bind to endothelial cells in a dose dependent manner. The peptides tested were the CYNRS-DGMC (SEQ ID NO:464, filled squares) peptide, the CNHRYMQMC (SEQ ID NO:344, right-side-up filled triangles) peptide, the CNQRHQMSC (SEQ ID NO:336, upside-down filled triangles) peptide and a control peptide (filled diamonds). The peptide concentration is provided on the x-axis and the absorbance at 405 nm as a measure of peptide binding is provided on the y-axis. Similar peptide binding was observed with HT1080 cells (not shown).

[0047] FIG. 6B illustrates that purified TIMP-2 protein (0.05 μ M) inhibits binding of the CNHRYMQMC (SEQ ID NO:344) peptide, the CYNRS-DGMC (SEQ ID NO:464) peptide and the CNQRHQMSC (SEQ ID NO:336) peptide at 0.5 μ M. These data indicate that the peptides and TIMP-2 protein compete for a binding site on the surface of endothelial cells. A control peptide did not bind.

DETAILED DESCRIPTION OF THE INVENTION

[0048] The invention provides peptides that bind to selected biomolecules and tissues, for example, those biomolecules and tissues within discrete regions of the mammalian vascular system. In one embodiment the peptides bind to atherosclerotic lesions. Such peptides can selectively interact in vivo with atherosclerotic lesions and can be used as probes to characterize the changing expression profile of surface molecules in the lesion endothelium. These peptides can also be used for non-invasive imaging of atherosclerotic lesions and for therapy to control or diminish the growth and development of the lesions.

[0049] The invention also provides methods for isolating peptides that bind to any biomolecules or tissues of interest. Peptides are isolated by in vivo screening procedures. Naked cyclized peptides or phage display libraries can be injected or otherwise introduced into a mammal. Peptides or phage displaying peptides that bind to specific biomolecules or tissues of interest are identified and/or isolated.

[0050] Selected animal models that express biomolecules of interest or that develop conditions mimicking problematic human conditions can be used as the mammals for testing peptide and phage binding. For example, Apo E knockout mice on high fat atherogenic diets develop atherosclerotic lesions. Such mice can be used to isolate peptides that bind to atherosclerotic lesions. Animals bearing tumors can be used for identifying peptides that bind to the vascular endothelium and pseudoendothelium of those tumors, and to the vessels associated with the tumors. Through repeated exposure, collection and isolation of peptide bearing phage by the "panning" methods provided herein it is possible to obtain peptides that are capable of recognizing biochemical entities on the surface of a variety of cell and tissue types.

[0051] For example, after four rounds of in vivo panning, four peptide sequences were repeatedly identified as showing preferential binding to the atherosclerotic lesions in atherosclerotic Apo E knockout mice, but not in non-atherosclerotic Apo E knockout mice. These peptides were found to bind to atherosclerotic lesions in atherosclerotic Apo E knockout mice as well as to atherosclerotic lesions in human vascular tissue specimens.

Definitions

[0052] The term "control the size of an atherosclerotic lesion" refers to the ability of a therapeutic agent to prevent further enlargement of an atherosclerotic lesion or to prevent occlusion of a blood vessel by an atherosclerotic lesion. In many instances, the therapeutic agents linked to peptides of the invention can reduce the size of an atherosclerotic lesion.

[0053] A "deletion" is defined as a change in either nucleotide or amino acid sequence in which one or more nucleotides or amino acid residues, respectively, are absent.

[0054] "Hybridization" as used herein means "any process by which a strand of nucleic acid joins with a complementary strand through base pairing" (Coombs J (1994) Dictionary of Biotechnology, Stockton Press, New York N.Y.).

[0055] An "insertion" or "addition" is that change in a nucleotide or amino acid sequence that has resulted in the addition of one or more nucleotides or amino acid residues, respectively.

[0056] A "phage-display library" is a protein expression library that expresses a collection of peptide sequences as fusion proteins joined with a phage coat protein. Thus, in the context of the invention, a combinatorial library of peptide sequences is expressed on the exterior of the phage particle. Those of skill in the art will recognize that phage clones that express peptides specific for atherosclerotic lesions can be substantially purified by serial rounds of phage binding to an atherosclerotic lesion.

[0057] "Polynucleotide", "nucleotide" and "nucleic acid", used interchangeably herein, is defined as a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. These terms include a single-, double- or triple-stranded DNA, genomic DNA, cDNA, RNA, DNA-RNA hybrids, polymers comprising purine and pyrimidine bases, or other natural, chemically, biochemically modified, non-natural or derivatized nucleotide bases. The backbone of the polynucleotide can comprise sugars and phosphate groups (as may typically be found in RNA or DNA), or modified or substituted sugar or phosphate groups. Polynucleotides or nucleic acids of the invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA or synthetic DNA. As used herein, "DNA" includes not only bases A, T, C, and G, but also includes any of their analogs or modified forms of these bases, such as methylated nucleotides, internucleotide modifications such as uncharged linkages and thioates, use of sugar analogs, and modified and/or alternative backbone structures, such as polyamides.

[0058] A "reporter molecule" is any labeling or signaling moiety known to one of skill in the art including chemicals, proteins, peptides, biotin, radionuclides, enzymes, fluorescent, chemiluminescent, contrast agents, liposomes, MRI, NMR, and ESR signaling agents, and chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles and the like. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149 and 4,366,241.

[0059] The peptides of the present invention selectively bind to target molecules in vivo. A peptide "selectively binds" a target molecule when it interacts with a binding domain of the target molecule with a greater affinity, or is more specific for that binding domain as compared with other binding domains of other physiological molecules. The phrase "is specific for" refers to the degree of selectivity shown by a peptide with respect to the number and types of interacting molecules with which the peptide interacts and the rates and extent of these reactions, e.g. the degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines and the rates and the extent of these reactions. The phrase "selectively binds" in the present context also means binding sufficient to be useful in the method of the invention. As is known in the art, useful selective binding, for instance, to a

receptor, depends on both the binding affinity and the concentration of ligand achievable in the vicinity of the receptor. Thus, binding affinities lower than that found for any naturally occurring competing ligands may be useful, as long as the cell or tissue to be treated can tolerate concentrations of added ligand sufficient to compete, for example, for binding to a target biomolecule.

[0060] "Stringency" typically occurs in a range from about $T_m - 5^\circ \text{C}$. (5°C . below the T_m of the probe) to about 20°C . to 25°C . below T_m . As will be understood by those of skill in the art, a stringent hybridization can be used to identify or detect identical polynucleotide sequences or to identify or detect similar or related polynucleotide sequences.

[0061] A "substitution" results from the replacement of one or more nucleotides or amino acids by different nucleotides or amino acids, respectively.

[0062] As used herein, a "target" is a biomolecule or tissue to which a peptide identified according to the invention can bind.

[0063] A "therapeutic agent" is any drug, enzyme, protein, viral particle, toxin or other agent that one of skill in the art can use to beneficially treat a mammal having a target bound by a peptide of the invention. Such therapeutic agents include, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, anti-inflammatory agents or liposomes that contain thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, or anti-inflammatory agents. In another embodiment, the therapeutic agent is a nucleic acid useful for gene therapy. Such a nucleic acid can be directly attached to a peptide of the invention, or it can be present in a phage particle, liposome or other vector available to one of skill in the art.

[0064] A "variant" peptide is defined as a peptide with an amino acid sequence that differs by one or more amino acids from a reference peptide or amino acid sequence. Variant peptides will have substantially the same physical, chemical and/or functional properties as the reference peptide. In general, a variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, for example, replacement of leucine with isoleucine. Similar minor variations may also include amino acid deletions or insertions, or both. In contrast to a variant peptide, a derivative peptide may have somewhat different physical, chemical and/or functional properties compared to the reference peptide. For example, a derivative peptide can have enhanced binding properties relative to the reference peptide. A derivative may therefore have "non-conservative" changes, e.g., replacement of a glycine with a tryptophan. Guidance in determining which and how many amino acid residues may be substituted, inserted or deleted to retain or enhance the physical, chemical and/or functional properties (e.g. binding properties) of a peptide is provided herein and is available in the art, for example, in certain computer programs such as DNASTar.

Peptides

[0065] Peptides isolated by the in vivo methods provided by the invention bind to biomolecules and tissues of interest. In many instances, such peptides selectively bind to such biomolecules and tissues. In some embodiments, a peptide that selectively binds to a biomolecule or tissue of interest, binds with sufficient selectivity to permit the peptide to become localized in vivo at the site of the biomolecule or tissue. Peptides that selectively bind to biomolecules and tissues can therefore be detected at the site of such biomolecules and tissues. Desirable peptides that selectively bind to biomolecules and tissues permit reliable detection of those biomolecules and tissues in vivo. Desirable peptides that selectively bind to biomolecules and tissues may also permit reliable delivery of a therapeutic agent to the site of the biomolecule or tissue. However, because various types of reporter molecules and therapeutic agents may alter the physical and chemical properties of the peptide or sterically hinder binding, a peptide conjugated to such a reporter molecule or therapeutic agent may still "selectively bind" even though some modification of the peptide conjugate, reporter molecule or therapeutic agent is needed to optimize binding.

[0066] Table 1 provides an exemplary listing of peptides isolated according to the invention.

TABLE 1

<u>Peptides Isolated</u>		
SEQ ID NO:	Name	Sequence
SEQ ID NO:2		APGPSKS
SEQ ID NO:4		CAPGPSKSC
SEQ ID NO:6		QEPTRLK
SEQ ID NO:8		CQEPTRLKC
SEQ ID NO:10		KEPTRAH
SEQ ID NO:12		CKEPTRAHC
SEQ ID NO:14	Eo2-1	LAMLMDT
SEQ ID NO:16	Eo2-1	CLAMLMDTC
SEQ ID NO:18	Eo2-2	NKHTRPL
SEQ ID NO:20	Eo2-2	CNKHTRPLC
SEQ ID NO:22	Eo2-3	VHKLPES
SEQ ID NO:24	Eo2-3	CVHKLPESC
SEQ ID NO:26	Eo2-4	PTQASLH
SEQ ID NO:28	Eo2-4	CPTQASLHC
SEQ ID NO:30	Eo2-5	DTAPPSS
SEQ ID NO:32	Eo2-5	CDTAPPSSC
SEQ ID NO:34	Eo2-6	GVQTLA
SEQ ID NO:36	Eo2-6	CGVQTLLAC
SEQ ID NO:38	Eo2-7	DPVTKHT
SEQ ID NO:40	Eo2-7	CDPVTKHTC

TABLE 1-continued

<u>Peptides Isolated</u>		
SEQ ID NO:	Name	Sequence
SEQ ID NO:42	Eo2-8	DQSTIRA
SEQ ID NO:44	Eo2-8	CDQSTIRAC
SEQ ID NO:46	Eo2-9	RAATPSI
SEQ ID NO:48	Eo2-9	CRAATPSIC
SEQ ID NO:50	Eo2-10	KTSHAQE
SEQ ID NO:52	Eo2-10	CKTSHAQEC
SEQ ID NO:54	Eo3-3	KHPVGRV
SEQ ID NO:56	Eo3-3	CKHPVGRVC
SEQ ID NO:58	Eo3-5	TDTKNSQ
SEQ ID NO:60	Eo3-5	CTDTKNSQC
SEQ ID NO:62	Eo3-11	QPPMGRY
SEQ ID NO:64	Eo3-11	CQPPMGRYC
SEQ ID NO:66	Eo3-13	NERLNKD
SEQ ID NO:68	Eo3-13	CNERLNKDC
SEQ ID NO:70	Eo3-15	PPSNKQM
SEQ ID NO:72	Eo3-15	CPPSNKQMC
SEQ ID NO:74	Eo3-27	DSSSPAR
SEQ ID NO:76	Eo3-27	CDSSSPARC
SEQ ID NO:78	Eo3-28	TQSDNRR
SEQ ID NO:80	Eo3-28	CTQSDNRRC
SEQ ID NO:82	Eo3-29	KGLPAKT
SEQ ID NO:84	Eo3-29	CKGLPAKTC
SEQ ID NO:86	Eo3-31	LQPHLSL
SEQ ID NO:88	Eo3-31	CLQPHLSLC
SEQ ID NO:90	Eo3-33	AVPQNRS
SEQ ID NO:92	Eo3-33	CAVPQNRSC
SEQ ID NO:94	Eo3-34	MNQTPDL
SEQ ID NO:96	Eo3-34	CMNQTPDLC
SEQ ID NO:98	Eo3-36	FQMQPTL
SEQ ID NO:100	Eo3-36	CFQMQPTLC
SEQ ID NO:102	Eo3-37	SGASNKT
SEQ ID NO:104	Eo3-37	CSGASNKTC
SEQ ID NO:106	Eo3-38	TKMRLEQ
SEQ ID NO:108	Eo3-38	CTKMRLEQC
SEQ ID NO:110	Eo3-41	TSPIYPG
SEQ ID NO:112	Eo3-41	CTSPIYPGC

TABLE 1-continued

<u>Peptides Isolated</u>		
SEQ ID NO:	Name	Sequence
SEQ ID NO:114	E03-43	KTPSQSQ
SEQ ID NO:116	E03-43	CKTPSQSQC
SEQ ID NO:118	E03-46	LQAFKAT
SEQ ID NO:120	E03-46	CLQAFKATC
SEQ ID NO:122	E03-47	STTELNK
SEQ ID NO:124	E03-47	CSTTELNKC
SEQ ID NO:126	E03-48	RTHSSPT
SEQ ID NO:128	E03-48	CRTHSSPTC
SEQ ID NO:130	E03-50	NENFKGL
SEQ ID NO:132	E03-50	CNENFKGLC
SEQ ID NO:134	E03-51	SKTNHAS
SEQ ID NO:136	E03-51	CSKTNHASC
SEQ ID NO:138	E03-52	TPYPSNS
SEQ ID NO:140	E03-52	CTPYPSNSC
SEQ ID NO:142	E03-53	TLAAPH
SEQ ID NO:144	E03-53	CTLAAPHC
SEQ ID NO:146	E03-54	LNNSQAH
SEQ ID NO:148	E03-54	CLNNSQAH
SEQ ID NO:150	E03-56	IEHSAQQ
SEQ ID NO:152	E03-56	CIEHSAQQC
SEQ ID NO:154	E03-57	SAAGHHT
SEQ ID NO:156	E03-57	CSAAGHHTC
SEQ ID NO:158	E03-58	HNQKLN
SEQ ID NO:160	E03-58	CHNQKLNRC
SEQ ID NO:162	E03-59	KSTSHSM
SEQ ID NO:164	E03-59	CKSTSHSMC
SEQ ID NO:166	E03-60	PNNKSAS
SEQ ID NO:168	E03-60	CPNKNKASC
SEQ ID NO:170	E03-62	EDPTLKV
SEQ ID NO:172	E03-62	CEDPTLKVC
SEQ ID NO:174	E03-63	MSAMSRQ
SEQ ID NO:176	E03-63	CMSAMSRQC
SEQ ID NO:178	E03-64	PGKISRS
SEQ ID NO:180	E03-64	CPGKISRSC
SEQ ID NO:182	E03-65	LKLGSKQ
SEQ ID NO:184	E03-65	CLKLGSKQC

TABLE 1-continued

<u>Peptides Isolated</u>		
SEQ ID NO:	Name	Sequence
SEQ ID NO:186	E03-66	KTSPEST
SEQ ID NO:188	E03-66	CKTSPESTC
SEQ ID NO:190	E03-67	TLFPGNS
SEQ ID NO:192	E03-67	CTLFPGNSC
SEQ ID NO:194	E03-68	LPSSTRL
SEQ ID NO:196	E03-68	CLPSSTRLC
SEQ ID NO:198	E03-69	SSQRTPP
SEQ ID NO:200	E03-69	CSSQRTPPC
SEQ ID NO:202	E03-70	LPTMTPT
SEQ ID NO:204	E03-70	CLPTMTPTC
SEQ ID NO:206	E03-71	LMTPSKR
SEQ ID NO:208	E03-71	CLMTPSKRC
SEQ ID NO:210	E03-72	EHFFSR
SEQ ID NO:212	E03-72	CEHFFSRSC
SEQ ID NO:214	E03-73	TNQFLQQ
SEQ ID NO:216	E03-73	CTNQFLQQC
SEQ ID NO:218	E03-75	PANKSSF
SEQ ID NO:220	E03-75	CPANKSSF
SEQ ID NO:222	E03-77	STTQSSW
SEQ ID NO:224	E03-77	CSTTQSSWC
SEQ ID NO:226	E03-78	VTPDRLT
SEQ ID NO:228	E03-78	CVTPDRLTC
SEQ ID NO:230	E03-80	TWQTQRS
SEQ ID NO:232	E03-80	CTWQTQRSC
SEQ ID NO:234	E03-81	PHPGTRH
SEQ ID NO:236	E03-81	CPHPGTRHC
SEQ ID NO:238	E03-82	APKPQSQ
SEQ ID NO:240	E03-82	CAPKPQSQC
SEQ ID NO:242	E03-84	SQAQIPA
SEQ ID NO:244	E03-84	CSQAQIPAC
SEQ ID NO:246	E03-85	PQNKGA
SEQ ID NO:248	E03-85	CPQNKGAC
SEQ ID NO:250	E03-86	HTAHPRS
SEQ ID NO:252	E03-86	CHTAHPRSC
SEQ ID NO:254	E03-87	KQSGPVS
SEQ ID NO:256	E03-87	CKQSGPVSC

TABLE 1-continued

<u>Peptides Isolated</u>		
SEQ ID NO:	Name	Sequence
SEQ ID NO:258	Eo3-88	SQYPSRS
SEQ ID NO:260	Eo3-88	CSQYPSRSC
SEQ ID NO:262	Eo3-89	SRDGKTT
SEQ ID NO:264	Eo3-89	CSRDGKTTC
SEQ ID NO:266	Eo3-90	TTLMPNI
SEQ ID NO:268	Eo3-90	CTTLMPNIC
SEQ ID NO:270	Eo3-92	TNKL DNT
SEQ ID NO:272	Eo3-92	CTNKL DNTC
SEQ ID NO:274	Eo3-93	TKMRLEQ
SEQ ID NO:276	Eo3-93	CTKMRLEQC
SEQ ID NO:278	Eo3-94	SPDPGSK
SEQ ID NO:280	Eo3-94	CSPDPGSKC
SEQ ID NO:282	Eo3-97	EHFFSRS
SEQ ID NO:284	Eo3-97	CEHFFSRSC
SEQ ID NO:286	Eo3-98	GAPSDHV
SEQ ID NO:288	Eo3-98	CGAPSDHVC
SEQ ID NO:290	Eo3-99	PHPGTRH
SEQ ID NO:292	Eo3-99	CPHPGTRHC
SEQ ID NO:294	Eo3-100	IKQSLSR
SEQ ID NO:296	Eo3-100	CIKQSLSRC
SEQ ID NO:298	Eo3-101	TTHNAKW
SEQ ID NO:300	Eo3-101	CTTHNAKWC
SEQ ID NO:302	Eo3-102	LTTKPRM
SEQ ID NO:304	Eo3-102	CLTTKPRMC
SEQ ID NO:306	Eo3-103	KLKSGSL
SEQ ID NO:308	Eo3-103	CKLKSGSLC
SEQ ID NO:310	Eo3-105	LPSKVSR
SEQ ID NO:312	Eo3-105	CLPSKV SRC
SEQ ID NO:314	Eo3-106	APGPSKS
SEQ ID NO:316	Eo3-106	CAPGPSKSC
SEQ ID NO:318	Eo3-107	SPLKSL
SEQ ID NO:320	Eo3-107	CSPLKSLSC
SEQ ID NO:322	Eo3-108	APGPSKS
SEQ ID NO:324	Eo3-108	CAPGPSKSC
SEQ ID NO:326	Eo3-109	PSGLTKQ
SEQ ID NO:328	Eo3-109	CPSGLTKQC

TABLE 1-continued

<u>Peptides Isolated</u>		
SEQ ID NO:	Name	Sequence
SEQ ID NO:330	Eo3-111	KSNMPLT
SEQ ID NO:332	Eo3-111	CKSNMPLTC
SEQ ID NO:334	Eo3-112	NQRHQMS
SEQ ID NO:336	Eo3-112	CNQRHQMSC
SEQ ID NO:338	Eo3-113	QRADQKQ
SEQ ID NO:340	Eo3-113	CQRADQKQC
SEQ ID NO:342	Eo3-114	NHRYMQM
SEQ ID NO:344	Eo3-114	CNHRYMQMC
SEQ ID NO:346	Eo3-115	ITPMSRT
SEQ ID NO:348	Eo3-115	CITPMSRTC
SEQ ID NO:350	Eo3-116	SPTIGQK
SEQ ID NO:352	Eo3-116	CSPTIGQKC
SEQ ID NO:354	Eo3-117	SNYSLGM
SEQ ID NO:356	Eo3-117	CSNYSLGMC
SEQ ID NO:358	Eo3-118	TNTGHRH
SEQ ID NO:360	Eo3-118	CTNTGHRHC
SEQ ID NO:362	Eo3-119	TMRTNSS
SEQ ID NO:364	Eo3-119	CTMRTNSSC
SEQ ID NO:366	Eo3-120	TAPLERR
SEQ ID NO:368	Eo3-120	CTAPLERRC
SEQ ID NO:370	Eo3-122	LLGEPRT
SEQ ID NO:372	Eo3-122	CLLGEPRTC
SEQ ID NO:374	Eo3-123	SRASTND
SEQ ID NO:376	Eo3-123	CSRASTNDC
SEQ ID NO:378	Eo3-124	NKSNKEF
SEQ ID NO:380	Eo3-124	CNKSNKEFC
SEQ ID NO:382	Eo3-125	HARVPLV
SEQ ID NO:384	Eo3-125	CHARVPLVC
SEQ ID NO:386	Eo3-126	LNNSQAH
SEQ ID NO:388	Eo3-126	CLNNSQAHC
SEQ ID NO:390	Eo3-127	NPSRSTS
SEQ ID NO:392	Eo3-127	CNPSRSTSC
SEQ ID NO:394	Eo3-128	TPTQKSL
SEQ ID NO:396	Eo3-128	CTPTQKSLC
SEQ ID NO:398	Eo3-129	SQRPVQM
SEQ ID NO:400	Eo3-129	CSQRPVQMC

TABLE 1-continued

Peptides Isolated		
SEQ ID NO:	Name	Sequence
SEQ ID NO:402	Eo3-130	APGPSKS
SEQ ID NO:404	Eo3-130	CAPGPSKSC
SEQ ID NO:406	Eo3-132	KGSSILN
SEQ ID NO:408	Eo3-132	CKGSSILNC
SEQ ID NO:410	Eo3-133	VNRSDGM
SEQ ID NO:412	Eo3-133	CVNRSDGMC
SEQ ID NO:414	Eo3-134	PHPGTRH
SEQ ID NO:416	Eo3-134	CPHPGTRHC
SEQ ID NO:418	Eo3-135	MNQRVQN
SEQ ID NO:420	Eo3-135	CMNQRVQNC
SEQ ID NO:422	Eo3-137	NQWKSVS
SEQ ID NO:424	Eo3-137	CNQWKSVC
SEQ ID NO:426	Eo3-138	QTHARHV
SEQ ID NO:428	Eo3-138	CQTHARHVC
SEQ ID NO:430	Eo3-139	FQNRQPM
SEQ ID NO:432	Eo3-139	CFQNRQPMC
SEQ ID NO:434	Eo3-140	RALDTAN
SEQ ID NO:436	Eo3-140	CRALDTANC
SEQ ID NO:438	Eo3-141	QEPTRLK
SEQ ID NO:440	Eo3-141	CQEPTRLKC
SEQ ID NO:442	Eo3-142	KEPTKAH
SEQ ID NO:444	Eo3-142	CKEPTKAHC
SEQ ID NO:446	Eo3-143	NGKANWK
SEQ ID NO:448	Eo3-143	CNGKANWKC

Preferred peptides include peptides having amino acid sequences SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 and/or SEQ ID NO:464. Additional amino acids can be added or inserted into these peptides, for example, to enhance binding activity, to permit cyclization or to link a reporter molecule or a therapeutic agent to the peptide.

Peptide Variants and Derivatives

[0067] The invention is also directed to variants and derivatives of the isolated peptides that can bind to the biomolecule or tissue to which the isolated peptide bound. Such variants and derivatives have identity with at least about four of the amino acid positions of any of the even-numbered SEQ ID NOs provided in Table 1 and are capable of binding to an atherosclerotic lesion. In a preferred embodiment, the variants and derivatives have identity with

at least about five of the amino acid positions of any of the even-numbered SEQ ID NOs in Table 1 and can bind to an atherosclerotic lesion. More preferably, peptide variants and derivatives have identity with at least about six of the amino acid positions of any of the even-numbered SEQ ID NOs in Table 1 and can bind to an atherosclerotic lesion.

[0068] Amino acid residues of the isolated peptides and peptide variants can be genetically encoded L-amino acids, naturally occurring non-genetically encoded L-amino acids, synthetic L-amino acids or D-enantiomers of any of the above. The amino acid notations used herein for the twenty genetically encoded L-amino acids and common non-encoded amino acids are conventional and are as shown in Table 2.

TABLE 2

Amino Acid	One-Letter Symbol	Abbreviation
Alanine	A	Ala
Arginine	R	Arg
Asparagine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamine	Q	Gln
Glutamic acid	E	Glu
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val
β -Alanine		bAla
2,3-Diaminopropionic acid		Dpr
α -Aminoisobutyric acid		Aib
N-Methylglycine (sarcosine)		MeGly
Ornithine		Orn
Citrulline		Cit
t-Butylalanine		t-BuA
t-Butylglycine		t-BuG
N-methylisoleucine		Melle
Phenylglycine		Phg
Cyclohexylalanine		Cha
Norleucine		Nle
Naphthylalanine		Nal
Pyridylalanine		
3-Benzothienyl alanine		
4-Chlorophenylalanine		Phe(4-Cl)
2-Fluorophenylalanine		Phe(2-F)
3-Fluorophenylalanine		Phe(3-F)
4-Fluorophenylalanine		Phe(4-F)
Penicillamine		Pen
1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acid		Tic
β -2-thienylalanine		Thi
Methionine sulfoxide		MSO
Homoarginine		hArg
N-acetyl lysine		AcLys
2,4-Diamino butyric acid		Dbu
P-Aminophenylalanine		Phe(pNH ₂)
N-methylvaline		MeVal
Homocysteine		hCys
Homoserine		hSer

TABLE 2-continued

Amino Acid	One-Letter Symbol	Abbreviation
E-Amino hexanoic acid		Aha
δ -Amino valeric acid		Ava
2,3-Diaminobutyric acid		Dab

[0069] Peptides that are encompassed within the scope of the invention can have one or more amino acids substituted with an amino acid of similar or different chemical and/or physical properties, so long as these variant and derivative peptides retain the ability to bind to the biomolecule or tissue.

[0070] When generating a variant or derivative peptide, amino acids that reside within similar classes or subclasses can be substituted for amino acids in a reference peptide or amino acid sequence. As known to one of skill in the art, amino acids can be placed into three main classes: hydrophilic amino acids, hydrophobic amino acids and cysteine-like amino acids, depending primarily on the characteristics of the amino acid side chain. These main classes may be further divided into subclasses.

[0071] Hydrophilic amino acids include amino acids having acidic, basic or polar side chains and hydrophobic amino acids include amino acids having aromatic or apolar side chains. Apolar amino acids may be further subdivided to include, among others, aliphatic amino acids. The definitions of the classes of amino acids as used herein are as follows:

[0072] “Hydrophobic Amino Acid” refers to an amino acid having a side chain that is uncharged at physiological pH and that is repelled by aqueous solution. Examples of genetically encoded hydrophobic amino acids include Ile, Leu and Val. Examples of non-genetically encoded hydrophobic amino acids include t-BuA.

[0073] “Aromatic Amino Acid” refers to a hydrophobic amino acid having a side chain containing at least one ring having a conjugated π -electron system (aromatic group). The aromatic group may be further substituted with substituent groups such as alkyl, alkenyl, alkynyl, hydroxyl, sulfonyl, nitro and amino groups, as well as others. Examples of genetically encoded aromatic amino acids include phenylalanine, tyrosine and tryptophan. Commonly encountered non-genetically encoded aromatic amino acids include phenylglycine, 2-naphthylalanine, β -2-thienylalanine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine and 4-fluorophenylalanine.

[0074] “Apolar Amino Acid” refers to a hydrophobic amino acid having a side chain that is generally uncharged at physiological pH and that is not polar. Examples of genetically encoded apolar amino acids include glycine, proline and methionine. Examples of non-encoded apolar amino acids include Cha.

[0075] “Aliphatic Amino Acid” refers to an apolar amino acid having a saturated or unsaturated straight chain, branched or cyclic hydrocarbon side chain. Examples of genetically encoded aliphatic amino acids include Ala, Leu, Val and Ile. Examples of non-encoded aliphatic amino acids include Nle.

[0076] “Hydrophilic Amino Acid” refers to an amino acid having a side chain that is attracted by aqueous solution. Examples of genetically encoded hydrophilic amino acids include Ser and Lys. Examples of non-encoded hydrophilic amino acids include Cit and hCys.

[0077] “Acidic Amino Acid” refers to a hydrophilic amino acid having a side chain pK value of less than 7. Acidic amino acids typically have negatively charged side chains at physiological pH due to loss of a hydrogen ion. Examples of genetically encoded acidic amino acids include aspartic acid (aspartate) and glutamic acid (glutamate).

[0078] “Basic Amino Acid” refers to a hydrophilic amino acid having a side chain pK value of greater than 7. Basic amino acids typically have positively charged side chains at physiological pH due to association with hydronium ion. Examples of genetically encoded basic amino acids include arginine, lysine and histidine. Examples of non-genetically encoded basic amino acids include the non-cyclic amino acids ornithine, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid and homoarginine.

[0079] “Polar Amino Acid” refers to a hydrophilic amino acid having a side chain that is uncharged at physiological pH, but where a bond in the side chain has a pair of electrons that are held more closely by one of the atoms involved in the bond. Examples of genetically encoded polar amino acids include asparagine and glutamine. Examples of non-genetically encoded polar amino acids include citrulline, N-acetyl lysine and methionine sulfoxide.

[0080] “Cysteine-Like Amino Acid” refers to an amino acid having a side chain capable of forming a covalent linkage with a side chain of another amino acid residue, such as a disulfide linkage. Typically, cysteine-like amino acids generally have a side chain containing at least one thiol (SH) group. An example of a genetically encoded cysteine-like amino acid is cysteine. Examples of non-genetically encoded cysteine-like amino acids include homocysteine and penicillamine.

[0081] As will be appreciated by those having skill in the art, the above classifications are not absolute. Several amino acids exhibit more than one characteristic property, and can therefore be included in more than one category. For example, tyrosine has both an aromatic ring and a polar hydroxyl group. Thus, tyrosine has dual properties and can be included in both the aromatic and polar categories. Similarly, in addition to being able to form disulfide linkages, cysteine also has an apolar character. Thus, while not strictly classified as a hydrophobic or an apolar amino acid, in many instances cysteine can be used to confer hydrophobicity to a peptide.

[0082] Certain commonly encountered amino acids that are not genetically encoded and that can be present, or substituted for an amino acid, in the peptides, peptide variants and peptide derivatives of the invention include, but are not limited to, β -alanine (b-Ala) and other omega-amino acids such as 3-aminopropionic acid (Dap), 2,3-diaminopropionic acid (Dpr), 4-aminobutyric acid and so forth; α -aminoisobutyric acid (Aib); ϵ -aminohexanoic acid (Aha); δ -aminovaleric acid (Ava); N-methylglycine (MeGly); ornithine (Orn); citrulline (Cit); t-butylalanine (t-BuA); t-butylglycine (t-BuG); N-methylisoleucine (Melle); phenylglycine (Phg); cyclohexylalanine (Cha); norleucine (Nle); 2-naph-

thylalanine (2-Nal); 4-chlorophenylalanine (Phe(4-Cl)); 2-fluorophenylalanine (Phe(2-F)); 3-fluorophenylalanine (Phe(3-F)); 4-fluorophenylalanine (Phe(4-F)); penicillamine (Pen); 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic); β -2-thienylalanine (Thi); methionine sulfoxide (MSO); homoarginine (hArg); N-acetyl lysine (AcLys); 2,3-diaminobutyric acid (Dab); 2,3-diaminobutyric acid (Dbu); p-aminophenylalanine (Phe(pNH₂)); N-methyl valine (MeVal); homocysteine (hCys) and homoserine (hSer). These amino acids also fall into the categories defined above.

[0083] The classifications of the above-described genetically encoded and non-encoded amino acids are summarized in Table 3, below. It is to be understood that Table 3 is for illustrative purposes only and does not purport to be an exhaustive list of amino acid residues that may comprise the peptides, variants and derivatives described herein. Other amino acid residues that are useful for making the peptides, peptide variants and peptide derivatives described herein can be found, e.g., in Fasman, 1989, CRC Practical Handbook of Biochemistry and Molecular Biology, CRC Press, Inc., and the references cited therein. Amino acids not specifically mentioned herein can be conveniently classified into the above-described categories on the basis of known behavior and/or their characteristic chemical and/or physical properties as compared with amino acids specifically identified.

TABLE 3

Classification	Genetically Encoded	Genetically Non-Encoded
<u>Hydrophobia</u>		
Aromatic	F, Y, W	Phg, Nal, Thi, Tic, Phe(4-Cl), Phe(2-F), Phe(3-F), Phe(4-F), Pyridyl Ala, Benzothenyl Ala
Apolar	M, G, P	Cha
Aliphatic	A, V, L, I	t-BuA, t-BuG, Melle, Nle, MeVal, Cha, bAla, MeGly, Aib
<u>Hydrophilic</u>		
Acidic	D, E	
Basic	H, K, R	Dpr, Orn, hArg, Phe(p-NH ₂), DBU, A ₂ BU
Polar	Q, N, S, T, Y	Cit, AcLys, MSO, hSer
Cysteine-Like	C	Pen, hCys, β -methyl-Cys

Peptides of the invention can have any amino acid substituted by any similarly classified amino acid to create a variant or derivative peptide, so long as the peptide variant or derivative retains an ability to bind to the biomolecule or tissue to which the unaltered or reference peptide bound.

Peptides Conjugated to Reporter Molecules

[0084] According to the invention, peptides isolated or identified as described herein can be attached or conjugated to any known reporter molecule or other label or signaling agent. While the peptides of the invention have utility for identifying the location of, and for imaging, atherosclerotic lesions, the invention is not limited to imaging just atherosclerotic lesions. The peptides of the invention can be used to detect, identify, locate and/or image any target molecule to which a peptide of the invention can bind, either in vitro and in vivo.

[0085] In one embodiment, the peptides and methods provided herein can be used to diagnose the location, extent, and pathologic composition of atherosclerotic lesions anywhere within the body of a mammal. For example, detection of a peptide-conjugate capable of binding to atherosclerotic lesion can provide information regarding the location, shape, extent and pattern of expression of a target biomolecule in relation to the lesion. Peptides isolated as being able to bind to atherosclerotic lesions of different stages can be used to diagnose the staging or severity of the lesions and potential risk of thrombosis. Any reporter molecule, label or signaling agent known to one of skill in the art can be attached to the peptides of the invention as well as any and all agents used as diagnostic tools or to enhance diagnostic tools. Such peptide-conjugates can then be used in vivo or in vitro to image, locate or otherwise detect the biomolecule or tissue to which the peptide binds.

[0086] The peptide-conjugates of the invention can serve as a signal enhancing agent for medical diagnostic imaging, for example, for MRI, ultrasound, infrared and other imaging procedures. Peptide conjugates used for MRI, and radio-diagnostic imaging can, for example, have one or more amino acid side chains or linkers that are attached to chelating moieties, contrast agents or liposomes, such as unilamellar gadolinium-liposomes, manganese-liposomes, and iron-DTPA-stearate-liposomes.

[0087] One of skill in the art can conjugate such reporter molecules, labels and signaling agents to the present peptides using known techniques. For example, the followings references provide guidance on conjugation and use of such reporter molecules, labels and signaling agents in various diagnostic imaging procedures.

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[0089] Bartolozzi, C., F. Donati, et al. (2000). "MnDPDP-enhanced MRI vs dual-phase spiral CT in the detection of hepatocellular carcinoma in cirrhosis." *Eur Radiol* 10(11): 1697-702.

[0090] Bockhorst, K., M. Hoehn-Berlage, et al. (1993). "NMR-contrast enhancement of experimental brain tumors with MnTPPS: qualitative evaluation by in vivo relaxometry." *Magn Reson Imaging* 11(5): 655-63.

[0091] Colet, J. M., L. Vander Elst, et al. (1998). "Dynamic evaluation of the hepatic uptake and clearance of manganese-based MRI contrast agents: a ³¹P NMR study on the isolated and perfused rat liver." *J Magn Reson Imaging* 8(3): 663-9.

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[0093] Fiel, R., E. Mark, et al. (1993). "Tumor-selective contrast enhancing agent, Mn(III)meso-[tri(4-sulfonatophenyl)phenyl]porphine (MnTPPS3)." *Magn Reson Imaging* 11(7): 1079-81.

[0094] Kim, S. W. and T. Kozuka (1990). "[Mn-TPPS4; a potential MRI contrast agent for localizing the normal aortic wall in rabbits]." *Nippon Igaku Hoshasen Gakkai Zasshi* 50(2): 192-94.

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- [0096] Marchal, G., X. Zhang, et al. (1993). "Comparison between Gd-DTPA, Gd-EOB-DTPA, and Mn-DPDP in induced HCC in rats: a correlation study of MR imaging, microangiography, and histology." *Magn Reson Imaging* 11(5): 665-74.
- [0097] Maurer, J., A. Strauss, et al. (2000). "Contrast-enhanced high resolution magnetic resonance imaging of pigmented malignant melanoma using Mn-TPPS4 and Gd-DTPA: experimental results." *Melanoma Res* 10(1): 40-6.
- [0098] Maurer, J., A. Strauss, et al. (1999). "[Mn-TPPS4 in the diagnosis of malignant skin tumors. In vivo studies with high resolution magnetic resonance tomography in melanotic melanoma]." *Radiologe* 39(5): 422-7.
- [0099] Navon, G., R. Panigel, et al. (1986). "Liposomes containing paramagnetic macromolecules as MRI contrast agents." *Magn Reson Med* 3(6): 876-80.
- [0100] Ni, Y., G. Marchal, et al. (1994). "Prolonged positive contrast enhancement with Gd-EOB-DTPA in experimental liver tumors: potential value in tissue characterization." *J Magn Reson Imaging* 4(3): 355-63.
- [0101] Plowchalk, D. R., J. P. Jordan, et al. (1987). "Effects of manganese (Mn++) and iron (Fe+++) on magnetic resonance imaging (MRI) characteristics of human placenta and amniotic fluid." *Physiol Chem Phys Med NMR* 19(1): 35-41.
- [0102] Rofsky, N. M. and J. C. Weinreb (1992). "Manganese (II) N,N'-dipyridoxylethylene-diamine-N,N'-diacetate 5,5'-bis(phosphate): clinical experience with a new contrast agent." *Magn Reson Q* 8(3): 156-68.
- [0103] Runge, V. M. (2000). "Safety of approved MR contrast media for intravenous injection." *J Magn Reson Imaging* 12(2): 205-13.
- [0104] Saeed, M., S. Wagner, et al. (1989). "Occlusive and reperfused myocardial infarcts: differentiation with Mn-DPDP—enhanced MR imaging." *Radiology* 172(1): 59-64.
- [0105] Schmiedl, U. P., J. A. Nelson, et al. (1992). "Hepatic contrast-enhancing properties of manganese-mesoporphyrin and manganese-TPPS4. A comparative magnetic resonance imaging study in rats." *Invest Radiol* 27(7): 536-42.
- [0106] Schwendener, R. A., R. Wuthrich, et al. (1990). "A pharmacokinetic and MRI study of unilamellar gadolinium-, manganese-, and iron-DTPA-stearate liposomes as organ-specific contrast agents." *Invest Radiol* 25(8): 922-32.
- [0107] Wang, C. (1998). "Mangafodipir trisodium (Mn-DPDP)-enhanced magnetic resonance imaging of the liver and pancreas." *Acta Radiol Suppl* 415: 1-31.
- [0108] Wilmes, L. J., M. Hoehn-Berlage, et al. (1993). "In vivo relaxometry of three brain tumors in the rat: effect of Mn-TPPS, a tumor-selective contrast agent." *J Magn Reson Imaging* 3(1): 5-12.
- [0109] Wolf, G. L., K. R. Burnett, et al. (1985). "Contrast agents for magnetic resonance imaging." *Magn Reson Annu*: 231-66.
- [0110] Wytenbach, R., M. Saeed, et al. (1999). "Detection of acute myocardial ischemia using first-pass dynamics of MnDPDP on inversion recovery echoplanar imaging." *J Magn Reson Imaging* 9(2): 209-14.
- [0111] Yamamoto, T., A. Matsumura, et al. (1998). "Manganese-metalloporphyrin (ATN-10) as a tumor-localizing agent: magnetic resonance imaging and inductively coupled plasma atomic emission spectroscopy study with experimental brain tumors." *Neurosurgery* 42(6): 1332-7; discussion 1337-8.
- [0112] The present peptide-conjugates can also be used for ultrasound imaging. For example, the peptide can be grafted to the surface of a liposome that contains gas through conjugation of the peptide to a PEGylated lipid. The microbubbles so formed serve as signal enhancing agents for the ultrasound detection and imaging procedure. Such liposomes are described in U.S. Pat. No. 6,139,819 to Unger et al.
- [0113] Useful chelating moieties tightly bind metal ions such as technetium-99 m and indium-111. One of skill in the art can employ known procedures to make such technetium-99 m and indium-111 labeled peptides for diagnostic imaging. See, for example, U.S. Pat. No. 6,107,459 to Dean. Peptide conjugates with radionuclides are also useful for therapy, including radiotherapy.
- [0114] The peptides of the invention can also be conjugated with any available dye or fluorescent moiety or intermediate such as biotin. Such peptide-dye conjugates can, for example, be used with infrared spectroscopy to detect and locate the biomolecules or tissues to which the peptide can bind.
- [0115] In one embodiment, the peptide-conjugate is targeted to the luminal surface of atherosclerotic lesions. When coupled with a reporter molecule, the peptide-conjugate renders the surface of the atherosclerotic lesions visible using different appropriate detection methods. Lipid laden plaques that are soft and not fibrous tend to have subtle changes in the lesion surface contour under flow conditions, which are indicative of the characteristics of the plaque. These type of plaques are prone to rupture and initiation of a series of events leading the thrombotic occlusion of the affected artery. Such plaques are associated with unstable angina and sudden death; they are likely to rupture and to produce thrombosis and/or unstable angina and thereby myocardial infarction or subinfarctive myocardial injury. Currently, no markers are known that can uniquely identify these types of susceptible plaques. Zena and Michael A. Wiener, *Clinical imaging of the high-risk or vulnerable atherosclerotic plaque*. (Aug. 17, 2001) CIRCULATION RESEARCH 89(4):305-16. However, these medical conditions can be diagnosed and treated by visualizing the surface of the atherosclerotic lesion using the present peptide-conjugates and then by targeting those lesions with a therapeutic agent conjugated to a peptide of the invention that uniquely associates or binds to those susceptible lesions. Alternatively, conventional treatments may be employed (e.g. stent insertion, angioplasty, etc.) after the susceptible plaques are identified.
- Therapeutic Agents
- [0116] The invention also contemplates conjugating peptides to any therapeutic agent available to one of skill in the

art. In the present context “a therapeutic agent” is also intended to comprise active metabolites and prodrugs thereof. An active “metabolite” is an active derivative of a therapeutic agent produced when the therapeutic agent is metabolised. A “prodrug” is a compound that is either metabolised to a therapeutic agent or is metabolised to an active metabolite(s) of a therapeutic agent. This invention can be used to administer therapeutic agents such as small molecular weight compounds, radionuclides, drugs, enzymes, peptides and/or proteins with biological activity, nucleic acids or genes that encode therapeutic polypeptides, expression vectors or other nucleic acid constructs, for example, naked plasmid DNAs, any vector carrying one or more genes, any sense or antisense RNA, any ribozyme, or any antibody.

[0117] For example, the peptides of the invention can be used to deliver fusion proteins or fibrinolytic agents. Such therapeutic agents include, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), anti-inflammatory agents, metalloproteinase inhibitors, nematode-extracted anticoagulant proteins (NAPs) and the like. Liposomes can be used to facilitate delivery of such agents, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), anti-inflammatory agents, metalloproteinase inhibitors, nematode-extracted anticoagulant proteins (NAPs) and the like.

[0118] The peptides of the invention can be linked to such proteins or polypeptides. Upon administration, these therapeutic agents will become localized at the site of atherosclerotic lesions and will help control, diminish or otherwise facilitate improved arterial blood flow in the region of the atherosclerotic lesion. The peptides of the invention can also be used to deliver nanoparticles, such as vectors for gene therapies (in a manner similar to the phage particles used for isolation of the peptides), as well as liposomes containing therapeutic agents like those listed herein.

[0119] Examples of therapeutic agents that can be linked to the peptides of the invention include the following:

[0120] 1) Agents that and modulate lipid levels (for example, HMG-CoA reductase inhibitors, thymimetics, fibrates, agonists of peroxisome proliferator-activated receptors (PPAR) (including PPAR-alpha, PPAR-gamma and/or PPAR-delta).

[0121] 2) Agents that control and modulate oxidative processes such as modifiers of reactive oxygen species or treatments that modify the production and/or activity of modified lipoproteins;

[0122] 3) Agents that control and modulate insulin resistance and/or activity or glucose metabolism or activity including, but not limited to, agonists of PPAR-alpha, PPAR-gamma and/or PPAR-delta, modifiers of DPP-IV, and modifiers of glucocorticoid receptors;

[0123] 4) Agents that control and modulate expression of receptors or adhesion molecules or integrins on endothelial cells or smooth muscle cells in any vascular location

[0124] 5) Agents that control and modulate the activity of endothelial cells or smooth muscle cells in any vascular location;

[0125] 6) Agents that control and modulate inflammation associated receptors including, but not limited to chemokine receptors, RAGE, toll-like receptors, angiotensin receptors, TGF receptors, interleukin receptors, TNF receptors, C-reactive protein receptors, and other receptors involved in inflammatory signaling pathways including the activation of NF-kb.

[0126] 7) Agents that control and modulate proliferation, apoptosis or necrosis of endothelial cells, vascular smooth muscle or lymphocytes, monocytes, and neutrophils adhering to or within the vessel;

[0127] 8) Agents that control and modulate production, degradation, or cross-linking of any extracellular matrix proteins including, but not limited to, collagen, elastin, and proteoglycans;

[0128] 9) Agents that control and modulate activation, secretion or lipid loading of any cell type within mammalian vessels;

[0129] 10) Agents that control and modulate the activation, proliferation or any other modification of dendritic cells within mammalian vessels; and

[0130] 11) Agents that control and modulate the activation, adhesion, or other processes that modify platelet events at the level of the vessel wall.

[0131] Examples of these types of agents and procedures for using these physiological agents are described in more detail below.

[0132] In one embodiment, the therapeutic agent is a pre-selected nucleic acid that encodes a protein whose activity can benefit a mammal suffering from any atherosclerotic lesion. The gene therapy agent can, for example, reduce the size of a lesion, prevent platelet interaction with the lesion, reduce or prevent the growth of smooth muscle cells or otherwise stabilize or beneficially interact with the atherosclerotic lesion. In another embodiment, the therapeutic agent is a pre-selected nucleic acid that can generate an antisense RNA useful for reducing the expression of a deleterious protein at the site of the atherosclerotic lesion. Such a therapeutic nucleic acids can be directly attached to a peptide of the invention, or it can be present in a phage particle, liposome or other transformation vector available to one of skill in the art.

[0133] For example, in one embodiment a peptide of the invention (e.g. CAPGPSKSC, SEQ ID NO:4) is attached to a pre-selected therapeutic nucleic acid, phage, liposome or other molecule to form a peptide-therapeutic agent. In one embodiment, a nucleic acid encoding a polypeptide therapeutic agent is directly administered in vivo, where it is targeted to the site of atherosclerotic lesions via linkage to a peptide of the invention (e.g. CAPGPSKSC, SEQ ID NO:4). A cell specific peptide of the invention can also be used to deliver “naked” DNA, for example, by use of controlled pressure-mediated delivery of the naked DNA using methods available in the art. See, e.g., von der Leyen, Braun-Dullaeus, et al, A pressure-mediated nonviral method for efficient arterial gene and oligonucleotide transfer, Hum. Gene Ther. 1999. 10:2355-64. Such methods provide safe and efficient arterial transfer to cells at the site of atherosclerotic lesions for nucleic acids, genes and oligonucleotides.

[0134] In another embodiment, a nucleic acid encoding a peptide of the invention is joined with another nucleic acid that encodes a biologically active therapeutic agent to form a hybrid or recombinant nucleic acid. The hybrid or recombinant nucleic acid is placed within an appropriate vector to generate a gene therapy construct that may be expressed in a cell type of interest. The peptide-therapeutic agent and/or the gene therapy construct can be delivered to the tissue of interest by attachment to a peptide of the invention followed by in vivo administration to a selected mammal. The peptide of the invention guides the agent or construct to the intended biomolecule or tissue. For example, if the CAPGPSKSC (SEQ ID NO:4) peptide is attached to such agents and therapeutic constructs, the CAPGPSKSC (SEQ ID NO:4) peptide will home to and bind an 82 kilodalton and/or a 120 kilodalton target protein that is present in atherosclerotic lesions of a mammal. The 82 kilodalton target protein may be a membrane protein. Hence, the CAPGPSKSC (SEQ ID NO:4) peptide can deliver the therapeutic nucleic acid, phage, liposome or other vector or therapeutic agent to membranes of cells within the atherosclerotic lesion.

[0135] Nucleic acids that may be used with the peptides of the invention include the following.

[0136] 1. Genes or nucleic acids that encode proteins or antisense RNAs that inhibit inflammatory events at the sites of atherosclerosis lesion progression or at sites of vulnerable atherosclerotic lesions. Such genes or nucleic acids include the dominant-negative form or mutants or decoys of various chemokine genes (e.g. any of the CCR, CXCR, or CX3CR chemokines including but not limited to RANTES, CCR1, 2,3,4,5,6,7,8,9,10; CXCR2, CXCR5, CX3CR1) or soluble forms of the receptors for such chemokines. Likewise, dominant-negative forms or mutant genes or decoys for soluble forms of encoding toll-like receptors (e.g. TLR-1, TLR-2, TLR-3, TLR-4 or TLR-5), angiotensin I or II receptors, interleukin receptors, integrins such as I-CAM, V-CAM, E-selectin, P-selectin, LFA1, alpha(v)beta(3) or any other receptor or molecule that stimulates a signalling cascade involved in activation of NFkappaB, inflammation or proliferation, such as, but not limited to CD40, CD40L, GRO-alpha, Rho-kinase, MCP-1, Il-6, Il-8, leukotriene B4, or leukotactin-1.

[0137] 2. Genes or nucleic acids that encode proteins or antisense RNAs that inhibit foam cell formation and thus retard progression and/or stimulate regression of atherosclerotic lesions. Such genes or nucleic acids can, for example, encode secreted "decoys" or mutants of macrophage scavenger receptors MSR (sMSR) (in particular, one containing an extracellular portion of the human MSR type AI), apoE, or mutants or decoys that would block activation of receptors including but not limited to platelet factor 4, Lox-1, Lox-2, Lox-3, leukotriene B4, lipoxygenases such as, but not limited to LO-12 or LO-15. In addition, other antisense nucleic acids that could be targeted to the site of atherosclerotic lesions via incorporation of a peptide of the invention include E2F decoy, NF-kappa B decoy, and other decoys.

[0138] 3. Genes or nucleic acids that encode proteins or antisense RNAs that enhance vasodilation and/or stabilize arterial vessel and/or prevent vascular spasm to prevent myocardial infarction or stroke. Such genes or nucleic acids include: heme oxygenase-1 (HO-1), eNOS, iNOS, superoxide dismutases, estrogen receptors or soluble or mutated forms of estrogen receptors.

[0139] 4. Genes or nucleic acids that encode proteins or antisense RNAs that inhibit local thrombosis, for example, a tissue factor pathway inhibitor or tPA.

[0140] 5. Genes or nucleic acids that encode proteins or antisense RNAs that stabilize a plaque by promoting fibrous cap thickening and/or by healing the endothelial lining on top of such lesions. Examples include FGF, PDGF, TGFbeta, EGF, or HGF. Some genes or nucleic acids that would inhibit apoptosis in the fibrous cap include bc12, crmA.

[0141] 6. Genes or nucleic acids that encode proteins or antisense RNAs that inhibit inflammation such as NFkB decoys, dominant-negative Rho-kinase, p57Kip2, IL-18 binding protein, IL-10, mutants of MCP-1

[0142] 7. Genes or nucleic acids that encode proteins or antisense RNAs that inhibit cell proliferation such as p57Kip2, cyclin dependent kinase inhibitors, kallikrein, p53 and the like.

[0143] 8. Genes or nucleic acids that encode proteins or antisense RNAs that improve vascular dilation such as eNOS, iNOS, superoxide dismutases, estrogen receptors and the like.

[0144] 9. Genes or nucleic acids that encode proteins or antisense RNAs that decrease matrix degradation such as tissue inhibitors of matrix metalloproteinases (TIMPs) including but not limited to TIMP1,2,3,4,5,6,7

[0145] 10. Genes or nucleic acids that encode proteins or antisense RNAs that have anti-angiogenesis and/or growth factor/cytokine inhibitory activities. Examples include VEGF/VEGFR antagonists (sFlt-1, sFlk, sNRP1), Angiopoietin/Tie antagonists (sTie-2), anti-chemokines (IP-10, PF-4, Gro-beta, IFN-gamma (Mig)), FGF/FGFR antagonists (sFGFR), inhibitors of PDGF, TGFbeta, IGF-1, various fragments of extracellular matrix proteins (such as Angiostatin, Endostatin, Kininostatin, Fibrinogen-E fragment, Thrombospondin, Tumstatin, Canstatin, Restin) Ephrin/Eph antagonists (sEphB4, sephrinB2), vasostatin, PEDF, Prolactin fragment, proliferin-related protein, TrpRS fragments, METH-1 and METH-2.

[0146] The peptides of the invention can also be linked or incorporated into antisense nucleic acids or oligonucleotides that can inhibit or stimulate synthesis of target genes and nucleic acids, for example, those listed herein.

[0147] A preselected nucleic acid can encode an antisense RNA as the therapeutic agent. Such an antisense RNA is typically a "sense" DNA sequence cloned into an expression cassette in the opposite orientation relative to its normal orientation (i.e., 3' to 5' rather than 5' to 3'). When operably linked to a promoter in the expression cassette in such an opposite orientation, an RNA that is complementary to the natural mRNA encoded by the nucleic acid is synthesized.

[0148] Double-stranded RNA (dsRNA) can trigger silencing of homologous gene expression by a mechanism termed RNAi (for RNA-mediated interference) (Fire, A., Xu, S., Montgomery, M. K., Kostas, S. A., Driver, S. E. & Mello, C. C. (1998) *Nature (London)* 391, 806-811). RNAi is an evolutionarily conserved phenomenon and a multistep process that involves generation of active small interfering RNA (siRNA) in vivo through the action of an RNase III endonuclease, Dicer. The resulting 21- to 23-nt siRNA mediates degradation of the complementary homologous

RNA (Bernstein, E., Denli, A. M. & Hannon, G. J. (2001) *RNA* 7, 1509-1521; Sharp, P. A. (2001) *Genes Dev.* 15, 485-490). Such RNAi technology could be employed with the current invention by linking or otherwise incorporating a peptide of the invention with the siRNAs. Hence, the peptides of the invention can be used to block expression of a specific gene by employing the RNAi. RNAs of interest whose expression can be blocked include those that encode the same target proteins, genes, RNA and DNA described herein.

[0149] Targeted delivery of a peptide of the invention that results in delivery of a polynucleotide or gene or ribozyme or growth factor to atherosclerotic plaque(s) can enhance endothelial coverage and healing at the site of atherosclerosis, especially in plaques that are vulnerable to rupturing and to producing thrombosis, unstable angina, myocardial infarction or subinfarctive myocardial injury. Other areas that could benefit from such targeted delivery to heal endothelium include the sites of vascular interventions such as angioplasty or stenting. Polynucleotides, DNA, peptides, growth factors (or agents that stimulate secretion of growth factors) that may be delivered to such sites would include, but not be limited to: VEGF (e.g. all forms of vascular endothelial growth factor including but not limited to VEGF121 and VEGF165), Fibroblast Growth Factors (e.g. FGF-1, 2), hepatocyte growth factor, placental growth factors (PIGFs), platelet derived endothelial cell growth factors, and TGF-beta.

[0150] Preselected nucleic acids useful for therapy can be placed in expression cassettes and/or expression vectors. To prepare expression cassettes for transformation, the nucleic acid encoding a therapeutic agent and/or peptide of the invention may be circular or linear, double-stranded or single-stranded. Generally, a vector is used to facilitate delivery and expression of an expression cassette or nucleic acid.

[0151] A peptide of the invention can be incorporated into any vector available to one of skill in the art, along with a nucleic acid that encodes a useful therapeutic agent. Such vectors include viral (adenovirus, retrovirus, lentivirus or other viruses) vectors or synthetic vectors (such as but not limited to liposomes, microparticles or nanoparticles) to allow improved delivery of genes, ribozymes, antisense oligonucleotides, or DNA to atherosclerotic lesions as well as to allow improved endothelial cell transduction with these genes, ribozymes, antisense or naked DNA. In addition, non-vector mediated targeted delivery of oligonucleotides could be achieved by linking a peptide of the invention onto or within an oligonucleotide or other nucleic acid.

[0152] A number of vector systems are known for the introduction of foreign or native genes into mammalian cells. These include SV40 virus (Okayama et al., 1985); bovine papilloma virus (DiMaio et al., 1982); adenovirus (Morin et al., 1987; Dai et al., 1995; Yang et al., 1996; Tripathy et al., 1996; Quantin et al., 1992; Rosenfeld et al., 1991; Wagner, 1992; Curiel et al., 1992; Curiel, 1991; LeGal LaSalle et al., 1993; Kass-Eisler et al., 1993); adeno-associated virus (Muzyczka, 1994; Xiao et al., 1996); herpes simplex virus (Geller et al., 1988; Huard et al., 1995; U.S. Pat. No. 5,501,979); lentivirus (Douglas, et al., Hum Gene Ther. 12(4):401-413 (2001), Miyoshi, et al., Virol. 72:8150-8157 (1999), Garvey et al. Virology, 175:391-409, 1990,

Berkowitz et al. J. Virol. 7(7):3371-3382 (2001), WO 01/44458, U.S. patent application Ser. No. 09/734,836, U.S. Pat. Nos. 6,277,633 and 5,380,830. The targeting peptides can be used in any mammalian expression vector to target the expression system to the appropriate target endothelial cells. See, for example, Wu et al. (1991); Wu and Wu (1988); Wu et al. (1989); Zenke et al. (1990); and Wagner et al. (1990). Grifman et al. (2001) describes the incorporation of tumor-targeting peptides into recombinant AAV capsids. For descriptive purposes only, this embodiment will be described with reference to an adenoviral vector, a preferred aspect of this embodiment. However, it will be understood that the embodiment is applicable to any of the previously mentioned vector systems and others known in the art.

[0153] Any such vector to which a peptide of the invention has been linked or within which such a peptide is encoded, can also contain an inducible promoter operably linked to a coding region for the peptide or a polypeptide therapeutic agent. Such a promoter permits controllable expression of the nucleic acid through an appropriate inducer of transcription.

[0154] A vector can be in the form of chimeric DNA that contains the coding region of the selected nucleic acid flanked by control sequences that promote the expression of the nucleic acid within target cells. As used herein, "chimeric" means that a vector comprises DNA from at least two different species, or comprises DNA from the same species, which is linked or associated in a manner that does not occur in the "native" or wild type of the species.

[0155] Aside from preselected nucleic acid that encodes a beneficial protein, RNA or antisense RNA, a portion of the preselected nucleic acid may be serve a regulatory or a structural function. For example, the preselected nucleic acid may itself comprise a promoter that is active in the mammal, particularly in the cells present in the atherosclerotic lesions of the mammal. Alternatively, a promoter that is present within the vector or the genome of the mammal can be used. Many promoter elements well known to the art may be employed in the practice of the invention.

[0156] The term "control sequences" is defined to mean DNA sequences necessary for the expression of an operably linked coding region in a particular host organism. Control sequences that are suitable for eukaryotic cells include promoters, polyadenylation signals, and enhancers. Prokaryotic cells that are useful for designing, amplifying and maintaining nucleic acids for eukaryotic gene therapy, utilize control sequences such as promoters, and, optionally operator sequences and ribosome binding sites.

[0157] Other elements functional in eukaryotic host cells, such as introns, enhancers, polyadenylation sequences and the like, may also be a part of the preselected nucleic acid. Such elements may or may not be necessary for the function of the nucleic acid, but may provide improved expression of RNA from the nucleic acid by affecting transcription, stability of the mRNA, or the like. Such elements may be included in the nucleic acid or vector as desired by one of skill in the art to obtain the optimal performance of the transforming nucleic acid or vector in the cell.

[0158] "Operably linked" is defined to mean that the nucleic acids are placed in a functional relationship with another nucleic acid sequence. For example, control

sequences are operably linked to a nucleic acid encoding a beneficial protein; a promoter or enhancer is operably linked to a coding region if it affects the transcription of the coding region; or a ribosome binding site is operably linked to a coding region if it is positioned so as to facilitate translation. Generally, "operably linked" means that the nucleic acids being linked are contiguous and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is generally accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers can be used in accord with conventional practice.

[0159] The preselected nucleic acid to be introduced into target cells will generally also contain either a selectable marker gene or a reporter gene (or both) to facilitate identification and selection of transformed cells from the wider population of cells. Alternatively, the selectable marker may be carried on a separate nucleic acid and used in a co-transformation procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers are well known in the art and include, for example, antibiotic-resistance genes, such as neo, hpt, dhfr, and the like.

[0160] Reporter genes are used for identifying target cells and cells transformed by the vectors or therapeutic constructs of the invention. Reporter genes that encode for easily assayable proteins are well known in the art. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism or tissue and that encodes a protein whose expression is manifested by some easily detectable property, e.g., enzymatic activity or fluorescence. Preferred genes include the chloramphenicol acetyl transferase gene (cat) from Tn9 of *E. coli*, the beta-glucuronidase gene (gus) of the uidA locus of *E. coli*, the green fluorescence protein and the luciferase gene from firefly *Photinus pyralis*. Expression of the reporter gene is assayed at a suitable time after the vector or recombinant nucleic acid has been introduced into the mammal or recipient cells.

[0161] The general methods for constructing recombinant nucleic acids that can transform target cells are well known to those skilled in the art, and the same compositions and methods of construction may be utilized to produce nucleic acids and vectors useful herein. For example, J. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press (2d ed., 1989), provides suitable methods of construction.

[0162] The peptides of the invention can also be used to deliver pharmaceutical compounds (drugs) to sites of atherosclerotic lesions or to sites of revascularization procedures including stenting or access ports for dialysis. Such pharmaceutical compounds can be directly linked to the peptide. Alternatively, the peptide can be incorporated into a chemical composition containing the therapeutic agent or compound. In another embodiment, the peptide can be incorporated into an artificial carrier (e.g. a liposome or other microparticle) that contains the therapeutic agent or compound. Such drug therapies would include compounds regulate HMG-CoA reductase (e.g. statins), fibrates and other compounds effecting PPARs (e.g. PPAR alpha, gamma, and/or delta agonists), or thyromimetics.

[0163] HMG-CoA reductase inhibitors are also called β -hydroxy- β -methylglutaryl-coenzyme-A reductase inhibitors. These inhibitors are understood to be those active agents that may be used to lower the lipid levels including cholesterol, especially LDL-cholesterol, in blood. The class of HMG-Co-A reductase inhibitors comprises compounds having differing structural features. HMG-CoA reductase inhibitors suitable for use herein include, but are not limited to, pitavastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, cerivastatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, rosuvastatin, or lovastatin; or a pharmaceutically acceptable salt of pitavastatin, simvastatin, pravastatin, rivastatin, cerivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, rosuvastatin and lovastatin or, in each case, a pharmaceutically acceptable salt thereof. Information on such compounds is available to one of skill in the art, see for example, the information on atorvastatin (EP 680320), cerivastatin (EP 491226), fluvastatin (U.S. Pat. No. 5,354,772), pitavastatin (EP 304063), lovastatin (EP 22478), pravastatin (UK 2077264), rosuvastatin (ZD 4522 or S 4522) and simvastatin (EP 33538). Desirable HMG-Co-A reductase inhibitors are those agents that have been marketed, for example, fluvastatin, atorvastatin, pitavastatin or simvastatin or, in each case, a pharmaceutically acceptable salt thereof.

[0164] Fibrates are known to lower the levels of triglyceride-rich lipoproteins, such as VLDL, to raise HDL levels, and to have variable effects on LDL levels. The effects on VLDL levels may result primarily from an increase in lipoprotein lipase activity, especially in muscle. This leads to enhanced hydrolysis of VLDL triglyceride content and enhanced VLDL catabolism. These compounds are also reported to decrease hepatic VLDL triglyceride synthesis, possibly by inhibiting fatty acid synthesis and by promoting fatty acid oxidation as a result of peroxisomal proliferation.

[0165] Fibrates include fibric acid derivatives such as, for example, clofibrate, gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate. Fenofibrate is commercially available as Tricor™. Fenofibric acid, the active metabolite of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglycerides rich lipoprotein (i.e. VLDL). The recommended daily dose of fenofibrate is 67 mg, but this dosage may vary depending on the route of administration. For example, when linked to a peptide of the invention lower dosages of fenofibrate may be utilized, for example, because the peptide targets this therapeutic agent to the appropriate site.

[0166] Clofibrate is commercially available as Atromid-S™ capsules. Each capsule contains 500 mg of clofibrate. Clofibrate lowers elevated serum lipids by reducing the very low-density lipoprotein fraction that is rich in triglycerides and thereby reduces serum cholesterol. Clofibrate may also inhibit the hepatic release of lipoproteins (particularly VLDL) and potentiate the action of lipoprotein lipase. The recommended daily dose of clofibrate is 2 grams, administered in divided doses. However, this dosage may be modified as when clofibrate is linked to a peptide of the invention. In general, lower dosages of clofibrate may then be utilized.

[0167] Gemfibrozil is commercially available as Lopid™ tablets. Each tablet contains 600 mg of gemfibrozil. Gem-

fibrozil is a lipid regulating agent that decreases serum triglycerides and very low density lipoprotein cholesterol, and increases high density lipoprotein cholesterol. The recommended daily dose of gemfibrozil is 1200 mg, administered in two divided doses. However, this dosage may be modified as when gemfibrozil is linked to a peptide of the invention. In general, lower dosages of gemfibrozil may then be utilized.

[0168] Fibrate hypolipidemic agents can also be used as synthetic PPAR (peroxisome proliferator activated receptor) agonists. Fibrates include PPAR-alpha agonists that may also act as agonists for PPAR-gamma and/or PPAR-delta subtypes. Fibrates such as bezafibrate and fenofibrate exert hypolipidemic effects as PPAR α agonists by decreasing apolipoprotein C-III production (enhancing lipoprotein lipase activity) and increasing lipoprotein lipase (LPL) production in the liver (Lefebvre et al., *Arterioscler. Thromb. Vasc. Biol.* 1997; 17:1756). Moreover, in man but not in rodents, PPAR agonists increase levels of high-density lipoprotein cholesterol (HDL-C) by inducing apoA-I gene expression in the liver (Staels and Auwerx, *Atherosclerosis*. 1998; 137 Suppl: S19). PPAR α may also have a role in obesity. For example, PPAR α ligands lower body weight in rodents without any change in food intake (Guerre-Millo et al., *J. Biol. Chem.* 2000; 275:16638).

[0169] PPARs are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily (Djouadi et al., *J. Clin. Invest.* 1998; 102:1083, Kersten et al., *Nature* 2000; 405:421). These receptors function as heterodimeric complexes with the receptor for 9-cis retinoic acid (RXR). Activation of PPAR/RXR heterodimers occurs upon binding of the ligands, driving activation of specific PPAR-sensitive elements in the promoter region of target genes and leading to activation of gene expression (Kersten et al., *Nature* 2000; 405:421). The natural endogenous ligands shared by PPARs appear to be polyunsaturated and oxidized fatty acids. There are three subtypes of the PPARs: PPAR α , PPAR δ and PPAR γ .

[0170] PPAR α plays a key role in the control of lipid metabolism and is expressed primarily in tissues participating in fatty acid oxidation (e.g., liver, kidney, heart, and skeletal muscle). The natural ligands for this PPAR subtype include fatty acids and their acyl CoA derivatives (Issemann, *J. Mol. Endocrinol.* 1993; 11:37, Murakami et al., *Biochem. Biophys. Res. Comm.* 1999; 260:609). Activation of PPAR α results in the expression of genes encoding enzymes involved in the beta-oxidation of lipids. PPAR α activation also up-regulates enzymes involved in fatty acid uptake, mitochondrial beta-oxidation and ketone body synthesis as well as the induction of fatty acid transport proteins and acyl-CoA synthetase, responsible for cellular fatty acid esterification and entrapment. PPAR α up-regulates expression of liver and muscle carnitine palmitoyl transferase-1 (CPT-1) genes.

[0171] The importance of this nuclear hormone receptor in lipid homeostasis is supported by the observations that PPAR α knockout mice display hepatic and cardiac lipid accumulation (Djouadi et al., *J. Clin. Invest.* 1998; 102:1083) and late onset obesity (Costet et al., *J. Biol. Chem.* 1998; 273:29577). Furthermore, PPAR α may modulate inflammation, and has been implicated as a modulator of atherosclerosis and restenosis. PPAR α also may play a role

in the evolution of oxidative stress observed in aging (Devchand et al., *Nature* 1996; 384:39, Poynter and Daynes, *J. Biol. Chem.* 1998; 273:32833). PPAR α modulates cardiac energy metabolic shifts and has been implicated in the processes accompanying cardiac hypertrophy, heart failure and myocardial infarction (Barger et al., *Trends Cardiovasc. Med.* 2001; 10:238). In addition, PPAR α agonists are direct modulators of the vessel wall and thus might play a role in vascular diseases (Buchan et al., *Med. Res. Rev.* 2000; 20:350, Glass, *J. Endocrinol.* 2001; 169:461). PPAR α may also function to regulate fat homeostasis in the islet beta cell (Zhou et al., *Proc. Natl. Acad. Sci. U.S.A.* 1998; 95:8898).

[0172] While PPAR α promotes lipid oxidation, PPAR γ promotes lipid storage and consequently is expressed predominantly in adipocytes. PPAR γ activation drives adipogenesis in part through the formation of new adipocytes, which serve as lipid reservoirs (Tontonoz et al., *Cell* 1994; 79:1147, Lehmann et al., *J. Biol. Chem.* 1995; 270:12953). PPAR γ agonists induce expression of genes such as aP2, phosphoenol pyruvate carboxykinase (PEPCK), acyl-CoA synthetase (ACS), fatty acid binding protein (FABP) and lipoprotein lipase (LPL) (MacDougald and Lane, *Annu. Rev. Biochem.* 1995; 64:345-73:345, Robinson et al., *Biochem. Biophys. Res. Commun.* 1998; 244:671, Clarke, *Br. J. Nutr.* 2000; 83 Suppl 1:S59). The induction of LPL promotes fatty acid delivery to the adipocytes while FABP and ACS induction enhance fatty acid uptake and storage by the small new adipocytes. While PPAR γ is not expressed in the muscle, its activation increases skeletal muscle insulin sensitivity by a poorly characterized mechanism. Elevated muscle and β -cell lipid stores are correlated with muscle insulin resistance and β -cell secretory dysfunction (Zhou et al., *Metabolism* 1996; 45:981).

[0173] PPAR γ agonists may exert insulin-sensitizing effects by shifting lipid storage away from muscle, liver and β -cells, toward adipose tissue (Shimabukuro et al., *Proc. Natl. Acad. Sci. U.S.A.* 1998; 95:2498). PPAR γ agonists also inhibit muscle PDK4 leading to increased PDH activity and increased glucose utilization. In the liver, treatment with PPAR γ agonists inhibits PEPCK and G-6-Pase activities thereby decreasing gluconeogenesis, e.g., thiazolidinediones (TZDs), including troglitazone, rosiglitazone, and pioglitazone are synthetic PPAR γ ligands that exert antidiabetic effects by alleviating insulin resistance at the level of the muscle and liver. PPAR γ ligands also may play a role in vascular endothelial function by reducing the expression of endothelin-1 and thereby have a hypotensive effect (Satoh et al., *Biochem. Biophys. Res. Commun.* 1999; 254:757). It has been shown that two dominant negative mutations in PPAR γ were associated with severe hypertension in humans (Barroso et al., *Nature* 1999; 402:880). The anti-hypertensive effects of PPAR γ agonists have also been seen in animal models not associated with insulin resistance, suggesting the anti-hypertensive effects of PPAR γ agonists may be independent of their insulin sensitizing actions (Willson et al., *Annu. Rev. Biochem.* 2001; 70:341).

[0174] Like the other subtypes, PPAR δ receptor is also activated by fatty acids. PPAR δ subtype is widely expressed and plays a role in lipid metabolism (Leibowitz et al., *FEBS Letters* 2000; 473:333). In non-diabetic insulin resistant monkeys a specific PPAR δ ligand, GW501516, increased HDL-C (80%) and apoA-I (43%) and lowered triglyceride, LDL-C and insulin levels. GW501516 also promotes reverse

cholesterol transport via up-regulation of macrophage ABCA1 (Oliver et al., *Proc. Nat. Acad. Sci.* 2001; 98:5306).

[0175] PPAR α and PPAR γ ligands may also have an anti-atherosclerotic benefit through stimulation of macrophage ABCA1 expression and thereby promoting apoA1-mediated cholesterol efflux (Chinetti et al., *Nature Medicine* 2001; 7:53). Hence, the peptides of the invention may be linked to PPAR, PPAR agonists and/or to PPAR ligands and used to treat conditions such as dyslipidemia, hyperlipidemia, hypercholesterolemia, atherosclerosis, hypertriglyceridemia, heart failure, myocardial infarction, vascular diseases, cardiovascular diseases, and hypertension.

[0176] Compounds that are PPAR agonists include compounds such as those described in U.S. Pat. No. 6,008,239, WO 9727847, WO 9727857, WO 9728115, WO 9728137, WO 9728149, Hulin et al., *Current Pharm. Design* (1996) 2, pp. 85-102, and Willson et al. *J. Med. Chem.* 1996 vol. 39 pp. 665-669, hereby incorporated by reference. Non-glitazone type PPAR γ agonists include N-(2-benzoylphenyl)-L-tyrosine analogues, e.g. GI-262570, and JTT501. Preferred dual PPAR γ /PPAR α agonists include ω -[(oxoquinazolinylalkoxy)phenyl]alkanoates and analogs thereof, very especially the compound DRF-554158, described in WO 99/08501 and the compound NC-2100 described by Fukui in *Diabetes* 2000, 49(5), 759-767. Pharmaceutically acceptable salts and esters of PPAR-agonists are likewise included within the scope of this invention.

[0177] PPAR-alpha, PPAR-gamma, and PPAR-delta agonists may be identified according to an assay described in U.S. Pat. No. 6,008,239. PPAR agonists are also identified by the following assays.

[0178] Human PPAR-gamma 2, human PPAR-delta and human PPAR-alpha can be expressed as gst-fusion proteins in *E. coli*. Bacterial cells containing expression vectors encoding these fusion proteins can be propagated, expression of the proteins can be induced, and bacterial cells can be harvested by centrifugation. The pellet can be resuspended, cells disrupted in a French press and debris removed by centrifugation at 12,000xg. Recombinant human PPAR receptors can be further purified by affinity chromatography on glutathione sepharose. After application to the column, washing to remove non-specifically bound material, receptors can be eluted with glutathione. Glycerol (10%) can be added to stabilize the receptors and aliquots of the receptors can be stored at -80° C.

[0179] For binding to PPAR-gamma, an aliquot of receptor can be incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ l/100 mL β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/mL aprotinin, 2 μ g/mL leupeptin, 2 μ g/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 10 nM [^{3} H] AD5075 (21 Ci/mmol), $\pm$ test compound as described in Berger et al. (Novel peroxisome proliferator-activated receptor (PPAR-gamma) and PPAR-delta ligands produce distinct biological effects. *J. Biol. Chem.* (1999), 274: 6718-6725. Assays can be incubated for about 16 hr at 4° C., in a final volume of 150 μ L. Unbound ligand can be removed by incubation with 100 μ L dextran/gelatin-coated charcoal, on ice, for about 10 min. After centrifugation at 3000 rpm for 10 min at 4° C., 50 μ L of the supernatant fraction can be counted in a Topcount.

[0180] For binding to PPAR-delta, an aliquot of receptor can be incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ l/100 mL β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/mL aprotinin, 2 μ g/mL leupeptin, 2 μ g/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 2.5 nM [^{3} H]L-783483, (17 Ci/mmol), $\pm$ test compound as described in Berger et al (Novel peroxisome proliferator-activated receptor- γ (PPAR-gamma) and PPAR- δ (PPAR-delta) ligands produce distinct biological effects. 1999 *J Biol Chem* 274: 6718 6725). (L-783483 is 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxo)propylthio)-phenylacetic acid, Ex. 20 in WO 97128137). Assays can be incubated for about 16 hr at 4° C., in a final volume of 150 μ L. Unbound ligand can be removed by incubation with 100 μ L dextran/gelatin-coated charcoal, on ice, for about 10 min. After centrifugation at 3000 rpm for 10 min at 4° C., 50 μ L of the supernatant fraction can be counted in a Topcount.

[0181] For binding to PPAR- α , an aliquot of receptor can be incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ l/100 mL β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/mL aprotinin, 2 μ g/mL leupeptin, 2 μ g/mL benzamidine and 0.5 mM PMSF) containing 0.1% non-fat dry milk and 5.0 nM [^{3} H]L-797773, (34 Ci/mmol), $\pm$ test compound. (L-797773 is (3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxo)butyloxy)phenylacetic acid, Ex.62 in WO 97/28137). Assays can be incubated for about 16 hr at 4° C., in a final volume of 150 μ L. Unbound ligand can be removed by incubation with 100 μ L dextran/gelatin-coated charcoal, on ice, for about 10 min. After centrifugation at 3000 rpm for 10 min at 4° C., 50 μ L of the supernatant fraction can be counted in a Topcount.

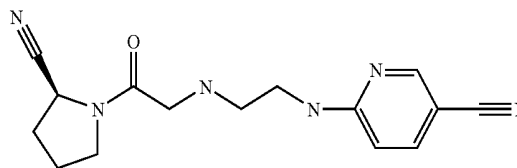
[0182] The invention also includes a method for reducing cholesterol synthesis comprising administering a peptide of the invention linked to a thyroid hormone receptor beta agonist, e.g., selected from CGS23425 and CGS26214, and/or a fibrate, e.g., selected from clofibrate, gemfibrozil, fenofibrate, ciprofibrate and benzafibrate, in therapeutically effective amounts to a patient in need of such treatment. Fibrates therefore can be used in combination with thyroid hormone receptor beta agonist to practice the instant invention.

[0183] The term "DPP-IV inhibitor" is intended to indicate a molecule that exhibits inhibition of the -IV and functionally related enzymes, such as from 1-100% inhibition, and specially preserves the action of substrate molecules, including but not limited to glucagon-like peptide-1, gastric inhibitory polypeptide, peptide histidine methionine, substance P, neuropeptide Y, and other molecules typically containing alanine or proline residues in the second amino-terminal position. Treatment with DPP-IV inhibitors prolongs the duration of action of peptide substrates and increases levels of their intact, undegraded forms leading to a spectrum of biological activities relevant to the disclosed invention.

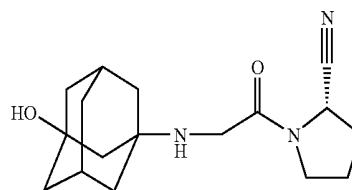
[0184] DPP-IV inhibitors that can be utilized are available to one of skill in the art. For example, DPP-IV inhibitors are generically and specifically disclosed, for example, in WO 98/19998, DE19616 486 A1, WO 00/34241, WO 95/15309, WO 01/72290, WO01/52825, WO 9310127, WO 9925719, WO 9938501, WO 9946272, WO 9967278 and WO 9967279, the subject matter of which are hereby incorporated into the present application by reference to these publications.

[0185] Published patent application WO 98/19998 discloses N-(N'-substituted glyceryl)-2-cyano pyrrolidines, in particular 1-[2-[5-Cyanopyridin-2-yl]amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine (NVP-DPP728). DE19616 486 A1 discloses val-pyr, val-thiazolidide, isoleucyl-thiazolidide, isoleucyl-pyrrolidide, and fumar salts of isoleucyl-thiazolidide and isoleucyl-pyrrolidide. Published patent application WO 0034241 and published patent U.S. Pat. No. 6,110,949 disclose N-substituted adamantyl-amino-acetyl-2-cyano pyrrolidines and W (substituted glyceryl)-4-cyano pyrrolidines respectively. DPP-IV inhibitors of interest are specially those cited in claims 1 to 4. Published patent application WO 95/15309 discloses amino acid 2-cyanopyrrolidine amides as inhibitors of DPP-IV. Published patent application WO 9529691 discloses peptidyl derivatives of diesters of alpha-aminoalkylphosphonic acids, particularly those with proline or related structures. DPP-IV inhibitors of interest are specially those cited in Table 1 to 8. In WO 01/72290 DPP-IV inhibitors of interest are specially those cited in example 1 and claims 1, 4, and 6. WO 01/52825 specially discloses (S)-1-[2-[5-cyanopyridin-2-yl]amino]ethyl-aminoacetyl)-2-cyano-pyrrolidine or (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine. Published patent application WO 9310127 discloses proline boronic esters useful as DPP-IV inhibitors. DPP-IV inhibitors of interest are specially those cited in examples 1 to 19. Published patent application WO 9925719 discloses sulphostin, a DPP-IV inhibitor prepared by culturing a *Streptomyces* microorganism. Published patent application WO 9938501 discloses N-substituted 4-8 membered heterocyclic rings. DPP-IV inhibitors of interest are specially those cited in claims 15 to 20. Published patent application WO 9946272 discloses phosphoric compounds as inhibitors of DPP-IV. DPP-IV inhibitors of interest are specially those cited in claims 1 to 23. Published patent applications WO 9967278 and WO 9967279 disclose DPP-IV prodrugs and inhibitors of the form A-B-C where C is either a stable or unstable inhibitor of DPP-IV. Any of the substances disclosed in the above mentioned patent documents, hereby included by reference, are considered potentially useful as DPP-IV inhibitors to be used in carrying out the present invention.

[0186] Preferred DPP-IV inhibitors are N-substituted adamantyl-amino-acetyl-2-cyano pyrrolidines, N (substituted glyceryl)-4-cyano pyrrolidines, N-(N'-substituted glyceryl)-2-cyanopyrrolidines, N-aminoacyl thiazolidines, N-aminoacyl pyrrolidines, L-allo-isoleucyl thiazolidine, L-threo-isoleucyl pyrrolidine, and L-allo-isoleucyl pyrrolidine, 1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine and pharmaceutical salts thereof. Especially preferred are 1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2 (S)-cyano-pyrrolidine dihydrochloride, of the following formula:



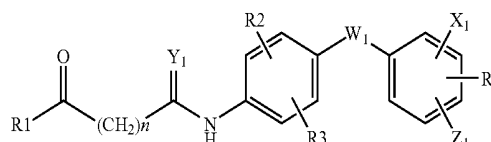
especially the dihydrochloride thereof. Another preferred DPP-IV inhibitor is pyrrolidine, 1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-, (S) of the following formula:



Another preferred DPP-IV inhibitor is L-threo-isoleucyl thiazolidine, and pharmaceutical salts thereof. Especially preferred are orally active DPP-IV inhibitors.

[0187] In another embodiment, the therapeutic agent is a thyromimetic compound. Examples of thyromimetic compounds to be employed in the present invention include those disclosed in EP 580 550, U.S. Pat. Nos. 5,654,468, 5,569,674 and 5,401,772 which are incorporated herein by reference as if set forth in their entirety. Thyromimetic compounds of the present invention also include those compounds disclosed in U.S. Pat. Nos. 4,069,343; 4,554,290; 4,766,121; 4,826,876; 4,910,305; 5,061,798; 5,232,947; 5,284,971; 5,401,772; WO 00/58279, and those disclosed in Yokoyama N. et al., *Journal of Medicinal Chemistry*, 38(4):695-707 (1995) and Stephan Z. F. et al., *Atherosclerosis*, 126:53-63 (1996), all of which are incorporated herein in their entirety as if set forth in full herein, especially the corresponding subject matter of the claims and the working examples directed to thyromimetic compounds.

[0188] Particularly preferred thyromimetic compounds also include compounds of formula I:



wherein:

[0189] W_1 is O, S, S(O) or S(O)₂;

[0190] X_1 is —SR₄, —S(O)R₄, —S(O)₂R₄, or —S(O)₂NR₅R₆; or X_1 is —C(O)NR₅R₆ provided that —C(O)NR₅R₆ is located at the 3'-, 4'- or 5'-position;

[0191] Y_1 is O or H₂;

[0192] Z_1 is hydrogen, halogen, hydroxy, optionally substituted alkoxy, aralkoxy, acyloxy or alkoxycarbonyloxy;

[0193] R_1 is hydroxy, optionally substituted alkoxy, aryloxy, heteroaryloxy, aralkoxy, cycloalkoxy, heteroaralkoxy or $-\text{NR}_5\text{R}_6$;

[0194] R_2 is hydrogen, halogen or alkyl;

[0195] R_3 is halogen or alkyl;

[0196] R_4 is optionally substituted alkyl, aryl, aralkyl, heteroaralkyl or heteroaryl;

[0197] R_5 , R_6 and R_7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R_5 and R_6 combined are alkylene optionally interrupted by O, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$ or NR_7 which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

[0198] R_8 is hydrogen, halogen, trifluoromethyl, lower alkyl or cycloalkyl;

[0199] n represents zero or an integer from 1 to 4; and pharmaceutically acceptable salts thereof.

[0200] Preferred are the compounds of formula I as defined above with the proviso that when X_1 is $-\text{C}(\text{O})\text{NR}_5\text{R}_6$, Z_1 is different from hydrogen (preferably hydroxy).

[0201] Preferred compounds of formula I include those compounds wherein:

[0202] R_1 is hydroxy, lower alkoxy or NR_5R_6 ; R_5 being hydrogen or lower alkyl and R_6 being hydrogen, lower alkyl, lower alkoxy or R_5 and R_6 combined being alkylene or alkylene interrupted by O which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

[0203] R_1 is more preferably hydroxy, lower alkoxy or aryloxy.

[0204] R_2 is hydrogen, halogen or lower alkyl.

[0205] R_3 is halogen or lower alkyl.

[0206] R_4 is phenyl or phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl.

[0207] R_5 is hydrogen.

[0208] R_6 is phenyl or phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl.

[0209] R_8 is hydrogen or lower alkyl, more preferably hydrogen.

[0210] W_1 is O or S, more preferably O.

[0211] X_1 is $-\text{S}(\text{O})_2\text{R}_4$; R_4 being lower alkyl, phenyl or phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl; or is $-\text{S}(\text{O})_2\text{NR}_5\text{R}_6$ or is $-\text{C}(\text{O})\text{NR}_5\text{R}_6$; R_5 , in each case, being hydrogen or lower alkyl and R_6 , in each case, being hydrogen, lower alkyl, lower alkyl substituted by NR_5R_6 , 3- to 7-membered cycloalkyl, phenyl, phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl; pyridyl or

N-lower alkyl-2-pyridone; or R_5 and R_6 combined, in each case, being alkylene or alkylene interrupted by O or $\text{S}(\text{O})_2$ which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring.

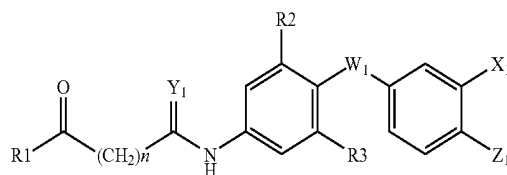
[0212] X_1 is preferably $-\text{S}(\text{O})_2\text{R}_4$ or $-\text{S}(\text{O})_2\text{NR}_5\text{R}_6$.

[0213] Y_1 is O or H_2 , more preferably O.

[0214] Z_1 is hydrogen or hydroxy.

[0215] The integer "n" preferably is zero, 1 or 2.

[0216] Preferred are the compounds of formula IA



wherein

[0217] W_1 is O or S;

[0218] X_1 is $-\text{SR}_4$, $-\text{S}(\text{O})\text{R}_4$, $-\text{S}(\text{O})_2\text{R}_4$, $-\text{S}(\text{O})_2\text{NR}_5\text{R}_6$ or $-\text{C}(\text{O})\text{NR}_5\text{R}_6$;

[0219] Y_1 is O or H_2 ;

[0220] Z_1 is hydrogen, halogen, hydroxy, alkoxy, aralkoxy, acyloxy or alkoxycarbonyloxy;

[0221] R_1 is hydroxy, lower alkoxy or aryloxy;

[0222] R_2 is hydrogen, halogen or lower alkyl;

[0223] R_3 is halogen or lower alkyl;

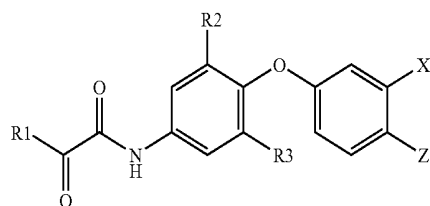
[0224] R_4 is optionally substituted alkyl, aryl, aralkyl, heteroaryl or heteroaralkyl;

[0225] R_5 , R_6 and R_7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R_5 and R_6 combined are alkylene optionally interrupted by O, S, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$ or NR_7 which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

[0226] n represents zero, 1 or 2;

and pharmaceutically acceptable salts thereof

[0227] Further preferred are the compounds of formula IB



in which

[0228] X_1 is $-\text{S}(\text{O})_2\text{R}_4$, $-\text{S}(\text{O})_2\text{NR}_5\text{R}_6$ or $-\text{C}(\text{O})\text{NR}_5\text{R}_6$;

[0229] Z_1 is hydroxy, lower alkanoyloxy or lower alkoxy;

[0230] R_1 is hydroxy or lower alkoxy;

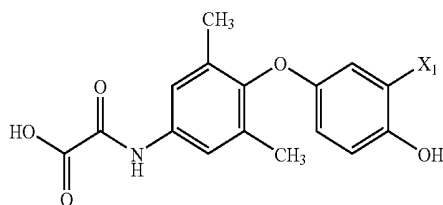
[0231] R_2 and R_3 are lower alkyl;

[0232] R_4 is aryl;

[0233] R_5 , R_6 and R_7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R_5 and R_6 combined are alkylene optionally interrupted by O, S, S(O), S(O)₂ or NR⁷ which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring; and pharmaceutically acceptable salts thereof.

[0234] Preferred are compounds of formula I, IA and IB, and pharmaceutically acceptable salts thereof, wherein X is —S(O)₂R₄ or —S(O)₂NR₅R₆.

[0235] Also preferred are the compounds of formula IC



in which

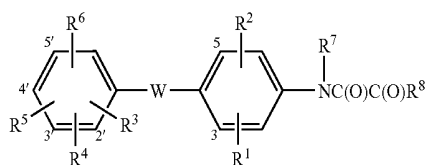
[0236] X_1 is —S(O)₂R₄ or —S(O)₂NR₅R₆;

[0237] R_4 is monocyclic aryl;

[0238] R_5 , R_6 and R_7 are independently hydrogen, optionally substituted alkyl or aryl; or R_5 and R_6 combined are CH₂CH₂-Q-CH₂CH₂ wherein Q is CH₂, O, NR⁷, S, S(O) or S(O)₂ which together with the nitrogen atom to which they are attached form a 6-membered ring; pharmaceutically acceptable prodrug esters thereof; and pharmaceutically acceptable salts thereof.

[0239] Particularly preferred are the compounds of formula IC wherein X_1 is S(O)₂R₄ and R_4 is phenyl optionally substituted by lower alkyl, halo, lower alkoxy or trifluoromethyl; pharmaceutically acceptable salts thereof; and prodrug derivatives thereof. Most preferred is the compound N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid.

[0240] Preferred thyromimetic compounds also include those disclosed in WO 00/51971, provided as formula II herein:



prodrugs thereof, geometric and optical isomers thereof, and pharmaceutically acceptable salts of said compounds, said prodrugs, and said isomers, wherein:

[0241] R^1 , R^2 and R^3 are each independently hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, —CN, —OCF₃ or —OC₁₋₆ alkyl;

[0242] R^4 is hydrogen, C₁₋₁₂ alkyl optionally substituted with one to three substituents independently selected from Group Z, C₂₋₁₂ alkenyl, halogen, —CN, aryl, heteroaryl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, —S(O)₂NR⁹R¹⁰, —C(O)NR⁹R¹⁰, —(C₁₋₆ alkyl)-NR⁹R¹⁰, —NR⁹C(O)R¹⁰, —NR⁹C(O)NR⁹R¹⁰, —NR⁹S(O)₂R¹⁰, —(C₁₋₆ alkyl)-OR¹¹, —OR¹¹ or —S(O)_aR¹², provided that, where R⁵ is not fluoro, R^4 is —S(O)₂NR⁹R¹⁰, —C(O)NR⁹R¹⁰, —(C₁₋₆ alkyl)-NR⁹R¹⁰, —NR⁹C(O)R¹⁰, —NR⁹C(O)NR⁹R¹⁰, —NR⁹S(O)₂R¹⁰, —(C₁₋₆ alkyl)-OR¹¹, —OR¹¹ or —S(O)_aR¹²;

[0243] or R^3 and R^4 may be taken together to form a carbocyclic ring A of the formula —(CH₂)_b— or a heterocyclic ring A selected from the group consisting of —Q-(CH₂)_c— and —(CH₂)_j-Q-(CH₂)_k— wherein Q is O, S or NR¹⁷, wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C₁₋₄ alkyl, halide or oxo;

[0244] R^5 is fluoro, hydroxy, C₁₋₄ alkoxy or OC(O)R⁹;

[0245] or R^4 and R^5 may be taken together to form a heterocyclic ring B selected from the group consisting of —CR⁹=CR¹⁰—NH—, —N=CR⁹—NH—, —CR⁹=CH—O— and —CR⁹=CH—S—;

[0246] R^6 is hydrogen, halogen, C₁₋₄ alkyl or trifluoromethyl;

[0247] R^7 is hydrogen or C₁₋₆ alkyl;

[0248] R^8 is —OR⁹ or —NR¹⁹R²⁰;

[0249] R^9 and R^{10} for each occurrence are independently (A) hydrogen, (B) C₁₋₁₂ alkyl optionally substituted with one or more substituents independently selected from Group V, (C) C₂₋₁₂ alkenyl, (D) C₃₋₁₀ cycloalkyl optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl, C₂₋₅ alkynyl, C₃₋₁₀ cycloalkyl, —CN, —NR¹³R¹⁴, oxo, —OR¹⁸, —COOR¹⁸ or aryl optionally substituted with X and Y, (E) aryl optionally substituted with X and Y, or (F) het optionally substituted with X and Y;

[0250] or R^9 and R^{10} for any occurrence may be taken together to form a heterocyclic ring C optionally further containing a second heterogroup selected from the group consisting of —O—, —NR¹³— and —S—, and optionally further substituted with one or more substituents independently selected from C₁₋₅ alkyl, oxo, —NR¹³R¹⁴, —OR¹⁸, —C(O)₂R¹⁸, —CN, —C(O)R⁹, aryl optionally substituted with X and Y, het optionally substituted with X and Y, C₅₋₆ spirocycloalkyl, and a carbocyclic ring B selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings, and including any bicyclic group in which said carbocyclic ring B is fused to a carbocyclic ring C selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings;

[0251] R^{11} is C₁₋₁₂ alkyl optionally substituted with one or more substituents independently selected from Group V, C₂₋₁₂ alkenyl, C₃₋₁₀ cycloalkyl, trifluoromethyl, difluorom-

ethyl, monofluoromethyl, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-\text{C}(\text{O})\text{NR}^{10}$ or $-\text{C}(\text{O})\text{R}^9$;

[0252] R^{12} is C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, C_{2-12} alkenyl, C_{3-10} cycloalkyl, aryl optionally substituted with X and Y, or het optionally substituted with X and Y;

[0253] R^{13} and R^{14} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, $-(\text{C}_{1-6} \text{ alkyl})-\text{C}_{1-6}$ alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-(\text{C}_{1-4} \text{ alkyl})$ -aryl optionally substituted with X and Y, $-(\text{C}_{1-4} \text{ alkyl})$ -heterocycle optionally substituted with X and Y, $-(\text{C}_{1-4} \text{ alkyl})$ -hydroxy, $-(\text{C}_{1-4} \text{ alkyl})$ -halo, $-(\text{C}_{1-4} \text{ alkyl})$ -poly-halo, $-(\text{C}_{1-4} \text{ alkyl})$ - $\text{CONR}^{15}\text{R}^{16}$ or C_{3-10} cycloalkyl;

[0254] R^{15} and R^{16} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or aryl optionally substituted with X and Y;

[0255] R^{17} is hydrogen, alkyl, C_{1-6} alkyl, $-\text{COR}^9$ or $-\text{SO}_2\text{R}^9$;

[0256] R^{18} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, $-(\text{C}_{1-6} \text{ alkyl})-\text{C}_{1-6}$ alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-(\text{C}_{1-4} \text{ alkyl})$ -aryl optionally substituted with X and Y, $-(\text{C}_{1-4} \text{ alkyl})$ -heterocycle optionally substituted with X and Y, $-(\text{C}_{1-4} \text{ alkyl})$ -hydroxy, $-(\text{C}_{1-4} \text{ alkyl})$ -halo, $-(\text{C}_{1-4} \text{ alkyl})$ -poly-halo, $-(\text{C}_{1-4} \text{ alkyl})$ - $\text{CONR}^{15}\text{R}^{16}$, $-(\text{C}_{1-4} \text{ alkyl})$ - $(\text{C}_{1-4} \text{ alkoxy})$ or C_{3-10} cycloalkyl;

[0257] R^{19} is hydrogen or C_{1-6} alkyl;

[0258] R^{20} is hydrogen or C_{1-6} alkyl;

[0259] W is O, $\text{S}(\text{O})_d$, CH_2 or NR^9 ;

[0260] Group Z is C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-\text{CF}_3$, $-\text{OCF}_3$, hydroxy, oxo, $-\text{CN}$, aryl, heteroaryl, C_{3-10} cycloalkyl, heterocycloalkyl, $-\text{S}(\text{O})_a\text{R}^{12}$, $-\text{S}(\text{O})_2\text{NR}^9\text{R}^{10}$, $-\text{C}(\text{O})\text{R}^9\text{R}^{10}$, and $-\text{NR}^9\text{R}^{10}$;

[0261] Group V is halogen, $-\text{NR}^{13}\text{R}^{14}$, $-\text{OCF}_3$, $-\text{OR}^9$, oxo, trifluoromethyl, $-\text{CN}$, C_{3-10} cycloalkyl, aryl optionally substituted with X and Y, and het optionally substituted with X and Y;

[0262] het for each occurrence is a heterocyclic ring D selected from the group consisting of 4-, 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S, and including any bicyclic group in which said heterocyclic ring D is fused to a benzene ring or a heterocyclic ring E selected from the group consisting of 4-, 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S;

[0263] X and Y for each occurrence are independently (A) hydrogen, (B) halogen, (C) trifluoromethyl, (D) $-\text{OCF}_3$, (E) $-\text{CN}$, (F) C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, $-\text{OCF}_3$, $-\text{CF}_3$ and phenyl, (G) C_{1-6} alkoxy, (H) aryl optionally substituted with one or more substituents independently selected from the group consist-

ing of halogen, $-\text{OCF}_3$, $-\text{CF}_3$, C_{1-4} alkyl and C_{1-4} alkoxy, (I) $-\text{C}(\text{O})_2\text{R}^{13}$, (J) $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, (K) $-\text{C}(\text{O})\text{R}^{13}$, (L) $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$ and (M) $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$; or X and Y for any occurrence in the same variable may be taken together to form (a) a carbocyclic ring D of the formula $-(\text{CH}_2)_e-$ or (b) a heterocyclic ring F selected from the group consisting of $-\text{O}(\text{CH}_2)_f\text{O}-$, $(\text{CH}_2)_g\text{NH}-$ and $-\text{CH}=\text{CHNH}-$;

[0264] a and d are each independently 0, 1 or 2;

[0265] b is 3, 4, 5, 6 or 7;

[0266] c, f, g, j and k are each independently 2, 3, 4, 5 or 6; and

[0267] e is 3, 4, 5, 6 or 7.

[0268] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the A Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein W is O.

[0269] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the A Group, designated the B Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 is located at the 3 position, R^2 is located at the 5 position, R^3 is located at the 2' position, R^4 is located at the 3' position, R^5 is located at the 4' position, and R^6 is located at the 5' position.

[0270] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group, designated the C Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is hydrogen, or R^3 and R^4 are taken together to form a carbocyclic ring A of the formula $-(\text{CH}_2)_b-$ or a heterocyclic ring A selected from the group consisting of $-\text{Q}-(\text{CH}_2)_c$ and $-(\text{CH}_2)_j-\text{Q}-(\text{CH}_2)_k-$ wherein Q is O, S or NR^{17} wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo, R^5 is hydroxy, R^6 is hydrogen and R^7 is hydrogen.

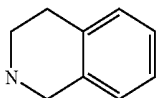
[0271] A preferred group of compounds pharmaceutically acceptable salts of such compounds, of the C Group, designated the D Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently methyl, bromo or chloro, and R^8 is hydroxy, methoxy, ethoxy, isopropoxy, NH_2 or $\text{NH}(\text{CH}_3)$.

[0272] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the E Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $\text{S}(\text{O})_2\text{NR}^9\text{R}^{10}$, and R^{10} is hydrogen or methyl.

[0273] Particularly preferred compounds of the E Group are compounds wherein (a) R^1 is chloro, R^2 is methyl, R^8 is ethoxy or hydroxy, R^9 is ethyl and R^{10} is hydrogen, (b) R^1 is chloro, R^2 is methyl, R^3 is ethoxy or hydroxy, R^5 is n-butyl and R^{10} is hydrogen, (c) R^1 is chloro, R^2 is methyl, R^8 is ethoxy or hydroxy, R^9 is $-\text{CH}_2$ -cyclopropyl and R^{10} is hydrogen and (d) R^1 is chloro, R^2 is methyl, R^3 is isopropoxy

or hydroxy, R^9 is cyclopropyl and R^{10} is hydrogen; and pharmaceutically acceptable salts of said compounds.

[0274] Another preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the F Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $S(O)_2NR^9R^{10}$, and R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_4$, $N(CH_2)_5$, morpholine or



[0275] Particularly preferred compounds of the F Group are those wherein R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_4$.

[0276] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the E Group, designated the G Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is hydrogen, isopropyl, $—CH_2-2$ -thienyl, $—CH_2$ -cyclopropyl, cyclopropyl, $—(CH_2)_2OH$, exo-2-norbornyl, methyl, ethyl, 4-fluorophenyl, cyclobutyl, cyclopentyl, cyclohexyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-octyl or n-decyl.

[0277] Particularly preferred compounds of the G Group are compounds wherein (a) R^1 is chloro, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is hydrogen, (b) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is methyl, (c) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is methyl, (d) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is hydrogen and (e) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is hydrogen; and pharmaceutically acceptable salts of said compounds.

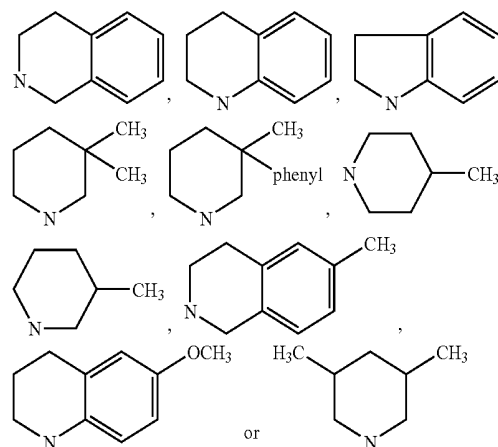
[0278] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the J Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $—C(O)NR^9R^{10}$, and R^{10} is hydrogen, methyl or ethyl.

[0279] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the J Group, designated the K group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is methyl, ethyl, isopropyl, n-propyl, isobutyl, n-butyl, n-pentyl, n-hexyl, 4-fluorophenyl, $—CH_2-2$ -thienyl, cyclopropyl, $—CH_2$ -cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $—CH_2$ -cyclohexyl, endo-2-norbornyl, exo-2-norbornyl, (S)-1-phenylethyl, (R)-1-phenylethyl, $—CH_2-2$ -chlorophenyl, $—CH_2-4$ -chlorophenyl, $—CH_2-4$ -fluorophenyl, $—CH_2-3$ -chloro-4-fluorophenyl, $—CH_2-2$ -chloro-4-fluorophenyl, $—CH_2-2$ -fluoro-4-chlorophenyl, $—CH_2-3,4$ -difluorophenyl, $—CH_2-4$ -isopropylphenyl, $—CH_2-2,3$ -dichlorophenyl, $—CH_2-2,4$ -dichlorophenyl, $—CH_2-3,4$ -dichlorophenyl, $—CH_2-3$ -

trifluoromethyl-4-chlorophenyl, 4-phenylphenyl, 3-(2,4-dimethyl)pentyl, (R)-1-(1-naphthyl)ethyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, (R)-1-(2-naphthyl)ethyl, (R)-2-(1-naphthyl)ethyl, $—CH_2$ -(1-naphthyl), (R)-1-cyclohexylethyl, (S)-1-cyclohexylethyl, $—CH_2-3,4$ -methylenedioxyphenyl, $—CH_2-4$ -t-butylphenyl, $—CH_2-2,3$ -dichlorophenyl, 1-indanyl, (R)-1-indanyl, (S)-1-indanyl, 5-indanyl, 1-(1,2,3,4-tetrahydronaphthyl) or (R)-1-cyclohexylethyl.

[0280] Particularly preferred compounds of the K Group are compounds wherein (a) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, R^9 is 3-(2,4-dimethyl)pentyl and R^{10} is hydrogen, (b) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is methyl, (c) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is methyl, (d) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is 3-(2,4-dimethyl)pentyl and R^{10} is hydrogen, (e) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is n-pentyl and R^{10} is methyl, (g) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is isopropyl and R^{10} is methyl, (h) R^1 is methyl, R^2 is methyl, R^8 is hydroxy, ethoxy or NH_2 , R^9 is cyclobutyl and R^{10} is methyl and (i) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is methyl; and pharmaceutically acceptable salts of said compounds.

[0281] Another preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the L Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $—C(O)NR^9R^{10}$, and R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_7$, $N(CH_2)_6$, $N(CH_2)_5$, $N(CH_2)_4$, morpholine,

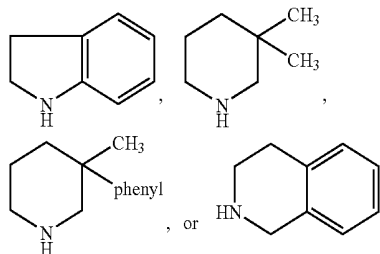


[0282] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the M Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $—CH_2NR^9R^{10}$, and R^{10} is hydrogen, methyl or $—COCH_3$.

[0283] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the M Group, designated the N group, contains those compounds of Formula II and pharmaceutically acceptable salts of such com-

pounds, as shown above, wherein R^9 is methyl, n-propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, exo-2-norbornyl, $-\text{CH}_2$ -4-fluorophenyl, $-\text{CH}_2$ -4-chlorophenyl, $-\text{CH}_2$ -4-isopropylphenyl, $-\text{CH}_2$ -3,4-methylenedioxyphenyl, (R)-1-(1-naphthyl)ethyl, (R)-1-phenylethyl, (S)-1-phenylethyl, (R)-1-cyclohexylethyl, 1-(1,2,3,4-tetrahydronaphthyl), 1-indanyl or $-\text{CH}_2$ -(1-naphthyl).

[0284] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the M Group, designated the O group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $\text{N}(\text{CH}_2)_6$, morpholine,



[0285] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the P Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $-\text{NHCOR}^9$.

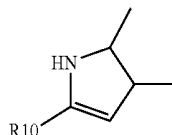
[0286] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the P Group, designated the Q Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is cyclopropyl or cyclobutyl.

[0287] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the R Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $-\text{S}(\text{O})_2\text{R}^{12}$, and R^{12} is 4-chlorophenyl, phenyl, 1-naphthyl, 2-naphthyl, CH_2 -cyclopropyl, isopropyl, CH_2 -cyclobutyl, CH_2 -cyclohexyl, cyclopentyl, CH_2 -4-fluorophenyl, 4-tolyl, methyl, ethyl, n-butyl, CH_2 -phenyl or n-propyl.

[0288] Particularly preferred compounds of the R Group are compounds wherein (a) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, and R^{12} is ethyl, (b) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy and R^{12} is $-\text{CH}_2$ -cyclobutyl, (c) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy and R^{12} is $-\text{CH}_2$ -cyclohexyl, (d) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy and R^{12} is cyclopentyl, (e) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, and R^{12} is $-\text{CH}_2$ -cyclopropyl, (f) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, and R^{12} is $-\text{CH}_2$ -cyclobutyl, and (g) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, and R^{12} is $-\text{CH}_2$ -cyclopropyl; and pharmaceutically acceptable salts of said compounds.

[0289] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group,

designated the S Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently methyl, bromo or chloro, R^3 is hydrogen, R^4 and R^5 are taken together to form



R^6 is hydrogen, R^7 is hydrogen, R^8 is ethoxy, hydroxy or NH_2 , and R^{10} is hydrogen or methyl.

[0290] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the T Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is hydrogen, and R^4 is $-\text{OR}^{11}$.

[0291] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the T Group, designated the U Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^{11} is phenyl, 4-chlorophenyl or 4-fluorophenyl.

[0292] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the V Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is hydrogen, and R^4 is $-(\text{C}_{1-6} \text{ alkyl})-\text{OR}^{11}$. Particularly preferred compounds of the V Group are compounds wherein R^4 is $-\text{CH}_2-\text{OR}^{11}$.

[0293] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the V Group, designated the W Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^{11} is phenyl or 4-fluorophenyl.

[0294] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the X Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 and R^4 are taken together to form a carbocyclic ring A of the formula $-(\text{CH}_2)_6-$ or a heterocyclic ring A selected from the group consisting of $-\text{Q}-(\text{CH}_2)_c$ and $-(\text{CH}_2)_j-\text{Q}-(\text{CH}_2)_k-$ wherein Q is O, S or NR^{17} , wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo.

[0295] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the X Group, designated the Y Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 and R^4 are taken together to form said carbocyclic ring A.

[0296] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the Y Group,

designated the Z Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R³ and R⁴ are taken together to form $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$ or $-(CH_2)_4-$.

[0297] Particularly preferred compounds of the Z Group are compounds wherein (a) R¹ is methyl, R² is methyl, R⁸ is hydroxy or ethoxy, and R³ and R⁴ are taken together to form $-(CH_2)_3-$, (b) R¹ is chloro, R² is methyl, R⁸ is hydroxy or ethoxy, and R³ and R⁴ are taken together to form $-(CH_2)_3-$ and (c) R¹ is methyl, R² is methyl, R⁸ is hydroxy or ethoxy, and R³ and R⁴ are taken together to form $-(CH_2)_4-$; and pharmaceutically acceptable salts of said compounds.

[0298] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the AA Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R⁸ is $-OR^9$.

[0299] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AA Group, designated the AB Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R⁹ is C₁₋₁₂ alkyl.

[0300] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AB Group, designated the AC Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R⁹ is methyl, isopropyl or ethyl.

[0301] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AC Group, designated the AD Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R⁹ is ethyl.

[0302] A preferred group of the pharmaceutically acceptable salts of the compounds of Formula II, and the prodrugs, geometric and optical isomers thereof, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or a sodium salt.

[0303] A preferred group of compounds of Formula II, designated the AE Group, includes the specific compounds:

[0304] N-[3-chloro-4-(3-cyclopropylsulfamoyl)-4-hydroxy-phenoxy]-5-methyl-phenyl]-oxamic acid,

[0305] N-[4-(3-cyclopropylsulfamoyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl]-oxamic acid,

[0306] N-{4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid,

[0307] N-[3-chloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-5-methyl-phenyl]-oxamic acid,

[0308] N-[4-(7-hydroxy-indan-4-yloxy)-3,5-dimethyl-phenyl]-oxamic acid,

[0309] N-(3,5-dichloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-phenyl)-oxamic acid,

[0310] N-[3,5-dichloro-4-(3-cyclopentanesulfonyl)-4-hydroxy-phenoxy]-phenyl]-oxamic acid,

[0311] N-[3,5-dichloro-4-(3-cyclopropylmethanesulfonyl)-4-hydroxy-phenoxy]-phenyl]-oxamic acid,

[0312] N-[3,5-dichloro-4-(3-cyclobutylmethanesulfonyl)-4-hydroxy-phenoxy]-phenyl]-oxamic acid,

[0313] N-[4-(3-cyclopropylmethanesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl]-oxamic acid,

[0314] N-[3-chloro-4-(3-cyclobutylmethanesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl]-oxamic acid,

[0315] N-[4-(3-cyclobutylmethanesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl]-oxamic acid,

[0316] N-[4-(3-cyclopentylmethanesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl]-oxamic acid,

[0317] N-[3-chloro-4-(3-cyclopentylmethanesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl]-oxamic acid,

[0318] N-[3,5-dichloro-4-(3-cyclopentylmethanesulfonyl)-4-hydroxy-phenoxy]-phenyl]-oxamic acid,

[0319] N-[4-(3-cyclohexylmethanesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl]-oxamic acid,

[0320] N-[3-chloro-4-(3-cyclohexylmethanesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl]-oxamic acid,

[0321] N-[3,5-dichloro-4-(3-cyclohexylmethanesulfonyl)-4-hydroxy-phenoxy]-phenyl]-oxamic acid,

[0322] N-[3,5-dichloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-phenyl]-oxamic acid,

[0323] N-{4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid,

[0324] N-{3-chloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl}-oxamic acid, and the prodrugs and geometric and optical isomers thereof, and the pharmaceutically acceptable salts of the compounds, prodrugs and isomers.

[0325] A preferred group of the pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers of the AE Group, designated the AF Group, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or a sodium salt.

[0326] A preferred group of the compounds, and geometric and optical isomers thereof, of the compounds of the AE group, designated the AG Group, contains the ethyl esters of those compounds.

[0327] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group, designated the AH Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R⁵ is fluoro.

[0328] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AH Group, designated the AI Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R⁴ is hydrogen, fluoro, chloro, methyl or cyclobutyl-methyl-carbamoyl.

[0329] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AJ Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently methyl or chloro.

[0330] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AK Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each methyl.

[0331] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AL Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each chloro.

[0332] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AM Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^7 is hydrogen, and R^8 is hydrogen or $—OR^9$.

[0333] A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AM Group, designated the AN Group, contains those compounds of Formula II and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is methyl or ethyl.

[0334] A preferred group of compounds of Formula II, designated the AO Group, includes the specific compounds:

[0335] N-[4(4-Fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

[0336] N-[3,5-Dichloro-4-(4-fluoro-phenoxy)-phenyl]-oxamic acid,

[0337] N-[3,5-Dichloro-4-(3,4-difluoro-phenoxy)-phenyl]-oxamic acid,

[0338] N-[4-(3-Methyl-4-Fluoro-phenoxy)-3,5-dichloro-phenyl]-oxamic acid,

[0339] N-[3,5-Dichloro-4-(3-chloro-4-fluoro-phenoxy)-phenyl]-oxamic acid,

[0340] N-[4-(3,4-Difluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

[0341] N-[4-(3-Chloro-4-fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

[0342] N-[4-(3-Methyl-4-fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

[0343] N-[3,5-Dichloro-4-(4-fluoro-phenoxy)-phenyl]-oxamic acid,

[0344] N-[3,5-Dichloro-4-(3,4-difluoro-phenoxy)-phenyl]-oxamic acid,

[0345] N-[4-(3-(Cyclobutyl-methyl-carbamoyl)-4-fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

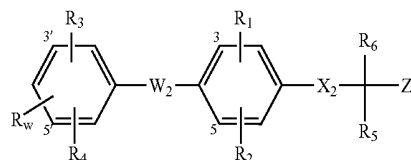
[0346] N-[4-(4-Fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid, and the prodrugs and geometric and optical

isomers thereof, and the pharmaceutically acceptable salts of the compounds, prodrugs and isomers.

[0347] A preferred group of the pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers of the AO Group, designated the AP Group, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or a sodium salt.

[0348] A preferred group of the compounds, and geometric and optical isomers thereof, of the compounds of the AO group, designated the AQ Group, contains the ethyl esters of those compounds.

[0349] Also preferred are those compounds disclosed in EP 580 550 and U S. Pat. Nos. 5,569,674 and 5,654,468 of formula III:



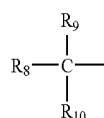
wherein R_w is hydroxy, esterified hydroxy or etherified hydroxy;

[0350] R_1 is halogen, trifluoromethyl or lower alkyl;

[0351] R_2 is halogen, trifluoromethyl or lower alkyl;

[0352] R_3 is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or

[0353] R_3 is the radical



wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;

[0354] R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;

[0355] X_2 is $—NR_7$;

[0356] W_2 is O or S;

[0357] R_5 and R_6 together represent oxo;

[0358] R_7 represents hydrogen or lower alkyl;

[0359] Z_2 represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; or a pharmaceutically acceptable salt thereof.

[0360] Listed below are definitions of various terms used to describe the thyromimetic compounds of the present invention. These definitions apply to the terms as they are

used throughout the specification (unless they are otherwise limited in specific instances either individually or as part of a larger group).

[0361] The term “optionally substituted alkyl” refers to unsubstituted or substituted straight or branched chain hydrocarbon groups having 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethyl-pentyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more (e.g. two or three) of the following groups: halo, lower alkenyl, hydroxy, cycloalkyl, alkanoyl, alkoxy, alkyloxy-alkoxy, alkanoyloxy, amino, alkylamino, dialkylamino, dialkylaminocarbonyl, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfonamido, nitro, cyano, carboxy, alkoxycarbonyl, aryl, aralkyl, aralkoxy, guanidino, heterocyclyl including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, piperidyl, morpholinyl and the like. Preferred substituents of substituted alkyl, especially of substituted alkyl of variable R1 being substituted alkoxy, are lower alkyl, cycloalkyl, lower alkenyl, benzyl, mono or disubstituted lower alkyl, e.g. ω -(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl, $\square$ -(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl, such as pivaloyloxy-methyl.

[0362] The term “lower alkyl” refers to those alkyl groups as described above having 1 to 7, preferably 1 to 4 carbon atoms.

[0363] The term “halogen” or “halo” refers to fluorine, chlorine, bromine and iodine.

[0364] The term “alkenyl” refers to any of the above alkyl groups having at least 2 carbon atoms and further containing at least one carbon to carbon double bond. Groups having two to four carbon atoms are preferred.

[0365] The term “alkylene” refers to a straight chain bridge of 1 to 6 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$ wherein x is 1 to 6), which may be substituted with 1 to 3 lower alkyl groups.

[0366] The term “cycloalkyl” refers to cyclic hydrocarbon groups of 3 to 8 carbon atoms.

[0367] The term “alkoxy” refers to alkyl-O—.

[0368] The term “acyl” refers to alkanoyl, aroyl, heteroaroyl, arylalkanoyl or heteroarylalkanoyl.

[0369] The term “alkanoyl” refers to alkyl-C(O)—.

[0370] The term “alkanoyloxy” refers to alkyl-C(O)—O—.

[0371] The terms “alkylamino” and “dialkylamino” refer to (alkyl)NH— and (alkyl)₂N—, respectively.

[0372] The term “alkanoylamino” refers to alkyl-C(O)—NH—.

[0373] The term “alkylthio” refers to alkyl-S—.

[0374] The term “alkylthiono” refers to alkyl-S(O)—.

[0375] The term “alkylsulfonyl” refers to alkyl-S(O)₂—.

[0376] The term “alkoxycarbonyl” refers to alkyl-O—C(O)—.

[0377] The term “alkoxycarbonyloxy” refers to alkyl-O—C(O)O—.

[0378] The term “alkyl” as referred to in the above definitions relates to optionally substituted alkyl as defined above.

[0379] The term “aryl” refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, and biphenyl groups, each of which may optionally be substituted by one to four substituents such as alkyl, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoyl-amino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, alkylthiono, alkyl-sulfonyl, sulfonamido, heterocyclyl and the like.

[0380] The term “monocyclic aryl” refers to optionally substituted phenyl as described under aryl.

[0381] The term “aralkyl” refers to an aryl group bonded directly through an alkyl group, such as benzyl.

[0382] The term “aralkoxy” refers to an aryl group bonded through an alkoxy group.

[0383] The term “arylsulfonyl” refers to aryl-S(O)₂—.

[0384] The term “aroyl” refers to aryl-C(O)—.

[0385] The term “heterocyclyl” refers to an optionally substituted, fully saturated or unsaturated, aromatic or non-aromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or carbon atom.

[0386] Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazoliny, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazoliny, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, 2-pyridone, N-lower alkyl-pyridone, e.g. N-lower alkyl-2-pyridone, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranly, morpholinyl, thiamorpholinyl, S-oxo-thiamorpholinyl S,S-dioxo-thiamorpholinyl, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like.

[0387] Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranly, indoliziny, benzofuryl, chromonyl, coumarinyl, benzopyranly, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl) or furo[2,3-b]pyridinyl, dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl) and the like.

[0388] Exemplary tricyclic heterocyclic groups include carbazolyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0389] The term "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 of the following:

- [0390] (a) alkyl;
- [0391] (b) hydroxy (or protected hydroxy);
- [0392] (c) halo;
- [0393] (d) oxo (i.e. =O);
- [0394] (e) amino, alkylamino or dialkylamino;
- [0395] (f) alkoxy,
- [0396] (g) cycloalkyl;
- [0397] (h) carboxy;
- [0398] (i) heterocycloxy;
- [0399] (j) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;
- [0400] (k) mercapto;
- [0401] (l) nitro;
- [0402] (m) cyano;
- [0403] (n) sulfonamido, sulfonamidoalkyl or sulfonamidodialkyl;
- [0404] (o) aryl;
- [0405] (p) alkylcarbonyloxy;
- [0406] (q) arylcarbonyloxy;
- [0407] (r) arylthio;
- [0408] (s) aryloxy;
- [0409] (t) alkylthio;
- [0410] (u) formyl;
- [0411] (v) aralkyl; or
- [0412] (w) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino or halo.

[0413] The term "heterocycloxy" denotes a heterocyclic group bonded through an oxygen bridge.

[0414] The term "heteroaryl" refers to an aromatic heterocycle, for example monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothieryl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl, and the like, optionally substituted by one or more substituents as described in connection with substituted aryl, e.g. by lower alkyl, lower alkoxy or halo.

[0415] The term "heteraryloxy" refers to heteroaryl-O—.

[0416] The term "heteroarylsulfonyl" refers to heteroaryl-S(O)₂—.

[0417] The term "heteroaryl" refers to heteroaryl-C(O)—.

[0418] The term "heteroalkyl" refer to a heteroaryl group bonded through an alkyl group.

[0419] Encompassed by the invention are prodrug derivatives, e.g., any pharmaceutically acceptable prodrug ester derivatives of the carboxylic acids of the invention (COR_x being carboxy) which are convertible by solvolysis or under physiological conditions to the free carboxylic acids. Examples of such carboxylic acid esters include esters defined by COR_x, and are preferably lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono or disubstituted lower alkyl esters, e.g. the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-, β-, γ-, or δ-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxy-methyl ester, and the like conventionally used in the art.

[0420] The thyromimetic compounds of the invention depending on the nature of the substituents, may possess one or more asymmetric centers. The resulting diastereoisomers, enantiomers and geometric isomers are encompassed by the instant invention.

[0421] Pharmaceutically acceptable salts of any acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethylammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

[0422] The compounds described above may be prepared and administered in accordance with the methods set forth in WO 00/58279. Similarly acid addition salts, such as of mineral acids, organic carboxylic, and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are possible provided a basic group, such as pyridyl, constitutes part of the structure.

Conjugation, Cyclization and Other Modifications of the Peptides

[0423] The invention contemplates conjugation of the peptides to other entities and cyclization of peptides using amino acids or other moieties that are capable of forming covalent linkages without interruption of peptide linkages.

[0424] Amino acids can be conjugated to other entities and/or peptides cyclized by any method available to one of skill in the art. For example, functional groups present on the side chains of amino acids in the peptides can be combined with functional groups in the entity to which the peptide is to be conjugated. Functional groups that can form covalent bonds include —COOH and —OH; —COOH and —NH₂; and —COOH and —SH. Pairs of amino acids that can be used to conjugate proteins to the present peptides or to cyclize a peptide include, Asp and Lys; Glu and Lys; Asp and Arg; Glu and Arg; Asp and Ser; Glu and Ser; Asp and Thr; Glu and Thr; Asp and Cys; and Glu and Cys. Other examples of amino acid residues that are capable of forming covalent linkages with one another include cysteine-like amino acids such as Cys, hCys, β-methyl-Cys and Pen, which can form disulfide bridges with one another. Preferred cysteine-like amino acid residues include Cys and Pen. Other pairs of amino acids that can be used for conjugation and cyclization of the peptide will be apparent to those skilled in the art.

[0425] The groups used to conjugate or cyclize a peptide need not be amino acids. Examples of functional groups capable of forming a covalent linkage with the amino terminus of a peptide include carboxylic acids and esters. Examples of functional groups capable of forming a covalent linkage with the carboxyl terminus of a peptide include —OH, —SH, —NH₂ and —NHR where R is (C₁–C₆) alkyl, (C₁–C₆) alkenyl and (C₁–C₆) alkynyl.

[0426] The variety of reactions between two side chains with functional groups suitable for forming such interlinkages, as well as reaction conditions suitable for forming such interlinkages, will be apparent to those of skill in the art. Preferably, the reaction conditions used to conjugate or cyclize the peptides are sufficiently mild so as not to degrade or otherwise damage the peptide. Suitable groups for protecting the various functionalities as necessary are well known in the art (see, e.g., Greene & Wuts, 1991, 2nd ed., John Wiley & Sons, NY), as are various reaction schemes for preparing such protected molecules.

[0427] Peptide conjugates and cyclic peptides as well as methods for preparing such peptides are well-known in the art (see, e.g., Spatola, 1983, Vega Data 1(3) for a general review); Spatola, 1983, "Peptide Backbone Modifications" In: Chemistry and Biochemistry of Amino Acids Peptides and Proteins (Weinstein, ed.), Marcel Dekker, New York, p. 267 (general review); Morley, 1980, Trends Pharm. Sci. 1:463-468; Hudson et al., 1979, Int. J. Prot. Res. 14:177-185 (—CH₂ NH—, —CH₂ CH₂—); Spatola et al., 1986, Life Sci. 38:1243-1249 (—CH₂—S); Hann, 1982, J. Chem. Soc. Perkin Trans. I. 1:307-314 (—CH=CH—, cis and trans); Almquist et al., 1980, J. Med. Chem. 23:1392-1398 (—CO CH₂—); Jennings-White et al., Tetrahedron. Lett. 23:2533 (—CO CH₂—); European Patent Application EP 45665 (1982) CA:97:39405 (—CH(OH)CH₂—); Holladay et al., 1983, Tetrahedron Lett. 24:4401-4404 (—C(OH)CH₂—); and Hruby, 1982, Life Sci. 31:189-199 (—CH₂—S—).

Target Molecules

[0428] Peptides of the invention can bind any biomolecule, tissue or protein of interest. Such biomolecules or proteins of interest may be involved in lipid transport or cellular uptake e.g. apolipoprotein (a, AI, AII, AIV, B, CI, CII, CIII or E), low density lipoprotein receptor (LDL-R), cholesterol ester transfer protein, hepatic TG lipase, lipoprotein lipase, high density lipoprotein receptor p110, LDL receptor like protein, ARPI, LDL-R protein kinase, apolipoprotein E receptor or oncostatin M. The biomolecule may be involved in the uptake of modified lipoproteins e.g. LDL-R, scavenger receptor, advanced glycosylated end-product receptor or macrophage FC receptor. The biomolecule may be involved in lipid metabolism e.g. AMP-activated protein kinase, AMP-activated protein kinase kinase, acetyl CoA cholesterol ester transferase, lecithin-cholesterol ester transferase, cholesterol 7 α -hydroxylase, hormone sensitive-lipase/cholesterol ester hydroxylase or HMG CoA reductase. The biomolecule may be involved in lipid oxidation e.g. 15-lipoxygenase, IL-4, IL-4 receptor, superoxide dismutase or 12 lipoxygenase. The biomolecule may be involved in smooth muscle cell growth such as platelet derived growth factor (PDGF-A), PDGF-B, PDGF- α receptor, PDGF- β receptor, heparin-binding EGF-like growth factor, basic fibroblast growth factor (bFGF), aFGF, FGF receptor, IL-1, IL-1 receptor p80, IL-1 receptor

protein kinase, interferon gamma, TGF- β 1, TGF- β 2, TGF- β 3, TGF receptor, tumor necrosis factor- α . (TNF- α), TNF- α receptor, α -thrombin, α -thrombin receptor, 9-hydroxyoctadeca-10,12-dienoic acid (9-HODE) receptor, insulin-like growth factor, platelet factor-4, TGF- α , thromboxane A₂ receptor, 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) receptor, 13-hydroxyoctadeca-9,11-dienoic acid (13-HODE) receptor, IL6, IL-6 receptor or EGF receptor. The biomolecule may be an endothelial cell growth factor or receptor (EGF) such as vascular EGF, VEGF receptor, bFGF, aFGF, FGF receptor or platelet-derived endothelial cell growth factor. The biomolecule may be associated with macrophage growth and chemotaxis e.g. CSF-1, CSF-1 receptor, monocyte chemoattractant protein-1 (MCP-1) or MCP-1 receptor. The biomolecule associated with atherosclerosis may be associated with endothelial cell adhesion such as VCAM-1, VLA-4 α ₄ subunit, VLA-4 β ₁ subunit, ELAM-1, ICAM-1, LFA-1 α _L subunit, LFA-1 β ₂ subunit, GMP-140 (PADGEM), neuropeptide Y, VLA-4 α ₁ subunit, vitronectin receptor or 13-hydroxyoctadeca-9,11-dienoic acid (13-HODE) receptor. The biomolecule associated with a peptide of the invention may also be phosphoenolpyruvate carboxylase (PEPCK).

[0429] In one embodiment the biomolecule is an 82 kilodalton protein that binds to the CAPGPSKSC (SEQ ID NO:4) peptide. This 82 kilodalton protein is referred to herein as the P82 protein. It may be a membrane protein. In another the biomolecule is an 120 kilodalton protein that binds to the CAPGPSKSC (SEQ ID NO:4) peptide. This 120 kilodalton protein is referred to herein as the P120 protein.

[0430] Peptides of the invention can bind to any target. Peptides conjugated to reporter molecules can be used in vivo to locate, image or otherwise identify where such targets are present in mammals and to ascertain what biological processes, physiological structures, intracellular structures, diseases, and the like with which the target is associated. Peptides conjugated to therapeutic agents can be used in vivo to treat any site where such targets are located within a mammal.

Therapeutic Methods

[0431] The peptides of the invention can be used in any therapeutic procedure available to one of skill in the art to treat any disease or physiological problem with which a target molecule bound by of a peptide of the invention is associated. An association with a disease or physiological problem means that the target molecule is localized at the site of the disease or physiological problem. The target molecule may be directly or indirectly involved in the disease or the physiological problem. For example, the target molecule can have an activity or structure that contributes to the disease or the physiological problem. However, the target molecule may also be merely localized to the region of a disease or physiological problem and may not be a direct or indirect cause of the disease or physiological problem. Thus, the target molecule may have no obvious involvement in the pathogenesis of the disease or the physiological problem, but rather have the potential to modify cell function and thereby minimize the pathogenetic process.

[0432] Any disease or physiological problem associated with a target molecule or cell bound by of a peptide of the invention can be treated with the present peptides through conjugation of the peptides to one or more therapeutic

agents. For example, peptides conjugated to therapeutic agents can be used to treat stroke, atherosclerosis, peripheral arterial diseases, peripheral limb disease, acute coronary syndromes including unstable angina, thrombosis and myocardial infarction, plaque rupture, both primary and secondary (in-stent) restenosis in coronary or peripheral arteries, vein graft stenosis, transplantation-induced sclerosis, reperfusion injuries, ischemic vascular diseases, myocardial ischemia, intermittent claudication and diabetic complications (including ischemic heart disease, peripheral artery disease, congestive heart failure, retinopathy, neuropathy and nephropathy), or thrombosis. This invention also can be used to treat bypass grafts or access port stenosis (e.g. dialysis access ports) in any vascular location. The methods and peptides of the invention can be used to stabilize atherosclerotic plaques at risk of rupture or other clinical events.

[0433] To treat these diseases and physiological conditions, peptides are conjugated to therapeutic agents using procedures provided herein or any other method known to one of skill in the art. Such peptide conjugates are then administered to a mammal in a therapeutically effective amount. Peptide conjugates can be administered for a time sufficient to beneficially treat the disease or physiological condition.

[0434] For example, the invention provides a method of treating atherosclerosis in a mammal that includes administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent, wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can beneficially treat atherosclerosis. Such therapeutic agents include, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, anti-inflammatory agents or liposomes that contain thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, or anti-inflammatory agents.

[0435] In another embodiment, the invention provides a method of preventing heart attack in a mammal that includes administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent, wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can help prevent heart attack. Such therapeutic agents include, for example, thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, anti-inflammatory agents or liposomes that contain thrombolytic agents such as streptokinase, tissue plasminogen activator, plasmin and urokinase, anti-thrombotic agents such as tissue factor protease inhibitors (TFPI), nematode-extracted anticoagulant proteins (NAPs) and the like, metalloproteinase inhibitors, or anti-inflammatory agents.

[0436] The peptides and peptide conjugates of the invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient

in a variety of dosage forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

[0437] Thus, the peptides and peptide conjugates may be systemically administered, for example, intravenously or intraperitoneally by infusion or injection. Solutions of the peptide or peptide conjugate can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0438] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient(s) that are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0439] Sterile injectable solutions are prepared by incorporating the peptide or peptide conjugate in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods for preparation of such powders are vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

[0440] In some instances, the peptides and peptide conjugates can also be administered orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. The peptides may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the peptide or peptide conjugate may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% to about 90% of the weight

of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

[0441] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

[0442] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use.

[0443] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

[0444] Useful dosages of the peptides and peptide conjugates can be determined by correlating their *in vitro* activity, and *in vivo* activity in animal models described herein.

[0445] The therapeutically effective amount of peptide or peptide conjugate necessarily varies with the subject and the disease or physiological problem to be treated. For example, a therapeutic amount between 30 to 112,000 μg per kg of body weight can be effective for intravenous administration. As one skilled in the art would recognize, the amount can be varied depending on the method of administration. The amount of the peptide or peptide conjugate, required for use in treatment will vary not with the route of administration, but also the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

[0446] The compound can conveniently be administered in unit dosage form; for example, containing 1 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 20 to 500 mg of peptide or peptide conjugate per unit dosage form.

[0447] Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active

compound of from about 0.1 to about 75 μM , preferably, about 1 to 50 μM , most preferably, about 2 to about 30 μM . This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

[0448] The desired dose may conveniently be presented in a single dose, as divided doses, or as a continuous infusion. The desired dose can also be administered at appropriate intervals, for example, as two, three, four or more sub-doses per day.

Methods for Isolating Peptides

[0449] The invention further contemplates *in vivo* methods of identifying and/or isolating peptides that can bind to a biomolecule of interest. Such methods involve contacting the biomolecule *in vivo* with a phage display library and isolating phage that selectively adhere to the biomolecule. See Pasqualini et al., 380 Nature 364-66 (1996).

[0450] The methods are performed *in vivo* by placing the phage display library within a suitable animal in a manner that permits the phage to come into contact with the biomolecule. For example, the phage can be injected into the tissues of an animal within the general region of the biomolecule. Preferably, the phage display library is placed or injected into a cavity or vessel of the animal. Such cavities or vessels preferably are filled or partially filled with fluids that permit diffusion and/or circulation of the phage. For example, phage libraries can be injected or placed within the vascular system, digestive system, lymph system, spinal fluid and the like.

[0451] In one embodiment, the invention provides a method of identifying a peptide capable of binding to mammalian vascular tissues that includes circulating a phage display library through the vascular tissues of a mammal. Phage that selectively adhere to the vascular tissues of the mammal can be isolated and the peptides displayed on the phage can be identified. Such methods are useful when identifying peptides that are capable of binding to the vascular tissues of the mammal, or to a biomolecule present in discrete portions of the vascular tissues of the mammal.

[0452] In many instances, the tissues or biomolecules can more advantageously be contacted and saturated with wild type phage identical to those used for the phage display library, but without peptide inserts. Such exposure blocks or saturates the tissue or biomolecules with wild type phage so that, when the tissue or biomolecules are contacted with phage displaying peptides, any phage bound will likely bind through the displayed peptide. Therefore, exposure to phage without peptide inserts can, for example, saturate the reticuloendothelial system of the animal, and diminish non-specific phage binding.

[0453] Prior to injection or exposure to the phage display library, the tissues or biomolecules of the animal are exposed to a sufficient number of wild type phage for a sufficient time to permit binding of wild type phage to all sites that have a propensity to bind such wild type phage.

[0454] A sufficient number of wild type phage to saturate all sites in the tissue or biomolecules of the animal that have a propensity to bind such wild type phage can be determined by one of skill in the art. Such a number of wild type phage depends on the size of the animal, the time for exposure to the phage and the complexity of biomolecules within the animal. For example, when mice are used as the experimental animal, about 10^3 pfu to about 10^{13} pfu of wild type helper phage can be injected into the mice. Alternatively, about 10^6 pfu to about 10^{12} pfu, about 10^9 pfu to about 10^{12} pfu, or about 10^{11} pfu to about 10^{12} pfu of wild type helper phage are injected into the mice.

[0455] A sufficient time to permit binding of wild type phage to all sites that have a propensity to bind such wild type phage and then binding of phage display libraries can also be determined by one of skill in the art. Such a time depends on the size of the animal and the complexity of biomolecules within the animal. For example, when mice are used as the experimental animal, about ten to about sixty minutes can be used. Preferably, the time to permit binding of wild type phage to all sites that have a propensity to bind such wild type phage, is about fifteen to about forty five minutes. In one embodiment 10^{12} pfu of wild type helper phage were injected into the atherosclerotic mice and were allowed to circulate for about thirty minutes. Such exposure was sufficient to diminish non-specific phage binding and saturate the reticuloendothelial system of the mice. Injection of wild type phage can be performed just prior to injection of the phage display library.

[0456] After injection or exposure to wild type phage, the tissues or biomolecules of the mammal are exposed to a sufficient number of the library phage or peptides for a sufficient time to permit binding of displayed peptides to biomolecules. A sufficient number of library phage to permit binding to biomolecules depends on the size of the animal and the complexity of phage in the library within the animal. In general, a selected library of phage will have less complexity than a library of all possible peptide sequences. Lower numbers of phage from such a selected library can be used. For example, when mice are used as the experimental animal, about 10^3 pfu to about 10^{13} pfu of library phage can be injected into the mice. Preferably, about 10^{10} pfu to about 10^{12} pfu of unselected library phage are injected into the mice initially. After selection of phage bound to the tissue or biomolecule of interest, about 10^3 pfu to about 10^7 pfu from a preselected library can be injected for a subsequent round of selection.

[0457] A sufficient time to permit binding of library phage to biomolecules can be determined by one of skill in the art. Such a time depends on the size of the animal and the complexity of library. For example, when mice are used as the experimental animal, about 10 to about 120 minutes can be used. Preferably, the time to permit binding of library phage to biomolecules is about fifteen to about sixty minutes.

[0458] The methods of the invention for identifying peptides can include several rounds of selection for adherence to the biomolecule, lesion or tissue of interest. For example, after isolating phage that selectively adhere to the biomolecule, lesion or tissue of interest, those phage can be replicated and again contacted with the biomolecule or tissue of interest. Preferably, the phage are minimally ampli-

fied to minimize the possibility of genetic selection during amplification that may lead to loss or mutation of the peptide. These methods provide a population of phage that selectively adhere the biomolecule or tissue of interest. After contacting this population with the biomolecule or tissue in vivo, one or more second selected phage are isolated. When one of skill in the art has performed sufficient rounds of selection, the peptide displayed on the selected phage can be identified and further characterized or tested to evaluate the peptide for its capability for binding to the biomolecule or tissues of interest.

[0459] In some instances, the methods of the invention are used to identify peptides that bind to a particular biomolecule. In other instances, the methods of the invention are used to identify peptides that bind to a particular tissue or a local lesion or site of pathology, but the biomolecule to which the peptides bind is not known. The biomolecule to which the peptide binds can be identified by methods readily available to one of skill in the art. For example, a biomolecule within a tissue bound by a peptide can be identified by first homogenizing the tissue to create a mixture of biomolecules. Such biomolecules can be separated and then contacted by a selected peptide. The peptides will then bind to the biomolecule to which it adhered when the peptide bound to the tissue and the biomolecule can be identified and characterized.

[0460] Hence, in one embodiment, the invention provides a method of identifying a protein or other biomolecule bound by a peptide that is capable of binding to the vascular tissues of a mammal. This method involves separating a mixture of proteins prepared from the vascular tissues of a mammal and contacting the separated mixture of proteins with a peptide that is capable of binding to the vascular tissues of the mammal. The protein that binds to peptide is then identified, and can be characterized.

[0461] The invention has particular utility for identifying and isolating peptides that bind to atherosclerotic lesions and biomolecules that are uniquely expressed on the surface of these lesions. Such methods involve circulating a phage display library through the vascular tissues of a mammal and isolating a phage that selectively adheres to atherosclerotic lesions in the mammal. The peptide displayed on the phage is then identified. As described above, further rounds of selection for adhesion to atherosclerotic lesions can be performed to insure that the peptide is capable of specifically binding to only atherosclerotic lesions or to particular types of atherosclerotic lesions in the mammal.

[0462] The protein or biomolecule within an atherosclerotic lesion that is bound by the peptide can also be identified. For example, a mixture of proteins or biomolecules prepared from atherosclerotic lesions of a mammal can be separated. The separated mixture of proteins or biomolecules can then be contacted with a peptide that is capable of binding to the atherosclerotic lesions in the mammal. The protein or biomolecule that binds the peptide is identified.

[0463] A peptide within a phage that selectively binds to a tissue or biomolecule of interest can be identified and/or isolated by dissecting out the tissue of interest or the tissue containing the bound phage. Such dissected tissue can be washed to remove phage that are non-specifically bound. To isolate phage displaying a selectively bound peptide, the phage that remain associated with the tissue of interest are

eluted. Such bound phage can be amplified and titered. After the desired rounds of selections are performed, the phage can be plated out and individual clones can be selected, recloned and the peptide inserts sequenced.

[0464] The potential significance of an isolated peptide, the ability of the phage displaying that peptide to localize in vivo can be assessed by injection of the cloned phage, sometimes mixed with wild type, into an appropriate animal model, such as mice, rats and later, rodents bearing human skin grafts with human vasculature. About 10 to about 60 min after injection, the animals were euthanized, the vasculature perfused, and the target and control tissues recovered for analysis by: (1) recovery of phage and determining the ratio of specific phage to wild type control phage by blue/white colony counts; and (2) confocal microscopy of cryostat sections of frozen tissue blocks to determine that the specific phage associates with endothelium and to determine the specific pattern of localization in the vasculature (e.g. capillaries vs. venules vs arterioles).

[0465] In one series of experiments, one hundred thirty individual phage clones were isolated and sequenced using these procedures. Two clones occurred twice and two additional clones occurred three times. Ninety-three independent sequence "sets" have been defined. The total number of recovered phage clones from three cycles of in vivo selection is about several hundred, indicating that a relatively large number of initial candidates can readily be obtained with these methods.

[0466] Peptide sequences isolated by the present methods can be scrutinized for homologies to known peptide and protein sequences. Database searches for common or similar protein domains are within the ken of one of skill in the art.

Animals

[0467] Any animal containing a tissue of interest or a tissue containing a biomolecule of interest can be used for the in vivo selection procedures of the invention. Such animals include mice, rats, rabbits, cats, dogs, goats, horses, pigeons and the like. In some instances, animals of a particular genotype and/or animals that exhibit a particular phenotype are used. One of skill in the art can readily identify the appropriate animal for use in the present methods. For example, for identification of peptides that bind to atherosclerotic lesions, hypercholesterolemic animals that are accepted models for atherosclerosis can be used. Such animals include: Apo E mice, LDL-R deficient mice, combined Apo E/LDL-R deficient mice, Watanabe rabbits, and pigeons.

Phage Display Libraries

[0468] While the invention contemplates identification of peptides capable of binding to biomolecules by any mechanism, one method involves the use of phage display libraries. Any available phage display library can be used.

[0469] For example, *filamentous bacteriophages* can be used to express a library of peptides on the surface of the *bacteriophage*. *Filamentous bacteriophages* are a group of related viruses that infect bacteria. They are termed *filamentous* because they are long and thin particles comprised of an elongated capsule that envelopes the deoxyribonucleic acid (DNA) that forms the *bacteriophage* genome. The F pili *filamentous bacteriophage* (Ff phage) infect only gram-

negative bacteria by specifically adsorbing to the tip of F pili, and include fd, fl and M13.

[0470] The mature capsule of Ff phage is comprised of a coat of five phage-encoded gene products: cpVIII, the major coat protein product of gene VIII that forms the bulk of the capsule; and four minor coat proteins, cpIII and cpIV at one end of the capsule and cpVII and cpIX at the other end of the capsule. The length of the capsule is formed by 2500 to 3000 copies of cpVIII in an ordered helix array that forms the characteristic filament structure. About five copies each of the minor coat proteins are present at the ends of the capsule. The gene III-encoded protein (cpIII) is typically present in 4 to 6 copies at one end of the capsule and serves as the receptor for binding of the phage to its bacterial host in the initial phase of infection. For detailed reviews of Ff phage structure, see Rasched et al., *Microbiol. Rev.*, 50:401-427 (1986); and Model et al., in "The *Bacteriophages*, Volume 2", R. Calendar, Ed., Plenum Press, pp. 375-456 (1988). One of skill in the art can fuse a combinatorial peptide library to any of these proteins to create a phage display library.

[0471] However, one of skill may prefer to choose to fuse peptide libraries with the cpVIII or cpIII proteins. No phage particles are assembled within a host cell; rather, they are assembled during extrusion of the viral genome through the host cell's membrane. Prior to extrusion, the major coat protein cpVIII and the minor coat protein cpIII are synthesized and transported to the host cell's membrane. Both cpVIII and cpIII are anchored in the host cell membrane prior to their incorporation into the mature particle. In addition, the viral genome is produced and coated with cpV protein. During the extrusion process, cpV-coated genomic DNA is stripped of the cpV coat and simultaneously re-coated with the mature coat proteins.

[0472] Both cpIII and cpVIII proteins include two domains that provide signals for assembly of the mature phage particle. The first domain is a secretion signal that directs the newly synthesized protein to the host cell membrane. The secretion signal is located at the amino terminus of the polypeptide and targets the polypeptide at least to the cell membrane. The second domain is a membrane anchor domain that provides signals for association with the host cell membrane and for association with the phage particle during assembly. This second signal for both cpVIII and cpIII comprises at least a hydrophobic region for spanning the membrane.

[0473] The cpVIII has been extensively studied as a model membrane protein because it can integrate into lipid bilayers such as the cell membrane in an asymmetric orientation with the acidic amino terminus toward the outside and the basic carboxyl terminus toward the inside of the membrane. The mature protein is about 50 amino acid residues in length of which 11 residues provide the carboxyl terminus, 19 residues provide the hydrophobic transmembrane region, and the remaining residues comprise the amino terminus.

[0474] The sequence of cpIII indicates that the C-terminal 23 amino acid residue stretch of hydrophobic amino acids normally responsible for a membrane anchor function can be altered in a variety of ways and still retain the capacity to associate with membranes. Ff phage-based expression vectors are available in which the entire cpIII amino acid residue sequence is modified by insertion of short polypeptide "epitopes" [Parmely et al., *Gene*, 73:305-318 (1988);

and Cwirla et al., Proc. Natl. Acad. Sci. USA, 87:6378-6382 (1991)] or an amino acid residue sequence defining a single chain antibody domain. McCafferty et al., Science, 348:552-554 (1990). These hybrid proteins were synthesized and assembled onto phage particles in amounts of about 5 copies per particle, a density at which normal cpIII is usually found. One of skill in the art can use these teachings to incorporate combinatorial peptide-encoding polynucleotide libraries into the normal cpIII or cpVIII genes. Further teachings in this regard are found in U.S. Pat. No. 6,235,469.

[0475] A gene repertoire useful for the practice of the invention is a collection of different peptide-encoding genes, which can be isolated from natural sources or can be generated artificially. A gene repertoire useful in practicing the present invention contains at least 10^3 , preferably at least 10^4 , more preferably at least 10^5 , and most preferably at least 10^7 different genes. Methods for evaluating the diversity of a repertoire of genes are well known to one skilled in the art.

[0476] For example, the present invention contemplates testing a library of peptides from known adhesive proteins. Many such proteins involved in cell attachment are members of a large family of related proteins termed integrins. Integrins are heterodimers comprised of a beta and an alpha subunit. Members of the integrin family include the cell surface glycoproteins platelet receptor GpIIb-IIIa, vitronectin receptor (VnR), fibronectin receptor (FnR) and the leukocyte adhesion receptors LFA-1, Mac-1, Mo-1 and 60.3. Rouslahti et al., Science, 238:491-497 (1987). Nucleic acid and protein sequence data demonstrate that regions of conserved sequences exist in the members of these families, particularly between the beta chain of GpIIb-IIIa, VnR and FnR, and between the alpha subunit of VnR, Mac-1, LFA-1, FnR and GpIIb-IIIa. Suzuki et al., Proc. Natl. Acad. Sci. USA, 83:8614-8618, 1986; Ginsberg et al., J. Biol. Chem., 262:5437-5440, 1987. Any of these proteins or peptides derived therefrom can be used to make peptide display libraries.

[0477] A library of DNA molecules can be produced where each DNA molecule comprises a cistron for expressing a fusion polypeptide on the surface of a *filamentous* phage particle. This can be done, for example, by (a) forming a ligation admixture by combining in a ligation buffer (i) a repertoire of peptide encoding genes and (ii) a plurality of DNA expression vectors in linear form adapted to form a fusion polypeptide, and (b) subjecting the admixture to ligation conditions for a time period sufficient for the repertoire of genes to become operatively linked (ligated) to the plurality of vectors to form the library.

[0478] At this point, the repertoire of peptide encoding genes is in the form of double-stranded (ds) DNA and each member of the repertoire has cohesive termini adapted for directional ligation. In addition, the plurality of DNA expression vectors are each linear DNA molecules having upstream and downstream cohesive termini that are (a) adapted for directionally receiving the polypeptide genes in a common reading frame, and (b) operatively linked to respective upstream and downstream translatable DNA sequences. The upstream translatable DNA sequence encodes a secretion signal, for example, a pelB secretion signal, and the downstream translatable DNA sequence encodes a *filamentous* phage coat protein membrane anchor

for a peptide. The translatable DNA sequences are also operatively linked to respective upstream and downstream DNA expression control sequences as defined for a DNA expression vector.

[0479] The library so produced can be utilized for expression and screening of the fusion polypeptides encoded by the resulting library of cistrons represented in the library by the screening methods described herein.

Nucleic Acids

[0480] The present invention provides purified and isolated nucleic acids encoding the peptides of the invention. Nucleic acids of the invention (both sense and anti-sense strands thereof) include genomic DNAs, cDNAs, and RNAs, as well as completely or partially synthetic nucleic acids. Nucleic acids of the invention include any DNA encoding peptides having even-numbered SEQ ID NO, as well as nucleic acids that hybridize to those DNAs under standard stringent hybridization conditions. DNAs encoding the peptides of the invention also include the odd-numbered SEQ ID NOs described herein as well as DNAs that, due to the degeneracy of the code, also encode the peptides of the invention. The odd-numbered SEQ ID NOs correspond to the phage display library DNAs that encode the even-numbered peptides isolated by the present methods.

[0481] Exemplary stringent hybridization conditions are as follows: hybridization at 65° C. in 50% formamide, 5×SSC, 20 mM sodium phosphate, pH 6.8 and washing in 0.2×SSC at 65° C. More preferred stringent hybridization conditions include hybridization in 6×SSC and at 55° C. It is understood by those of skill in the art that variation in these conditions occurs based on the length and GC nucleotide content of the sequences to be hybridized. Formulas standard in the art are appropriate for determining exact hybridization conditions. See Sambrook et al., §§9.47-9.51 in Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989); Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001). Preferred nucleic acids of the invention include DNAs encoding peptides having SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 and/or SEQ ID NO:464.

[0482] The following examples further illustrate the invention and are not intended to limit it in any way.

EXAMPLE 1

Screening Peptides for Binding to Atherosclerotic Lesions

[0483] The surface characteristics of endothelial cells from atherosclerotic lesions of atherosclerotic ApoE knockout mice were investigated by *in vivo* selection of phage displaying seven amino acid peptides flanked by cysteine residues. Apo-E knockout and LDL receptor knockout mice on atherogenic diets develop atherosclerotic lesions within 10-12 weeks at the aortic arch and the branch point of renal arteries. These animals are accepted animal models of human atherosclerotic lesions that have similar developmental and biochemical pathways.

Material and Methods

Phage Display Libraries

[0484] Gene III-fused libraries used included New England lab PHD™, 7-mer linear, 12-mer linear, and 7-mer cyclized libraries. The PHD™ phage peptide library was from New England Biolabs (Beverly, Mass.). Gene VIII fused libraries used were designed and constructed as 4-mer, 5-mer and 6-mer cyclized libraries. The inserted combinatorial elements were linear peptides of 4-7 amino acids in length, constrained at each end by cysteine residues.

Animals

[0485] The parental stock of C57BL/6J ApoE gene inactivated (knockout) mice was obtained from Jackson Laboratories. These and wild type C57BL/6J mice were bred in the Rodent Breeding Facility of The Scripps Research Institute and fed ad lib standard chow diet (No. 5015, Harlan Tekland, Madison, Wis.). To produce the atherosclerotic ApoE model lesions, the mice were fed atherogenic diet No. TD 88051 containing 15.8% (wt/wt) fat, 1.25% (wt/wt) cholesterol, and 0.5% (wt/wt) sodium cholate. All studies were reviewed and approved by the Institutional Animal Care and Use Committee and conducted in the Institutional facilities accredited by AAALAC, with an assurance from the Public Health Service, registered with the U.S. Department of Agriculture and in compliance with regulations.

In Vivo Panning with Phage Display Libraries

[0486] In vivo biopanning was performed in atherosclerotic ApoE knockout mice, after 12 weeks on the high fat diet. All animals had grossly visible atherosclerotic lesions of the aortic arch and the branch point of renal arteries within 10-12 weeks after being fed the high fat diet. Thirty minutes prior injection of the phage library, 10^{12} pfu of irradiated helper phage were infused via the tail vein of the mice and allowed to circulate for 30 minutes to block non-specific phage binding and to saturate the mouse reticuloendothelial system. Then, 10^{11} pfu of viable peptide library phage were injected and allowed to circulate for 30 min. The mouse was perfused via the heart at arterial pressure with warm physiological saline (Phosphate Buffered Saline (PBS), pH 7.4) for about 5 min. The aorta was removed, washed, and opened to expose lesions at the arch and the branch point of renal arteries. These were dissected free and bound phage were eluted with elution buffer (0.1 M glycine, pH 2.2) and neutralized with 0.1 volume of Tris buffer (2 M tris-HCl, pH 8). The eluted phage were amplified by infection of *E. coli* in medium, then plated and titered. Basic phage protocols used are from "Phage Display of Peptides and Proteins, A Laboratory Manual" (Brian K. Kay, Jill Winter, and John McCafferty, Academic Press). Up to 10^4 of library phage were recovered from the first round of selection. Three additional rounds of selection were performed. Phage recovered from the fourth round were plated and individual clones were selected for sequence analysis.

Analysis of peptide sequences.

[0487] Peptide sequences were analyzed with ClustalW (12) software from the European Molecular Biology Laboratory to identify amino acid motifs that are shared among multiple peptides. The peptide sequences were also searched by online databases using the BLAST program accessible at

NCBI (website at ncbi.nlm.nih.gov/BLAST). The value of a "hit" sequence was assessed by the following ordered set of criteria: (1) a sequence exhibits significant similarity to extracellular protein domains, including a variety of proteins with the same type of domain; (2) the sequence exhibits similarity with a known protein candidate for binding to cells; (3) scoring is increased if multiple phage hit sequences exhibit similarity to the same or closely adjacent linear sequence of a given protein; (4) a phage sequence shows similarity, overlap, or a common smaller motif with other "Mt" phage inserts. Independent of the exact sequence of the insert, or its similarity to known sequences, an insert that was recovered repeatedly from progressive in vivo selection experiments, was considered of interest and meritorious of further analysis.

[0488] The distribution of the account X of success in n independent trials with probability p of success on each trial is a binomial distribution B (n, p), and was approximated with equation:

$$P(X=k) = \{n!/k!(n-k)!\} p^k (1-p)^{n-k}$$

Here X is the number of times a given peptide motif occurred in n independent sequencing trials, and p is the probability of this peptide occurring in each trial.

Peptides

[0489] To assess whether a peptide recovered by the selection procedures provided above is truly specific for atherosclerotic lesions, selected peptides were synthesized with a triple-Gly spacer terminating in a biotin reporter molecule. Thus, peptides ACAPGPSKSCGGSYK^{-Biotin} (SEQ ID NO:468), ACNHRMQMCGGSYK^{-Biotin} (SEQ ID NO:470), ACNQRHQMSCGGSYK^{-Biotin} (SEQ ID NO:472) and ACVNRSDGMCSSYK^{-Biotin} (SEQ ID NO:474) were synthesized by the Scripps Peptide Core facility using Fmoc chemistry. A control peptide with a scrambled sequence but the same amino acid composition was also synthesized. An N-terminal alanine (underlined) that is encoded by the phage and present on the phage protein was added to the N-terminus of the peptides. An extension of GGSYK was added to the C-terminus of the peptides (underlined). The tyrosine permitted iodination and the lysine was added for biotinylation. Biotin was attached through the side chain amino group of the C-terminal while the peptides were attached to the beads. The peptides were de-blocked, cleaved, and HPLC purified. The purified peptides were characterized by mass spectrometry. The molecular weight of the peptides exactly matched the predicted mass. Control and experimental peptides were tested to insure that they could bind streptavidin.

[0490] Immunohistochemistry with confocal microscopy was used to observe whether the experimental and/or control peptides localize selectively to the endothelium. Streptavidin alone was used as a further control to assess background staining.

Intermolecular Disulfide Bond Formation in Cys-Containing Peptides

[0491] Analysis of the role of intact disulfide bond constraints was assessed by reduction and re-oxidization of the peptides. Two ml PBS was used to dissolve every five mg peptide, and 2-mercaptoethanol was added to a final concentration of 0.05 M. The reduction reaction was carried out

for four hours at room temperature. The reaction mixture was then lyophilized to remove the 2-mercaptoethanol. The reduced peptide preparations were analyzed and divided into two aliquots. One aliquot was stored as the reduced, lyophilized peptide preparation. The second aliquot was air oxidized in 0.1 mM in folding buffer (2 M Guanidinium HCl, 0.2 M Tris-HCl, pH 8.5) while being stirred vigorously with air overnight. The progress of intermolecular disulfide formation was monitored by the Ellman's reaction. The re-oxidized and folded peptides and the control reduced peptides were dialyzed against phosphate buffered saline. For in vivo experiments the peptides were dialyzed against sterile clinical physiologic saline and sterile filtered.

[0492] Molecular modeling of the peptide with sequence CAPGPSKSC (SEQ ID NO:4) suggested that it forms a very rigid ring structure. The refolding experiment also indicated that, under oxidizing condition, the peptide quickly circularizes, and the monomeric cysteine loop structure is the favored conformation for this peptide. Most peptides do not have such a defined and restricted conformation in solution.

Immunohistochemical Analysis.

[0493] Immunohistochemical analysis for binding was performed on frozen 5 micron sections of ApoE mouse atherosclerotic aortic valve and aorta on poly-L-lysine coated slides. Biotinylated peptide binding to aortic lesions was detected by streptavidin conjugated peroxidase and was developed with DAB substrate (Vector, Burlingame, Calif.). For endothelial identification, biotinylated rat CD-31 specific mouse monoclonal antibody was used and was detected with Texas red conjugated streptavidin. Phage staining was performed with rabbit anti-phage antibody followed by a fluorescein conjugated goat anti-rabbit antibody. The sections were analyzed by laser scanning confocal microscopy.

Phage Localization in Atherosclerotic Lesions

[0494] To observe phage or peptide association with atherosclerotic lesions, either phage carrying a homing peptide sequence or a circular synthetic peptide were injected into the mice via the tail vein. After 30 min circulation, the mice were perfused with sterile PBS (pH 7.4) through a cannula to the left ventricle, and the perfusate was drained out through an incision made in the inferior vena cava. Fixation was in situ by perfusion with 4% paraformaldehyde. The aortas were dissected under a microscope, and the associated fat tissue cleaned while attached. The aorta was then longitudinally opened from aortic valve to iliac bifurcation. The detached aorta was pinned flat.

[0495] Biotinylated anti-phage antibody (Sigma) diluted 1:500 was layered over the vascular tissue, followed by 1:500 dilution of avidin-peroxidase (Vector, Burlingame, Calif.), to detect phage that were associated with the atherosclerotic lesion in the aorta. The aorta samples were then washed three times in PBS and developed using DAB substrate as suggested by the manufacturer.

[0496] The atherosclerotic regions of human vessels were similarly dissected and pinned on to the dissecting pan. These tissues were then incubated with refolded biotinylated peptides (10.0 µg/ml) overnight at 4° C. The samples were washed three times. An avidin-peroxidase conjugate was used as a second tier probe, and each specimen was visualized with DAB substrate.

Target Protein Identification

[0497] Human umbilical cord venous endothelial cells (HUVEC) and EGM™ culture medium were from Clonetics, Walkersville, Md. Cells were cultivated in EGM with 5% fetal bovine serum (FBS) in flasks coated with 0.2% gelatin. The bEND.3 cells (ATCC) were cultured in Dulbecco's minimum essential medium (DMEM) (Invitrogen, Carlsbad, Calif.) supplemented with 10% FBS and 2 mM L-glutamine. The HT1080 cells were from ATCC and cultured in DMEM supplemented with 10% FBS, 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, and 0.1 mM NEAA (Non-essential amino acids, Invitrogen, Carlsbad, Calif.). The ECV304 were from ATCC and cultured in DMEM, 10% FBS.

[0498] The membrane fractions of endothelial cell lines were prepared using Triton 114 extraction. Endothelial cell pellets of approximately 5×10^6 cells were lysed with 1 ml 1% triton X-114 in 0.1 M Tris, 10 mM EDTA, 2000 U/ml Aprotinin, 100 µM PMSF by incubating with repeated mixing on ice for 15 min. The debris was removed by centrifugation at 16,000 g at 4° C. The resultant supernatant was then incubated for 5 min at 37° C. to permit phase separation and then centrifuged at 16,000 g for 2 min at room temperature. The lower membrane phase was recovered and re-extracted with 1% Triton X 114 solution as described above. Extracted membrane fractions were precipitated with cold acetone (-20 °C.) and centrifuged for 10 minutes at 16,000 g. The membrane protein pellet was air dried and re-suspended in SDS sample buffer. The membrane protein preparation was separated by either polyacrylamide gel electrophoresis under non-denaturing conditions or SDS polyacrylamide gel electrophoresis using a gradient Tris-glycine gel (8-16%). Separated proteins were transferred from the gel onto a nitrocellulose membrane and non-specific interactions were then blocked with non-fat milk. Biotinylated peptides identified by the in vivo panning procedures were used as probes. Nitrocellulose membranes were incubated with 10 µg/ml biotinylated peptide probes overnight at room temperature with gentle agitation. Nitrocellulose membranes were then washed three times with PBS, incubated with streptavidin-peroxidase for 15-30 min and developed with DAB substrate.

Peptide Binding Assay

[0499] Analysis of synthetic peptide binding to cells was performed in 96 well plates. Cells (10^5) were plated into each well, incubated overnight then briefly fixed with cold ethanol for 10 seconds. Serial concentrations of peptide in 100 µl PBS were added and incubated at room temperature with gentle shaking for four hours. The wells were washed three times with PBS and reaction developed using streptavidin-peroxidase substrate (Vector, Burlingame, Calif.). The reactions were quantified at 405 nm in a plate reader (Molecular Devices, Sunnyvale, Calif.). In the inhibition assay, TIMP-2 protein was included with the peptide in the initial incubation.

Results

Atherosclerotic Lesions in Apo E Knockout Mice have Intact Endothelial Surfaces

[0500] Immunohistochemical staining with antibody against an endothelial marker CD 31 was used to determine

whether the endothelial lining is intact over the atherosclerotic lesions of Apo E knockout mice. The presence of endothelium was detected in about 50 % of the early atherosclerotic lesions sample stained. However as the lesion progressed, gaps in endothelial coverage were sometimes observed. In humans, these gaps in endothelial coverage are believed to represent potential or actual thrombogenic sites that encourage formation of platelet mural thrombi. However, in atherosclerotic Apo E knockout mice, lesions of this severity do not occur and no such thrombogenic activity has been reported, indicating that the lesions observed in ApoE mice correspond to early human lesions.

Peptides Isolated by In Vivo Panning of Phage Displayed Peptide Libraries

[0501] After four rounds of panning, approximately 150 individual phage isolates were separately selected, cloned and sequenced. Of these 150 isolates, fifty had no peptide insert. Four phage isolates were repeatedly isolated. These data suggest that multiple target binding sites exist on the surface of the endothelium and that several rounds of selection can be used for enrichment of phage displaying peptides that truly bind to atherosclerotic lesions. Use of gene III-linked libraries limited the number of rounds of panning, because this phage vector did not tolerate cysteine-containing peptides well and insert-containing phage were rapidly out-grown by contaminating wild type phage.

[0502] The following peptides were isolated as being displayed on phage that repeatedly bound to atherosclerotic lesions:

CAPGPSKSC	(SEQ ID NO:4)
CQEPTRLKC	(SEQ ID NO:8)
CKEPTRAHC	(SEQ ID NO:12)

[0503] Four repeated phage clones were isolated having CAPGPSKSC (SEQ ID NO:4) by preferential binding to atherosclerotic lesions in vivo. A purified isolate of phage displaying the CAPGPSKSC (SEQ ID NO:4) sequence were amplified, then injected into atherogenic Apo E knockout mice. After circulation for 30 min, the mice were perfused with 4% paraformaldehyde, and aortic tissue was removed and stained with anti-phage antibody. Phage displaying the CAPGPSKSC (SEQ ID NO:4) sequence showed preferential binding to atherosclerotic lesions compared to wild type phage. No binding is detected in similarly-treated aortas from normal Balb/C mice and young Apo E knockout mice on a normal diet. These data indicate that phage displaying the CAPGPSKSC (SEQ ID NO:4) peptide are associated with an endothelial surface molecule that is expressed as atherosclerosis develops. A low degree of homology to some regions of laminin and laminin-like molecules was detected when protein databases were searched for homology to CAPGPSKSC (SEQ ID NO:4).

[0504] Two other peptides were separately isolated that had distinct but related sequences CQEPTRLKC (SEQ ID NO:8) and CKEPTRAHC (SEQ ID NO:12). These two peptides were homologous in an internal sequence of four amino acids EPTR (SEQ ID NO:450). Recovery of different phage that bear overlapping or homologous peptidyl sequences is statistically unlikely because of the diversity of

the library and the complexity of target molecules for binding. Homologous clones were rarely observed. Such observations indicate that homologous clones may bind to the same or similar targets that are consistently associated with atherosclerotic lesions.

[0505] The following nucleic acids and peptides were identified using the methods described above.

TABLE 4

Peptides and Nucleic Acids Isolated		SEQ ID NO:
Name	Sequence	
	GCGCCGGGTCCGTCTAAGAGT CGCGCCAGGCAGATTCTCA	1
APGPSKS		2
	TGTGCGCCGGGTCCGTCTAAGAGTTGC ACACGCGGCCAGGCAGATTCTCAACG	3
CAPGPSKSC		4
	CAGGAGCCGACGCGCTGAAG GTCCTCGGCTGCGCGACTTC	5
QEPTRLK		6
	TGTCAGGAGCCGACGCGCTGAAGTGC ACAGTCTCGGCTGCGCGACTTCAACG	7
CQEPTRLKC		8
	AAGGAGCCTACGCGGCGCAT TTCCTCGGATGCGCCGCGTA	9
KEPTRAH		10
	TGTAAGGAGCCTACGCGGCGCATTTGC ACATTCTCGGATGCGCCGCGTAACG	11
CKEPTRAHC		12
Eo2-1	TTGGCGATGCTTATGGATACG AACCCTACGAATACCTATGC	13
Eo2-1	LANLMDT	14
Eo2-1	TGTTTGGCGATGCTTATGGATACGTGC ACAAACCGCTACGAATACCTATGCACG	15
Eo2-1	CLAMLMDTC	16
Eo2-2	AATAAGCATACTAGGCCGCTT TTATTCGTATGATCCGGCGAA	17
Eo2-2	NKHTRPL	18
Eo2-2	TGTAATAAGCATACTAGGCCGCTTGC ACATTATTCGTATGATCCGGCGAAACG	19
Eo2-2	CNKHTRPLC	20
Eo2-3	GTGCATAAGCTGCCTGAGTCT TTCACGGACTCAGAACGCCA	21
Eo2-3	VHKLPEs	22
Eo2-3	TGTGTGCATAAGCTGCCTGAGTCTTGC ACATTGACGGACTCAGAACGCCAACG	23
Eo2-3	CVHKLPEsC	24

TABLE 4-continued

Peptides and Nucleic Acids Isolated		
Name	Sequence	SEQ ID NO:
Eo2-4	CCGACTCAGGCTTCTCTTCAT GGCTGAGTCCGAAGAGAAGTA	25
Eo2-4	PTQASLH	26
Eo2-4	TGTCCGACTCAGGCTTCTCTTCATTGC ACAGGCTGAGTCCGAAGAGAAGTAACG	27
Eo2-4	CPTQASLHC	28
Eo2-5	GATACTGCGCTCCGTCGTCG CTATGACGCGGAGGCAGCAGC	29
Eo2-5	DTAPPSS	30
Eo2-5	TGTGATACTGCGCTCCGTCGTCGTCG ACACTATGACGCGGAGGCAGCAGCAGC	31
Eo2-5	CDTAPPSSC	32
Eo2-6	GGGGTGACACTCTGCTTGCT CCCCACGTCTGAGACGAACGA	33
Eo2-6	GVQTLLA	34
Eo2-6	TGTGGGGTGACACTCTGCTTGCTTGC ACACCCACGTCTGAGACGAACGAACG	35
Eo2-6	CGVQTLLAC	36
Eo2-7	GATCCTGTGACGAAGCATACT CTAGGACACTGCTTCGTATGA	37
Eo2-7	DPVTKHT	38
Eo2-7	TGTGATCCTGTGACGAAGCATACTTGC ACACTAGGACACTGCTTCGTATGAACG	39
Eo2-7	CDPVTKHTC	40
Eo2-8	GATCAGAGTACGATTGCGGCG CTAGTCTCATGCTAAGCCCGC	41
Eo2-8	DQSTIRA	42
Eo2-8	TGTGATCAGAGTACGATTGCGGCGTGC ACACTAGTCTCATGCTAAGCCCGCACG	43
Eo2-8	CDQSTIRAC	44
Eo2-9	CGGGCTGCTACTCCTTCGATT GCCCGACGATGAGGAAGCTAA	45
Eo2-9	RAATPSI	46
Eo2-9	TGTGCGGCTGCTACTCCTTCGATTGC ACAGCCCGACGATGAGGAAGCTAAACG	47
Eo2-9	CRAATPSIC	48
Eo2-10	AAGACGTCGCATGCGCAGGAG TTCTGCAGCGTACGCGTCCTC	49
Eo2-10	KTSHAQE	50
Eo2-10	TGTAAGACGTCGCATGCGCAGGAGTGC ACATTCTGCAGCGTACGCGTCCTCACG	51
Eo2-10	CKTSHAQEC	52

TABLE 4-continued

Peptides and Nucleic Acids Isolated		
Name	Sequence	SEQ ID NO:
Eo3-3	AAGCATCCTGTTGGNCGGGTG TTCGTAGGACAACCGCCAC	53
Eo3-3	KHPVGRV	54
Eo3-3	TGTAAGCATCCTGTTGGNCGGGTGTGC ACATTCTGTTAGGACAACCGCCACAG	55
Eo3-3	CKHPVGRVC	56
Eo3-5	ACGGATACTAAGAATTCGCAG TGCCTATGATTCTTAAGCGTC	57
Eo3-5	TDTKNSQ	58
Eo3-5	TGTACGGATACTAAGAATTCGCAGTGC ACATGCCTATGATTCTTAAGCGTCACG	59
Eo3-5	CTDTKNSQC	60
Eo3-11	CAGCCCGCGATGGGGCGGTAT GTCGGCGGCTACCCCGCCATA	61
Eo3-11	QPPMGRY	62
Eo3-11	TGTCAGCCCGCGATGGGGCGGTATTGC ACAGTCGGCGGCTACCCCGCCATAACG	63
Eo3-11	CQPPMGRYC	64
Eo3-13	AATGAGAGGCTGAATAAGGAT TTACTCTCCGACTTATTCCTA	65
Eo3-13	NERLNKD	66
Eo3-13	TGTAATGAGAGGCTGAATAAGGATTGC ACATTACTCTCCGACTTATTCCTAACG	67
Eo3-13	CNERLNKDC	68
Eo3-15	CCGCCGTCGAATAAGCAGATG GGCGGCAGCTTATTCGTCTAC	69
Eo3-15	PPSNKQM	70
Eo3-15	TGTCCGCCGTCGAATAAGCAGATGTC ACAGGCGGCAGCTTATTCGTCTACAG	71
Eo3-15	CPPSNKQMC	72
Eo3-27	GATTCTTCGTGCGCTGCTCGG CTAAGAAGCAGCGACGAGCC	73
Eo3-27	DSSSPAR	74
Eo3-27	TGTGATTCTTCGTGCGCTGCTCGGTGC ACACTAAGAAGCAGCGGACGAGCCACG	75
Eo3-27	CDSSSPARC	76
Eo3-28	ACGCAGTCTGATAATAGCGGT TGCGTCAGACTATTATCCGCA	77
Eo3-28	TQSDNRR	78
Eo3-28	TGTACGCAGTCTGATAATAGCGGTGC ACATGCGTCAGACTATTATCCGCAACG	79
Eo3-28	CTQSDNRRC	80

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eco3-29	AAGGGTCTGCCGGCTAAGACT TTCCCAGACGCCGATTCTGA	81
Eco3-29	KGLPAKT	82
Eco3-29	TGTAAGGGTCTGCCGGCTAAGACTTGC ACATTCCCAGACGCCGATTCTGAACG	83
Eco3-29	CKGLPAKTC	84
Eo3-31	TTGCAGCCGCATCTGAGTCTT AACGTCGGCGTAGACTCAGAA	85
Eo3-31	LQPHLSL	86
Eo3-31	TGTTTGACGCCGCATCTGAGTCTTTC ACAAACGTCGGCGTAGACTCAGAAACG	87
Eo3-31	CLQPHLSLC	88
Eo3-33	GCGGTTCCGTAGAAATCGTTCT CGCCAAGGCATCTTAGCAAGA	89
Eo3-33	AVPQNRS	90
Eo3-33	TGTGCGGTTCCGTAGAAATCGTTCTTGC ACACGCCAAGGCATCTTAGCAAGAACG	91
Eo3-33	CAVPQNRSC	92
Eo3-34	ATGAATCAGACTCCTGATTG TACTTAGTCTGAGGACTAAAC	93
Eo3-34	MNQTPDL	94
Eo3-34	TGTATGAATCAGACTCCTGATTTGTGC ACATACCTTAGTCTGAGGACTAAACACG	95
Eo3-34	CMNQTPDLC	96
Eo3-36	TTTCAGATGCAGCCTACTCTT AAAGTCTACGTCGGATGAGAA	97
Eo3-36	FQMQPTL	98
Eo3-36	TGTTTTAGATGCAGCCTACTCTTTC ACAAAAGTCTACGTCGGATGAGAAACG	99
Eo3-36	CFQMQPTLC	100
Eo3-37	AGTGGGGCTTCTAATAAGACG TCACCCCGAAGATTATTCTGC	101
Eo3-37	SGASNKT	102
Eo3-37	TGTAGTGGGGCTTCTAATAAGACGTGC ACATCACCCGAAGATTATTCTGCACG	103
Eo3-37	CSGASNKTC	104
Eo3-38	ACTAAGATGCGGTTGGAGCAG TGATTCTACGCCAACCTCGTC	105
Eo3-38	TKMRLEQ	106
Eo3-38	TGTACTAAGATGCGGTTGGAGCAGTGC ACATGATTCTACGCCAACCTCGTCACG	107
Eo3-38	CTKMRLEQC	108

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-41	ACGTCTCCTATTTATCCGGGT TGCAGAGGATAAATAGGCCCA	109
Eo3-41	TSPIYPG	110
Eo3-41	TGTACGTCTCCTATTTATCCGGGTGTC ACATGCAGAGGATAAATAGGCCCAACG	111
Eo3-41	CTSPIYPGC	112
Eo3-43	AAGACTCCGTCGCAGAGTCAG TTCTGAGGCAGCGTCTCAGTC	113
Eo3-43	KTPSQSQ	114
Eo3-43	TGTAAGACTCCGTCGCAGAGTCAGTGC ACATTCTGAGGCAGCGTCTCAGTCACG	115
Eo3-43	CKTPSQSQC	116
Eo3-46	CTTCAGGCTTTTAAGGCGACT GAAGTCCGAAAATTCCGCTGA	117
Eo3-46	LQAFKAT	118
Eo3-46	TGTCTTCAGGCTTTTAAGGCGACTTGC ACAGAAGTCCGAAAATTCCGCTGAACG	119
Eo3-46	CLQAFKATC	120
Eo3-47	TCTACTACTGAGCTTAATAAG AGATGATGACTCGAATTATTTC	121
Eo3-47	STTELNK	122
Eo3-47	TGTTCTACTACTGAGCTTAATAAGTGC ACAAGATGATGACTCGAATTATTTCACG	123
Eo3-47	CSTTELNKC	124
Eo3-48	AGGACTCATAGTTCTCCGACT TCCTGAGTATCAAGAGGCTGA	125
Eo3-48	RTHSSPT	126
Eo3-48	TGTAGGACTCATAGTTCTCCGACTTGC ACATCCTGAGTATCAAGAGGCTGAACG	127
Eo3-48	CRTHSSPTC	128
Eo3-50	AATGAGAATTTTAAGGGGCTG TTACTCTTAAATTCCTCCGAC	129
Eo3-50	NENFKGL	130
Eo3-50	TGTAATGAGAATTTTAAGGGGCTGTGC ACATTACTCTTAAATTCCTCCGACACG	131
Eo3-50	CNENFKGLC	132
Eo3-51	AGTAAGACTAATCATGCTTCT TCATTCTGATTAGTACGAAGA	133
Eo3-51	SKTNHAS	134
Eo3-51	TGTAGTAAGACTAATCATGCTTCTTGC ACATCATTCTGATTAGTACGAAGAACG	135
Eo3-51	CSKTNHASC	136

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-52	ACGCCGTATCCTTCTAATTCG TGCGGCATAGGAAGATTAAAGC	137
Eo3-52	TPYPSNS	138
Eo3-52	TGTACGCCGTATCCTTCTAATTCGTGC ACATGCGGCATAGGAAGATTAAAGCAGC	139
Eo3-52	CTPYPSNSC	140
Eo3-53	ACGCTGTCTGCTGCTCCGCAT TGCGACAGACGACGAGGCGTA	141
Eo3-53	TLSAAPH	142
Eo3-53	TGTACGCTGTCTGCTGCTCCGCATTGC ACATGCGACAGACGACGAGGCGTAACG	143
Eo3-53	CTLSAAPHC	144
Eo3-54	CTTAATAATTCTCAGGCTCAT GAATTATTAAGAGTCCGAGTA	145
Eo3-54	LNNSQAH	146
Eo3-54	TGCTTTAATAATTCTCAGGCTCATTGC ACAGAATTATTAAGAGTCCGAGTAACG	147
Eo3-54	CLNNSQAHC	148
Eo3-56	ATTGAGCATTGCGCGCAGCAG TAACTCGTAAGCCGCGTCGTC	149
Eo3-56	IEHSAQQ	150
Eo3-56	TGTATTGAGCATTGCGCGCAGCAGTGC ACATAACTCGTAAGCCGCGTCGTCACG	151
Eo3-56	CIEHSAQQC	152
Eo3-57	TCGGCTGCGGGGCATCATACT AGCCGACGCCCCGTAGTATGA	153
Eo3-57	SAAGHHT	154
Eo3-57	TGTTCGGCTGCGGGGCATCATACTTGC ACAAGCCGACGCCCCGTAGTATGAACG	155
Eo3-57	CSAAGHHTC	156
Eo3-58	CATAATCAGAAGTTGAATCGT GTCTTCAACTTAGCAACGCCA	157
Eo3-58	HNQKLNLR	158
Eo3-58	TGTCATAATCAGAAGTTGAATCGTTGC ACAGTCTTCAACTTAGCAACGCCAACG	159
Eo3-58	CHNQKLNRC	160
Eo3-59	AAGTCGACTTCTCATAGTATG TTCAGCTGAAGAGTATCATAC	161
Eo3-59	KSTSHSM	162
Eo3-59	TGTAAGTCGACTTCTCATAGTATGTGC ACATTGAGCTGAAGAGTATCATACACG	163
Eo3-59	CKSTSHSMC	164

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-60	CCTAATAATAAGTCGGCTTCG GGATTATTATTTCAGCCGAAGC	165
Eo3-60	PNNKSAS	166
Eo3-60	TGTCCTAATAATAAGTCGGCTTCGTGC ACAGGATTATTATTTCAGCCGAAGCAGC	167
Eo3-60	CPNKSASAC	168
Eo3-62	GAGGATCTACGTTGAAGGTG CTCCTAGGATGCAACTTCCAC	169
Eo3-62	EDPTLVK	170
Eo3-62	TGTGAGGATCTACGTTGAAGGTGTGC ACACTCCTAGGATGCAACTTCCACACG	171
Eo3-62	CEDPTLVKC	172
Eo3-63	ATGCTGCGATGTCTCGTCAG TACAGACGCTACAGAGCAGTC	173
Eo3-63	MSAMSRQ	174
Eo3-63	TGTATGTCTGCGATGTCTCGTCAGTGC ACATACAGACGCTACAGAGCAGTCACG	175
Eo3-63	CMSAMSRQC	176
Eo3-64	CCTGGGAAGATTTGCGGTAGT GGACCCTTCTAAAGCGCATCA	177
Eo3-64	PGKISRS	178
Eo3-64	TGTCCTGGGAAGATTTGCGGTAGTTGC ACAGGACCCTTCTAAAGCGCATCAACG	179
Eo3-64	CPGKISRSC	180
Eo3-65	CTGAAGCTGGGGTCGAAGCAG GACTTCGACCCAGCTTCGTC	181
Eo3-65	LKLGSQ	182
Eo3-65	TGTCCTGAAGCTGGGGTCGAAGCAGTGC ACAGACTTCGACCCAGCTTCGTCACG	183
Eo3-65	CLKLGSQ	184
Eo3-66	AAGACTAGTCCGGAGTCTACT TTCTGATCAGGCTCAGATGA	185
Eo3-66	KTSPEST	186
Eo3-66	TGTAAGACTAGTCCGGAGTCTACTTGC ACATTCTGATCAGGCTCAGATGAACG	187
Eo3-66	CKTSPESTC	188
Eo3-67	ACGCTTTTTCGGGGAATTCT TGCAGAAAAGGCCCTTAAGA	189
Eo3-67	TLFPGNS	190
Eo3-67	TGTACGCTTTTTCGGGGAATTCTTGC ACATGCGAAAAGGCCCTTAAGAACG	191
Eo3-67	CTLFPGNSC	192

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-68	TTGCCGTCGTCTACGAGGCTG AACGGCAGCAGATGCTCCGAC	193
Eo3-68	LPSSTRL	194
Eo3-68	TGTTTGCCGTCGTCTACGAGGCTGTGC ACAAACGGCAGCAGATGCTCCGACAG	195
Eo3-68	CLPSSTRLC	196
Eo3-69	TCGAGTCAGAGGACTCCTCCG AGCTCAGTCTCCTGAGGAGGC	197
Eo3-69	SSQRTPP	198
Eo3-69	TGTTTCGAGTCAGAGGACTCCTCCGTGC ACAAGCTCAGTCTCCTGAGGAGGCAG	199
Eo3-69	CSSQRTPPC	200
Eo3-70	CTGCCTACGATGACGCCGACG GACGGATGCTACTGCGGCTGC	201
Eo3-70	LPTMTPT	202
Eo3-70	TGTTTCGCTACGATGACGCCGACGTGC ACAGACGGATGCTACTGCGGCTGCAG	203
Eo3-70	CLPTMTPTC	204
Eo3-71	CTTATGACGCCGTCGAAGAGG GAATACTGCGGCAGCTTCTCC	205
Eo3-71	LMTPSKR	206
Eo3-71	TGTTTATGACGCCGTCGAAGAGGTGC ACAGAATACTGCGGCAGCTTCTCCAG	207
Eo3-71	CLMTPSKRC	208
Eo3-72	GAGCATTTTTTTAGTCGGTCT CTCGTAAAAAATCAGCCAGA	209
Eo3-72	EHFFSR	210
Eo3-72	TGTGAGCATTTTTTTAGTCGGTCTTGC ACACTCGTAAAAAATCAGCCAGAAG	211
Eo3-72	CEHFFSRSC	212
Eo3-73	ACGAATCAGTTTTTGCAGCAG TGCTTAGTCAAAAACGTCGTC	213
Eo3-73	TNQFLQQ	214
Eo3-73	TGTACGAATCAGTTTTTGCAGCAGTGC ACATGCTTAGTCAAAAACGTCGTCAG	215
Eo3-73	CTNQFLQQC	216
Eo3-75	CCTGCGAATAAGTCTTCGTTT GGACGCTTATTTCAGAACAAA	217
Eo3-75	PANKSSF	218
Eo3-75	TGTCTGCGAATAAGTCTTCGTTTTGC ACAGGACGCTTATTTCAGAACAAAAC	219
Eo3-75	CPANKSSFC	220

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-77	AGTACGACGCAGTCTAGTTGG TCATGCTGCGTCAGATCAACC	221
Eo3-77	STTQSSW	222
Eo3-77	TGTAGTACGACGCAGTCTAGTTGGTGC ACATCATGCTGCGTCAGATCAACCAG	223
Eo3-77	CSTTQSSWC	224
Eo3-78	GTGACTCCGGATCGGCTGACG CACTGAGGCCTAGCCGACTGC	225
Eo3-78	VTPDRLT	226
Eo3-78	TGTTTGACTCCGGATCGGCTGACGTGC ACACACTGAGGCCTAGCCGACTGCAG	227
Eo3-78	CVTPDRLTC	228
Eo3-80	ACGTGGCAGACTTAGAGGTGC TGCACCGTCTGAATCTCCAGC	229
Eo3-80	TWQTQRS	230
Eo3-80	TGTACGTGGCAGACTTAGAGGTGCTGC ACATGCACCGTCTGAATCTCCAGCAG	231
Eo3-80	CTWQTQRSC	232
Eo3-81	CCGCATCTGGGACTCGTCAT GGCGTAGGACCTGAGCAGTA	233
Eo3-81	PHPGTRH	234
Eo3-81	TGTCCGCATCTGGGACTCGTCATTGC ACAGGCGTAGGACCTGAGCAGTAAC	235
Eo3-81	CPHPGTRHC	236
Eo3-82	GCGCCGAAGCCGAGTCTCAG CGCGGCTTCGGCGTCAGAGTC	237
Eo3-82	APKPQSQ	238
Eo3-82	TGTGCGCCGAAGCCGAGTCTCAGTGC ACACGCGGCTTCGGCGTCAGAGTCAG	239
Eo3-82	CAPKPQSQC	240
Eo3-84	AGTCAGGCGTAGATTCTGCG TCAGTCCGCATCTAAGGACGC	241
Eo3-84	SQAQIPA	242
Eo3-84	TGTAGTCAGGCGTAGATTCTGCGTGC ACATCAGTCCGCATCTAAGGACGCAG	243
Eo3-84	CSQAQIPAC	244
Eo3-85	CCGCGAATAAGGGGAAGGCT GGCGTCTTATTCGCCCTCCGA	245
Eo3-85	PQNKGA	246
Eo3-85	TGTCCGCGAATAAGGGGAAGGCTTGC ACAGGCGTCTTATTCGCCCTCCGAAC	247
Eo3-85	CPQNKGKAC	248

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-86	CATACTGCGCATCCGCGGTCT GTATGACGCGTAGGCGCCAGA	249
Eo3-86	HTAHPRS	250
Eo3-86	TGTCATACTGCGCATCCGCGGTCTTGC ACAGTATGACGCGTAGGCGCCAGAACG	251
Eo3-86	CHTAHPRSC	252
Eo3-87	AAGCAGTCTGGTCTGTTTCT TTCGTCAGACCAGGACAAAGA	253
Eo3-87	KQSGPVVS	254
Eo3-87	TGTAAGCAGTCTGGTCTGTTTCTTGC ACATTGTCGACAGCAGGACAAAGAACG	255
Eo3-87	CKQSGPVSC	256
Eo3-88	AGTCAGTATCCGTCGCGTTCT TCAGTCATAGGCAGCGCAAGA	257
Eo3-88	SQYPSRS	258
Eo3-88	TGTAGTCAGTATCCGTCGCGTTCTTGC ACATCAGTCATAGGCAGCGCAAGAACG	259
Eo3-88	CSQYPSRSC	260
Eo3-89	TCGAGGGATGGGAAGACTACG AGCTCCCTACCCTTCTGATGC	261
Eo3-89	SRDGKTT	262
Eo3-89	TGTTTCGAGGGATGGGAAGACTACGTGC ACAAGCTCCCTACCCTTCTGATGCACG	263
Eo3-89	CSRDGKTTT	264
Eo3-90	ACGACGCTGATGCCTAATATT TGCTGCGACTACGGATTATAA	265
Eo3-90	TTLMPNI	266
Eo3-90	TGTACGACGCTGATGCCTAATATTGTC ACATGCTGCGACTACGGATTATAAAGC	267
Eo3-90	CTTLNPNTC	268
Eo3-92	ACGAATAAGCTTGATAATACT TGCTTATTGCAACTATTATGA	269
Eo3-92	TNKLNT	270
Eo3-92	TGTACGAATAAGCTTGATAATACTTGC ACATGCTTATTGCAACTATTATGAACG	271
Eo3-92	CTNLNDNTC	272
Eo3-93	ACTAAGATGCGGTTGGAGCAG TGATTCTACGCCAACCTCGTC	273
Eo3-93	TKMRLEQ	274
Eo3-93	TGTACTAAGATGCGGTTGGAGCAGTGC ACATGATTCTACGCCAACCTCGTCACG	275
Eo3-93	CTKMRLEQC	276

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-94	TCGCCGGATCCGGGTAGTAAG AGCGGCCCTAGGCCCATCATT	277
Eo3-94	SPDPGSK	278
Eo3-94	TGTTCCCGGATCCGGGTAGTAAGTGC ACAAGCGGCCCTAGGCCCATCATTACG	279
Eo3-94	CSPDPGSKC	280
Eo3-97	GAGCATTTTTTTAGTCGGTCT CTCGTAAAAAATCAGCCAGA	281
Eo3-97	EHFFSRS	282
Eo3-97	TGTGAGCATTTTTTTAGTCGGTCTTGC ACACTCGTAAAAAATCAGCCAGAACG	283
Eo3-97	CEHFFSRSC	284
Eo3-98	GGGGCGCCGTCTGATCATGTG CCCCGCGCAGACTAGTACAC	285
Eo3-98	GAPSDHV	286
Eo3-98	TGTGGGGCGCCGTCTGATCATGTGTGC ACACCCGCGGCAGACTAGTACACACG	287
Eo3-98	CGAPSDHVC	288
Eo3-99	CCGCATCCTGGGACTCGTCAT GGCGTAGGACCCTGAGCAGTA	289
Eo3-99	PHPGTRH	290
Eo3-99	TGTCCGCATCCTGGGACTCGTCATTGC ACAGGCGTAGGACCCTGAGCAGTAACG	291
Eo3-99	CPHPGTRHC	292
Eo3-100	ATTAAGCAGTCGCTGTCTCGT TAATTGTCAGCGACAGAGCA	293
Eo3-100	IKQSLSR	294
Eo3-100	TGTATTAAGCAGTCGCTGTCTCGTTGC ACATAATTGTCAGCGACAGAGCAACG	295
Eo3-100	CIKQSLSRC	296
Eo3-101	ACGACGCATAATGCGAAGTGG TGCTGCGTATTACGCTTCACC	297
Eo3-101	TTHNAKW	298
Eo3-101	TGTACGACGCATAATGCGAAGTGGTGC ACATGCTGCGTATTACGCTTCACCACG	299
Eo3-101	CTTHNAKWC	300
Eo3-102	CTGACTACGAAGCCTAGGATG GACTGATGCTTCGGATCCTAC	301
Eo3-102	LTTKPRM	302
Eo3-102	TGTCGACTACGAAGCCTAGGATGTGC ACAGACTGATGCTTCGGATCCTACACG	303
Eo3-102	CLTTKPRMC	304

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-103	AAGCTGAAGTCGGGGTCGCTG TTCGACTTCAGCCCCAGCGAC	305
Eo3-103	KLKSGSL	306
Eo3-103	TGTAAGCTGAAGTCGGGGTCGCTGTGC ACATTTCGACTTCAGCCCCAGCGACACG	307
Eo3-103	CKLKSGSLC	308
Eo3-105	CTTCCGTCGAAGGTGTCTCGG GAAGGCAGCTTCACAGAGCC	309
Eo3-105	LPSKVSRR	310
Eo3-105	TGTCTTCCGTCGAAGGTGTCTCGGTGC ACAGAAGGCAGCTTCACAGAGCCACG	311
Eo3-105	CLPSKVSRC	312
Eo3-106	GCGCCGGTCCGCTAAGAGT CGCGGCCAGGCAGATTCTCA	313
Eo3-106	APGPSKS	314
Eo3-106	TGTGCGCCGGTCCGCTAAGAGTTGC ACACGCGGCCAGGCAGATTCTCAACG	315
Eo3-106	CAPGPSKSC	316
Eo3-107	TCTCCGCTTAAGTCTCTTTTCG AGAGCGAATTTCAGAGAAAGC	317
Eo3-107	SPLKSLS	318
Eo3-107	TGTCTCCGCTTAAGTCTCTTTTCGTC ACAAGAGCGCAATTTCAGAGAAAGCAGC	319
Eo3-107	CSPLKSLS	320
Eo3-108	GCGCCGGTCCGCTAAGAGT CGCGGCCAGGCAGATTCTCA	321
Eo3-108	APGPSKS	322
Eo3-108	TGTGCGCCGGTCCGCTAAGAGTTGC ACACGCGGCCAGGCAGATTCTCAACG	323
Eo3-108	CAPGPSKSC	324
Eo3-109	CCGTCGGGTCTTACTAAGCAG GGCAGCCAGAAATGATTCGTC	325
Eo3-109	PSGLTKQ	326
Eo3-109	TGTCCGTCGGGTCTTACTAAGCAGTGC ACAGGCAGCCAGAAATGATTCGTCACG	327
Eo3-109	CPSGLTKQC	328
Eo3-111	AAGTCGAATATGCCTCTGAGT TTCAGCTTATACGGAGACTCA	329
Eo3-111	KSNMPLT	330
Eo3-111	TGTAAGTCGAATATGCCTCTGAGTTGC ACATTTCAGCTTATACGGAGACTCAACG	331
Eo3-111	CKSNMPLTC	332

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-112	AATCAGCGGCATTAGATGTCT TTAGTCGCCGTAATCTACAGA	333
Eo3-112	NQRHQMS	334
Eo3-112	TGTAATCAGCGGCATTAGATGTCTTGC ACATTAGTCGCCGTAATCTACAGAAGC	335
Eo3-112	CNQRHQMSC	336
Eo3-113	CAGCGGGCGGATCAGAAGCAG GTCGCCGCCCTAGTCTTCGTC	337
Eo3-113	QRADQKQ	338
Eo3-113	TGTGCGGGCGGATCAGAAGCAGTGC ACAGTCGCCGCCCTAGTCTTCGTCACG	339
Eo3-113	CQRADQKQC	340
Eo3-114	AATCATCGGTATATGCAGATG TTAGTAGCCATATACGTCTAC	341
Eo3-114	NHRYMQM	342
Eo3-114	TGTAATCATCGGTATATGCAGATGTGC ACATTAGTAGCCATATACGTCTACAGC	343
Eo3-114	CNHRYMQMC	344
Eo3-115	ATTACTCCTATGTCTCGTACT TAATGAGGATACAGAGCATGA	345
Eo3-115	ITPMSRT	346
Eo3-115	TGTATTACTCCTATGTCTCGTACTTGC ACATAATGAGGATACAGAGCATGAACG	347
Eo3-115	CITPMSRTC	348
Eo3-116	AGTCCTACGATTGGGCAGAAG TCAGGATGCTAACCCGTCTTC	349
Eo3-116	SPTIGQK	350
Eo3-116	TGTAGTCCTACGATTGGGCAGAAGTGC TAATCAGGATGCTAACCCGTCTTCACG	351
Eo3-116	CSPTIGQKC	352
Eo3-117	TCTAATTATTCGCTGGGTATG AGATTAATAAGCGACCCATAC	353
Eo3-117	SNYSLGM	354
Eo3-117	TGTTCTAATTATTCGCTGGGTATGTGC ACAAGATTAATAAGCGACCCATACACG	355
Eo3-117	CSNYSLGMC	356
Eo3-118	ACGAATACGGGCATAGGCAT TGCTTATGCCCGTATCCGTA	357
Eo3-118	TNTGHRH	358
Eo3-118	TGTACGAATACGGGCATAGGCATTGC ACATGCTTATGCCCGTATCCGTAACG	359
Eo3-118	CTNTGHRHC	360

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-119	ACTATGCGTACTAATTCTAGT	361
Eo3-119	TGATACGCATGATTAAGATCA	362
Eo3-119	TMRTNSS	363
Eo3-119	TGTACTATGCGTACTAATTCTAGTTGC	364
Eo3-119	ACATGATACGCATGATTAAGATCAACG	365
Eo3-119	CTMRTNSSC	366
Eo3-120	ACGGCGCGCTTGGAGCGGAGG	367
Eo3-120	TGCCGCGGCAACCTCGCCTCC	368
Eo3-120	TAPLERR	369
Eo3-120	TGTACGGCGCGCTTGGAGCGGAGGTGC	370
Eo3-120	ACATGCGCGGCAACCTCGCCTCCACG	371
Eo3-120	CTAPLERRC	372
Eo3-122	CTGCTTGGGAGCCTCGGACT	373
Eo3-122	GACGAACCCCTCGGAGCCTGA	374
Eo3-122	LLGEPRT	375
Eo3-122	TGTCTGCTTGGGAGCCTCGGACTTGC	376
Eo3-122	ACAGACGAACCCCTCGGAGCCTGAACG	377
Eo3-122	CLLGEPRTC	378
Eo3-123	TCTCGTGTAGTACTAATGAT	379
Eo3-123	AGAGCAGATCATGATTACTA	380
Eo3-123	SRASTND	381
Eo3-123	TGTTCTCGTGTAGTACTAATGATTGC	382
Eo3-123	ACAAGAGCAGATCATGATTACTAACG	383
Eo3-123	CSRASTNDC	384
Eo3-124	AATAAGTCGAATAAGGAGTTT	385
Eo3-124	TTATTCAGCTTATTCCTCAAAA	386
Eo3-124	NKSNKEF	387
Eo3-124	TGTAATAAGTCGAATAAGGAGTTTGC	388
Eo3-124	ACATTATTACGCTTATTCCTCAAAAACG	389
Eo3-124	CNKSNEFC	390
Eo3-125	CATGCGCGGGTGCCGCTGGTT	391
Eo3-125	GTACGCGCCACGCGACCAA	392
Eo3-125	HARVPLV	393
Eo3-125	TGTCATGCGCGGGTGCCGCTGGTTTGC	394
Eo3-125	ACAGTACGCGCCACGCGACCAAACG	395
Eo3-125	CHARVPLVC	396
Eo3-126	CTTAATAATTCTCAGGCTCAT	397
Eo3-126	GAATTATTAAGAGTCCGAGTA	398
Eo3-126	LNNSQAH	399
Eo3-126	TGTCTTAATAATTCTCAGGCTCATTGC	400
Eo3-126	ACAGAATTATTAAGAGTCCGAGTAACG	401
Eo3-126	CLNNSQAH	402
Eo3-126	CLNNSQAH	403
Eo3-126	CLNNSQAH	404
Eo3-126	CLNNSQAH	405
Eo3-126	CLNNSQAH	406
Eo3-126	CLNNSQAH	407
Eo3-126	CLNNSQAH	408
Eo3-126	CLNNSQAH	409
Eo3-126	CLNNSQAH	410
Eo3-126	CLNNSQAH	411
Eo3-126	CLNNSQAH	412
Eo3-126	CLNNSQAH	413
Eo3-126	CLNNSQAH	414
Eo3-126	CLNNSQAH	415
Eo3-126	CLNNSQAH	416
Eo3-127	AATCCGTCGCGTTCTACGTCG	417

TABLE 4-continued

<u>Peptides and Nucleic Acids Isolated</u>		
Name	Sequence	SEQ ID NO:
Eo3-127	TTAGGCAGCGCAAGATGCAGC	390
Eo3-127	NPSRSTS	391
Eo3-127	TGTAATCCGTCGCGTTCTACGTCGTGC	392
Eo3-127	ACATTAGGCAGCGCAAGATGCAGCACG	393
Eo3-127	CNPSRSTSC	394
Eo3-128	ACGCCGACTTAGAAGAGTTTG	395
Eo3-128	TGCGGCTGAATCTTCTCAAAC	396
Eo3-128	TPTQKSL	397
Eo3-128	TGTACGCCGACTTAGAAGAGTTTGTGC	398
Eo3-128	ACATGCGGCTGAATCTTCTCAAACACG	399
Eo3-128	CTPTQKSLC	400
Eo3-129	TCGCAGCGGCTGTTCAGATG	401
Eo3-129	AGCGTCGCGGACAAGTCTAC	402
Eo3-129	SQRPVQM	403
Eo3-129	TGTTTCGAGCGGCTGTTCAGATGTGC	404
Eo3-129	ACAAGCGTCGCGGACAAGTCTACACG	405
Eo3-129	CSQRPVQMC	406
Eo3-130	GCGCCGGTCCGCTCTAAGAGT	407
Eo3-130	CGCGCCAGGAGATTCTCA	408
Eo3-130	APGPSKS	409
Eo3-130	TGTGCGCGGGTCCGCTCTAAGAGTTGC	410
Eo3-130	ACACGCGCCAGGAGATTCTCAACG	411
Eo3-130	CAPGPSKSC	412
Eo3-132	AAGGGTCTGCTATTCTTAAT	413
Eo3-132	TTCCCCAGCAGATAAGAATTA	414
Eo3-132	KGSSILN	415
Eo3-132	TGTAAGGGTCTGCTATTCTTAATTGC	416
Eo3-132	ACATTCCCCAGCAGATAAGAATTAACG	417
Eo3-132	CKGSSILNC	418
Eo3-133	GTTAATCGGAGTGATGGGATG	419
Eo3-133	CAATTAGCCTCACTACCCTAC	420
Eo3-133	VNRS DGM	421
Eo3-133	TGTGTTAATCGGAGTGATGGGATGTGC	422
Eo3-133	ACACAATTAGCCTCACTACCCTACACG	423
Eo3-133	CVNRS DGM	424
Eo3-134	CCGCATCTGGGACTCGTCAT	425
Eo3-134	GGCGTAGGACCCTGAGCAGTA	426
Eo3-134	PHPGTRH	427
Eo3-134	TGTCCGCATCTGGGACTCGTCATTGC	428
Eo3-134	ACAGGCGTAGGACCCTGAGCAGTAACG	429
Eo3-134	CPHPGTRHC	430

TABLE 4-continued

Peptides and Nucleic Acids Isolated		
Name	Sequence	SEQ ID NO:
Eo3-135	ATGAATCAGCGGGTTCAGAAT TACTTAGTCGCCCAAGTCTTA	417
Eo3-135	MNQRVQN	418
Eo3-135	TGTATGAATCAGCGGGTTCAGAATTGC ACATACCTTAGTCGCCCAAGTCTTAACG	419
Eo3-135	CMNQRVQNC	420
Eo3-137	AATCAGTGGAAGTCGGTGTCT TTAGTCACCTTCAGCCACAGA	421
Eo3-137	NQWKSVS	422
Eo3-137	TGTAATCAGTGGAAGTCGGTGTCTTGC ACATTAGTCACCTTCAGCCACAGAACG	423
Eo3-137	CNQWKSVC	424
Eo3-138	CAGACGCATGCTCGGCATGTT GTCTGCGTACGAGCCGTACAA	425
Eo3-138	QTHARHV	426
Eo3-138	TGTCAGACGCATGCTCGGCATGTTTGC ACAGTCTGCGTACGAGCCGTACAAACG	427
Eo3-138	CQTHARHVC	428
Eo3-139	TTTCAGAAATCGTCAGCCGATG AAAGTCTTAGCAGTCGGCTAC	429
Eo3-139	FQNRQPM	430
Eo3-139	TGTTTTTCAGAAATCGTCAGCCGATGTGC ACAAAAGTCTTAGCAGTCGGCTACACG	431
Eo3-139	CFQNRQPMC	432
Eo3-140	AGGGCTCTGGATACGGCGAAT TCCCGAGACCTATGCCGCTTA	433
Eo3-140	RALDTAN	434
Eo3-140	TGTAGGGCTCTGGATACGGCGAATTGC ACATCCCGAGACCTATGCCGCTTAACG	435
Eo3-140	CRALDTANC	436
Eo3-141	CAGGAGCCGACGCGGCTGAAG GTCCTCGGCTGCGCCGACTTC	437
Eo3-141	QEPTRLK	438
Eo3-141	TGTCAGGAGCCGACGCGGCTGAAGTGC ACAGTCTCTCGGCTGCGCCGACTTCACG	439
Eo3-141	CQEPTRLKC	440
Eo3-142	AAGGAGCCTACGAAGGCGCAT TTCCTCGGATGCTTCCGCGTA	441
Eo3-142	KEPTKAH	442
Eo3-142	TGTAAGGAGCCTACGAAGGCGCATTCG ACATTCTCTCGGATGCTTCCGCGTAACG	443
Eo3-142	CKEPTKAHC	444

TABLE 4-continued

Peptides and Nucleic Acids Isolated		
Name	Sequence	SEQ ID NO:
Eo3-143	AATGGTAAGGCTAATTGGAAG TTACCATTCGATTAACCTTC	445
Eo3-143	NGKANWK	446
Eo3-143	TGTAATGGTAAGGCTAATTGGAAGTGC ACATTACCATTCGATTAACCTTCACG	447
Eo3-143	CNGKANWKC	448

[0506] The sequences were analyzed with ClustalW software to identify amino acid motifs that are shared by different peptides. The NCBI/NIH/NLM database was searched for each amino acid peptide sequence. The peptidyl sequence data set was also prioritized according to similarity, that is: a. exact, b. similar, or c. homologous to known proteins. The peptides with greater than 50% homology were aligned and the shared motifs were searched in the online database using BLAST.

[0507] Some sequences bore significant homology to the sequences of known proteins. For example, SEQ ID NO:334 (Eo3-112), SEQ ID NO:336 (Eo3-112), SEQ ID NO:342 (Eo3-114), SEQ ID NO:344 (Eo3-114), SEQ ID NO:410 (Eo3-133) and SEQ ID NO:412 (Eo3-133) were similar to Tissue Inhibitor of Metalloproteinase 2 (TIMP-2). In particular, SEQ ID NO:412 with sequence CVNRSDGMC is homologous to CIKRS DGSC (SEQ ID NO:452) of TIMP-2. Similarly, SEQ ID NO:334 and 336 with sequence NQRHQMSC is homologous to TIMP-2 at positions 145-152 (NQRYQMGC, SEQ ID NO:454). Also, SEQ ID NO:342 and 344 with sequence NHRYMQM is homologous to chicken TIMP-2 at positions 145-152 (NHRY-QMGC, SEQ ID NO:456).

[0508] Some proteins were homologous to peptide CAPGPSKSC (SEQ ID NO:4), including subtilisin inhibitor at positions 66-77 (CAPGPS, SEQ ID NO:458), chymase at positions 46-51 (GPSKSC, SEQ ID NO:460) and CDA05 (Genbank Accession No. AAK14929.1) at positions 221-226 (APGPSK, SEQ ID NO:462).

[0509] The considerable number of peptidyl sequences found to associate with plaque surfaces suggests expression of multiple membrane targets on these endothelial cells, indicative of a positional gene expression or molecular processing different from endothelium elsewhere in the vascular tree.

In Vivo Imaging Using Phage Displaying Peptides

[0510] Mice were injected with about 10^{11} phage bearing CAPGDSKSD (SEQ ID NO:4) or with control phage without this peptide sequence. After about 30 min, the aortic tissue was perfusion-fixed with paraformaldehyde and removed. Aortic tissue was then stained with streptavidin hydroxylase conjugate.

[0511] FIG. 1 provides images of aortic specimens from mice injected with such phage. Binding of phage to aorta

was visualized with biotinylated anti-phage antibody and avidin-linked enzyme activation of DAB. Phage bearing the CAPGDSKSD (SEQ ID NO:4) peptide showed preferential binding to atherosclerotic lesions (FIG. 1D). FIG. 1A shows a young non-atherosclerotic Apo E knockout mouse injected with CAPGPSKSC (SEQ ID NO:4) phage. In the aorta of these mice, atherosclerotic lesions have not yet developed, and no phage binding to the aorta is detectable. FIG. 1B shows a normal aorta from a Balb/C mouse injected with CAPGPSKSC (SEQ ID NO:4) phage. No association of phage with the aortic surface is observed, suggesting that the molecule that binds CAPGPSKSC (SEQ ID NO:4) is not present in detectable quantity on the surface of normal aorta endothelium. FIG. 1C shows an aorta from an Apo B knockout mouse fed a high fat diet that was injected with 10^{11} control phage. Atherosclerotic lesions are clearly visible, however no detectable association of control phage with the lesions is observed. FIG. 1D shows an aorta of an atherosclerotic Apo E knockout mouse fed a high fat diet and injected with 10^{11} CAPGPSKSC (SEQ ID NO:4) phage. Phage binding to the lesions is readily visualized.

[0512] Immunostaining showed that the phage expressing CAPGPSKSC (SEQ ID NO:4) preferentially bound to atherosclerotic lesions in the Apo B knockout mouse aorta. Binding of the CAPGPSKSC (SEQ ID NO:4) expressing phage was more intense at the edge of the lesions.

[0513] The intensity of the phage binding at the edge of lesions indicates that the target for this peptide must be present on the surface of these potentially activated endothelial cells. Endothelial cells grow as strict monolayers. When wounding occurs that disrupts the endothelial monolayer at the center of atherosclerotic lesions, cells at the edge of the lesion will replicate and migrate into the lesion to reestablish the integrity of the endothelial lining. In aortic arch lesions, binding of the peptide was consistently absent in the center of lesions that coincide with endothelial quiescence, possibly denudation and/or wounding. These data suggest the CAPGPSKSC (SEQ ID NO:4) expressing phage is recognizing a target molecule on the endothelial cell surface, rather than binding to the sub-endothelial matrix proteins, and/or that the target molecule may be associated with activated endothelial cells.

Peptide CAPGPSKSC (SEQ ID NO:4) Binds In Vivo to Atherosclerotic Lesions

[0514] To verify that the peptidyl sequence CAPGPSKSC (SEQ ID NO:4) that is expressed on phage protein m was responsible for the selective localization to atherosclerotic lesions, a biotinylated peptide containing the core sequence CAPGPSKSC (SEQ ID NO:4) was synthesized, folded, disulfide bonds constituted by oxidization, and compositional validity established by mass spectrometry. The peptide was injected into atherosclerotic ApoE knockout mice via tail vein, and the tissues were fixed by in vivo perfusion, and aortas were freed by dissection. The binding of biotinylated peptide to the aorta was visualized with streptavidin conjugated peroxidase and DAB substrate. The peptide binding replicated the CAPGPSKSC (SEQ ID NO:4) phage binding to the lesions (FIG. 2A), supporting that the association of CAPGPSKSC (SEQ ID NO:4) phage with atherosclerotic lesions was mediated by the fused peptidyl sequence.

[0515] The association of this peptide to the atherosclerotic lesions was also analyzed on tissue sections. The

experiment was replicated in atherosclerotic ApoE mice by infusing CAPGPSKSC (SEQ ID NO:4) peptide and sections of the aorta were prepared, detected with streptavidin-conjugated peroxidase and developed with DAB substrate. Peptide binding to the surface of atherosclerotic lesions (FIG. 2B) was quite evident. In contrast, no substantial signal was evident elsewhere. Further, there was a differential pattern observed in which the peptide appeared to bind more to the endothelium at the periphery of the lesions and less to the central aspect of the lesions. This suggests that the endothelium at the periphery express the target at greater density. These areas are likely involved in lesion formation and differ to some degree in their phenotype compared to that of the overlying endothelium.

Peptide CAPGPSKSC (SEQ ID NO:4) Binds to Human Atherosclerotic Lesions

[0516] The biotinylated CAPGPSKSC (SEQ ID NO:4) peptide was used to probe the human vascular samples with atherosclerotic lesions. FIG. 3B shows an atherosclerotic lesion in a human arterial specimen after application of biotinylated CAPGPSKSC (SEQ ID NO:4) peptide directly to the luminal surface. The biotinylated CAPGPSKSC (SEQ ID NO:4) peptide exhibited no observable binding to non-atherosclerotic arterial samples or veins. Instead, the peptide preferentially bound to the atherosclerotic plaque (compare FIGS. 3A and 3B) indicating the molecular target of this peptide exists in human lesions. In contrast, a peptide control with the same amino acid composition as CAPGPSKSC (SEQ ID NO:4) but with a scrambled sequence exhibited no observable binding to atherosclerotic arterial samples.

An 82 Kd Protein Is the Target of the CAPGPSKSC (SEQ ID NO:4) Peptide

[0517] Peptide CAPGPSKSC (SEQ ID NO:4) bound two protein bands on a blot of a protein lysate of the mouse endothelial cells (bEND.3). See FIG. 4. The sizes of the two proteins that bound the CAPGPSKSC (SEQ ID NO:4) peptide were 82 kilodaltons (P82) and 120 kilodaltons (P120). The sharpness of the detected bands suggests that these target proteins are not glycoproteins. The P82 protein was also detected in cell membrane fractions partially purified by Triton X 114 extraction. These data suggest that the P82 protein is a membrane protein. The sizes of these proteins indicates that neither one is vascular cell adhesion molecule-1 (VCAM-1), which is a member of the immunoglobulin (Ig) supergene family expressed on activated, but not resting, endothelium.

[0518] FIG. 4 is a photograph of a Western blot identifying the target biomolecule of the CAPGPSKSC (SEQ ID NO:4) peptide in mouse endothelial cells (Bend-3). The total protein lysate (lane 1) or membrane preparations were separated on a SDS polyacrylamide gel and then transferred to a nitrocellulose membrane. The membrane was probed with biotinylated peptide CAPGPSKSC (SEQ ID NO:4). Two sharp bands are observed on a Western blot of a whole cell lysate of mouse endothelial cell line (Bend-3), using the biotinylated CAPGPSKSC (SEQ ID NO:4) peptide to detect target proteins. The sizes of the proteins bound by the CAPGPSKSC (SEQ ID NO:4) peptide were about 82 kilodaltons (P82) and about 120 kilodaltons (P120). The sharpness of the detected bands suggests that these target proteins are not glycoproteins. The P82 protein was also detected,

and apparently enriched, in membrane fractions partially purified by Triton X 114 extraction. These data suggest that the P82 protein is a membrane protein.

The TIMP-2 Homologous Peptides Bind to Endothelium

[0519] Three TIMP-2 peptidyl homologues were further analyzed to investigate whether peptides from this data set with homology to known proteins mimic the binding activity of their homologous proteins. The CNQRHQMSC (SEQ ID NO:336) phage bound to aortic endothelium of ApoE knock-out mice. However association was indiscriminate, binding rather widely to endothelium whether involved in atherosclerotic lesions or not (FIG. 5).

TIMP-2 Homologous Peptide Binding to HUVEC

[0520] All three TIMP-2 homologous peptides (CYNRS-DGMC, SEQ ID NO:464; CNHRYMQMC, SEQ ID NO:344; and CNQRHQMSC, SEQ ID NO:336) showed dose dependent binding to HUVEC endothelial cells (FIG. 6A) as well as the fibroblast line HT1080 (not shown), and ECV304 (not shown). The binding of these peptides to cells was competitively inhibited by TIMP-2 protein (FIG. 6B) consistent with the presence of a TIMP-2 binding site on the surface of these cells. The regions of TIMP-2 homologous to the peptides differ from the contact regions of TIMP-2 to known TIMP-2 binding molecules such as TM-MMP as revealed by crystallography (Fernandez-Catalan, 1998). The presence of a TIMP-2 binding site other than a member of the metalloproteinase family has been postulated (Chesler, 1995; Corcoran, 1995). Binding of these peptides to cell surfaces is consistent with the presence of a novel receptor for TIMP-2. However, the CNQRHQMSC (SEQ ID NO:336) localization pattern indicates that it is not entirely selective for atherosclerotic lesion endothelium.

[0521] The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 22

Val His Lys Leu Pro Glu Ser

1

5

<210> SEQ ID NO 23

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 23

tgtgtgcata agctgcctga gtcttgc

27

<210> SEQ ID NO 24

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 24

Cys Val His Lys Leu Pro Glu Ser Cys

1

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<210> SEQ ID NO 25

<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 25

ccgactcagg cttctcttca t 21

<210> SEQ ID NO 26
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 26

Pro Thr Gln Ala Ser Leu His
1 5

<210> SEQ ID NO 27
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 27

tgtccgactc aggtcttctct tcattgc 27

<210> SEQ ID NO 28
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 28

Cys Pro Thr Gln Ala Ser Leu His Cys
1 5

<210> SEQ ID NO 29
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 29

gatactgcgc ctccgtcgtc g 21

<210> SEQ ID NO 30
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 30

Asp Thr Ala Pro Pro Ser Ser

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1	5
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<210> SEQ ID NO 31
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 31

tgtgatactg cgctccgctc gtcgtgc 27

<210> SEQ ID NO 32
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 32

Cys Asp Thr Ala Pro Pro Ser Ser Cys
1 5

<210> SEQ ID NO 33
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 33

gggggtgcaga ctctgcttgc t 21

<210> SEQ ID NO 34
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 34

Gly Val Gln Thr Leu Leu Ala
1 5

<210> SEQ ID NO 35
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 35

tgtgggggtgc agactctgct tgcttgc 27

<210> SEQ ID NO 36
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage

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display library.

<400> SEQUENCE: 36

Cys Gly Val Gln Thr Leu Leu Ala Cys
1 5

<210> SEQ ID NO 37

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 37

gatacctgtga cgaagcatat t 21

<210> SEQ ID NO 38

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 38

Asp Pro Val Thr Lys His Thr
1 5

<210> SEQ ID NO 39

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 39

tgtgatcctg tgacgaagca tacttgc 27

<210> SEQ ID NO 40

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 40

Cys Asp Pro Val Thr Lys His Thr Cys
1 5

<210> SEQ ID NO 41

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 41

gatcagagta cgattcgggc g 21

<210> SEQ ID NO 42

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 42

Asp Gln Ser Thr Ile Arg Ala
1 5

<210> SEQ ID NO 43
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 43

tgtgatcaga gtacgattcg ggcgtgc 27

<210> SEQ ID NO 44
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 44

Cys Asp Gln Ser Thr Ile Arg Ala Cys
1 5

<210> SEQ ID NO 45
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 45

cgggctgcta ctccttcgat t 21

<210> SEQ ID NO 46
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 46

Arg Ala Ala Thr Pro Ser Ile
1 5

<210> SEQ ID NO 47
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 47

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tgtcgggctg ctactccttc gatttgc

27

<210> SEQ ID NO 48

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 48

Cys Arg Ala Ala Thr Pro Ser Ile Cys

1

5

<210> SEQ ID NO 49

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 49

aagacgtcgc atgcgcagga g

21

<210> SEQ ID NO 50

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 50

Lys Thr Ser His Ala Gln Glu

1

5

<210> SEQ ID NO 51

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 51

tgtaagacgt cgcattgcgca ggagtgc

27

<210> SEQ ID NO 52

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 52

Cys Lys Thr Ser His Ala Gln Glu Cys

1

5

<210> SEQ ID NO 53

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(21)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 53

aagcatcctg ttggncgggt g 21

<210> SEQ ID NO 54
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 54

Lys His Pro Val Gly Arg Val
1 5

<210> SEQ ID NO 55
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(27)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 55

tgtaagcatc ctgttggncc ggtgtgc 27

<210> SEQ ID NO 56
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 56

Cys Lys His Pro Val Gly Arg Val Cys
1 5

<210> SEQ ID NO 57
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 57

acggatacta agaattcgca g 21

<210> SEQ ID NO 58
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 58

Thr Asp Thr Lys Asn Ser Gln
1 5

<210> SEQ ID NO 59

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 59

tgtacggata ctaagaattc gcagtgc 27

<210> SEQ ID NO 60

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 60

Cys Thr Asp Thr Lys Asn Ser Gln Cys
1 5

<210> SEQ ID NO 61

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 61

cagccgccga tggggcggtg t 21

<210> SEQ ID NO 62

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 62

Gln Pro Pro Met Gly Arg Tyr
1 5

<210> SEQ ID NO 63

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 63

tgtcagccgc cgaatggggcg gtattgc 27

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<210> SEQ ID NO 64
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 64

Cys Gln Pro Pro Met Gly Arg Tyr Cys
1 5

<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 65

aatgagaggc tgaataagga t 21

<210> SEQ ID NO 66
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 66

Asn Glu Arg Leu Asn Lys Asp
1 5

<210> SEQ ID NO 67
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 67

tgtaatgaga ggctgaataa ggattgc 27

<210> SEQ ID NO 68
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 68

Cys Asn Glu Arg Leu Asn Lys Asp Cys
1 5

<210> SEQ ID NO 69
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 69

ccgccgtcga ataagcagat g

21

<210> SEQ ID NO 70

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 70

Pro Pro Ser Asn Lys Gln Met

1

5

<210> SEQ ID NO 71

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 71

tgtccgccgt cgaataagca gatgtgc

27

<210> SEQ ID NO 72

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 72

Cys Pro Pro Ser Asn Lys Gln Met Cys

1

5

<210> SEQ ID NO 73

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 73

gattcttcgt cgctgtctcg g

21

<210> SEQ ID NO 74

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 74

Asp Ser Ser Ser Pro Ala Arg

1

5

<210> SEQ ID NO 75

<211> LENGTH: 27

<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 75

tgtgattcctt cgtcgccctgc tcggtgc 27

<210> SEQ ID NO 76
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 76

Cys Asp Ser Ser Ser Pro Ala Arg Cys
1 5

<210> SEQ ID NO 77
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 77

acgcagtcctg ataataggcg t 21

<210> SEQ ID NO 78
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 78

Thr Gln Ser Asp Asn Arg Arg
1 5

<210> SEQ ID NO 79
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 79

tgtacgcagc ctgataatag gcgttgc 27

<210> SEQ ID NO 80
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 80

Cys Thr Gln Ser Asp Asn Arg Arg Cys
1 5

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<210> SEQ ID NO 81
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 81

aagggtctgc cggctaagac t 21

<210> SEQ ID NO 82
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 82

Lys Gly Leu Pro Ala Lys Thr
1 5

<210> SEQ ID NO 83
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 83

tgtaagggtc tgccggctaa gacttgc 27

<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 84

Cys Lys Gly Leu Pro Ala Lys Thr Cys
1 5

<210> SEQ ID NO 85
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 85

ttgcagccgc atctgagtct t 21

<210> SEQ ID NO 86
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 86

Leu Gln Pro His Leu Ser Leu
1 5

<210> SEQ ID NO 87

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 87

tgtttgcagc cgcactctgag tctttgc 27

<210> SEQ ID NO 88

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 88

Cys Leu Gln Pro His Leu Ser Leu Cys
1 5

<210> SEQ ID NO 89

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 89

gcggttccgt agaatcggtc t 21

<210> SEQ ID NO 90

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 90

Ala Val Pro Gln Asn Arg Ser
1 5

<210> SEQ ID NO 91

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 91

tgtgcggttc cgtagaatcg ttcttgc 27

<210> SEQ ID NO 92

<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 92

Cys Ala Val Pro Gln Asn Arg Ser Cys
1 5

<210> SEQ ID NO 93
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 93

atgaatcaga ctcttgattt g 21

<210> SEQ ID NO 94
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 94

Met Asn Gln Thr Pro Asp Leu
1 5

<210> SEQ ID NO 95
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 95

tgtatgaatc agactcctga tttgtgc 27

<210> SEQ ID NO 96
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 96

Cys Met Asn Gln Thr Pro Asp Leu Cys
1 5

<210> SEQ ID NO 97
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 97

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tttcagatgc agctactct t 21

<210> SEQ ID NO 98
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 98

Phe Gln Met Gln Pro Thr Leu
1 5

<210> SEQ ID NO 99
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 99

tgttttcaga tgcagcctac tctttgc 27

<210> SEQ ID NO 100
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 100

Cys Phe Gln Met Gln Pro Thr Leu Cys
1 5

<210> SEQ ID NO 101
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 101

agtggggctt ctaataagac g 21

<210> SEQ ID NO 102
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 102

Ser Gly Ala Ser Asn Lys Thr
1 5

<210> SEQ ID NO 103
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 103

tgtagtgggg cttctaataa gacgtgc

27

<210> SEQ ID NO 104

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 104

Cys Ser Gly Ala Ser Asn Lys Thr Cys

1

5

<210> SEQ ID NO 105

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 105

actaagatgc ggttgagca g

21

<210> SEQ ID NO 106

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 106

Thr Lys Met Arg Leu Glu Gln

1

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<210> SEQ ID NO 107

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 107

tgtactaaga tgcggttgga gcagtc

27

<210> SEQ ID NO 108

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 108

Cys Thr Lys Met Arg Leu Glu Gln Cys

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<210> SEQ ID NO 109
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 109

acgtctccta tttatccggg t 21

<210> SEQ ID NO 110
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 110

Thr Ser Pro Ile Tyr Pro Gly
1 5

<210> SEQ ID NO 111
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 111

tgtacgtctc ctatttatcc gggttgc 27

<210> SEQ ID NO 112
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 112

Cys Thr Ser Pro Ile Tyr Pro Gly Cys
1 5

<210> SEQ ID NO 113
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 113

aagactccgt cgcagagtca g 21

<210> SEQ ID NO 114
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 114

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Lys Thr Pro Ser Gln Ser Gln
1 5

<210> SEQ ID NO 115
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 115

tgtaagactc cgtcgagag tcagtgc 27

<210> SEQ ID NO 116
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 116

Cys Lys Thr Pro Ser Gln Ser Gln Cys
1 5

<210> SEQ ID NO 117
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 117

cttcaggctt ttaaggcgac t 21

<210> SEQ ID NO 118
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 118

Leu Gln Ala Phe Lys Ala Thr
1 5

<210> SEQ ID NO 119
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 119

tgtcttcagg cttttaaggc gacttgc 27

<210> SEQ ID NO 120
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 120

Cys Leu Gln Ala Phe Lys Ala Thr Cys
1 5

<210> SEQ ID NO 121

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 121

tctactactg agcttaataa g 21

<210> SEQ ID NO 122

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 122

Ser Thr Thr Glu Leu Asn Lys
1 5

<210> SEQ ID NO 123

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 123

tggttctacta ctgagcttaa taagtgc 27

<210> SEQ ID NO 124

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 124

Cys Ser Thr Thr Glu Leu Asn Lys Cys
1 5

<210> SEQ ID NO 125

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 125

aggactcata gttctccgac t 21

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<210> SEQ ID NO 126
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 126

Arg Thr His Ser Ser Pro Thr
1 5

<210> SEQ ID NO 127
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 127

tgtaggactc atagttctcc gacttgc 27

<210> SEQ ID NO 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 128

Cys Arg Thr His Ser Ser Pro Thr Cys
1 5

<210> SEQ ID NO 129
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 129

aatgagaatt ttaaggggct g 21

<210> SEQ ID NO 130
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 130

Asn Glu Asn Phe Lys Gly Leu
1 5

<210> SEQ ID NO 131
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 131

tgtaatgaga attttaaggg gctgtgc

27

<210> SEQ ID NO 132

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 132

Cys Asn Glu Asn Phe Lys Gly Leu Cys

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<210> SEQ ID NO 133

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 133

agtaagacta atcatgcttc t

21

<210> SEQ ID NO 134

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 134

Ser Lys Thr Asn His Ala Ser

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<210> SEQ ID NO 135

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 135

tgtagtaaga ctaatcatgc ttcttg

27

<210> SEQ ID NO 136

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 136

Cys Ser Lys Thr Asn His Ala Ser Cys

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<210> SEQ ID NO 137

<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 137

acgccgtatc cttctaattc g 21

<210> SEQ ID NO 138
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 138

Thr Pro Tyr Pro Ser Asn Ser
1 5

<210> SEQ ID NO 139
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 139

tgtacgccgt atccttctaa ttcgtgc 27

<210> SEQ ID NO 140
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 140

Cys Thr Pro Tyr Pro Ser Asn Ser Cys
1 5

<210> SEQ ID NO 141
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 141

acgctgtctg ctgctccgca t 21

<210> SEQ ID NO 142
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 142

Thr Leu Ser Ala Ala Pro His

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<210> SEQ ID NO 143
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 143

tgtacgctgt ctgctgctcc gcattgc 27

<210> SEQ ID NO 144
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 144

Cys Thr Leu Ser Ala Ala Pro His Cys
1 5

<210> SEQ ID NO 145
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 145

cttaataatt ctcaggctca t 21

<210> SEQ ID NO 146
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 146

Leu Asn Asn Ser Gln Ala His
1 5

<210> SEQ ID NO 147
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 147

tgtcttaata attctcaggc tcattgc 27

<210> SEQ ID NO 148
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage

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display library.

<400> SEQUENCE: 148

Cys Leu Asn Asn Ser Gln Ala His Cys
1 5

<210> SEQ ID NO 149

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 149

attgagcatt cggcgcagca g 21

<210> SEQ ID NO 150

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 150

Ile Glu His Ser Ala Gln Gln
1 5

<210> SEQ ID NO 151

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 151

tgtattgagc attcggcgca gcagtgc 27

<210> SEQ ID NO 152

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 152

Cys Ile Glu His Ser Ala Gln Gln Cys
1 5

<210> SEQ ID NO 153

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 153

tcggctgcgg ggcacatac t 21

<210> SEQ ID NO 154

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 154

Ser Ala Ala Gly His His Thr
1 5

<210> SEQ ID NO 155
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 155

tgttcggctg cggggcatca tacttgc 27

<210> SEQ ID NO 156
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 156

Cys Ser Ala Ala Gly His His Thr Cys
1 5

<210> SEQ ID NO 157
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 157

cataatcaga agttgaatcg t 21

<210> SEQ ID NO 158
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 158

His Asn Gln Lys Leu Asn Arg
1 5

<210> SEQ ID NO 159
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 159

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tgtcataatc agaagttgaa tcgttgc

27

<210> SEQ ID NO 160
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 160

Cys His Asn Gln Lys Leu Asn Arg Cys
1 5

<210> SEQ ID NO 161
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 161

aagtcgactt ctcatagtat g

21

<210> SEQ ID NO 162
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 162

Lys Ser Thr Ser His Ser Met
1 5

<210> SEQ ID NO 163
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 163

tgtaagtcga cttctcatag tatgtgc

27

<210> SEQ ID NO 164
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 164

Cys Lys Ser Thr Ser His Ser Met Cys
1 5

<210> SEQ ID NO 165
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 165

cctaataata agtcggcttc g 21

<210> SEQ ID NO 166

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 166

Pro Asn Asn Lys Ser Ala Ser
1 5

<210> SEQ ID NO 167

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 167

tgtcctaata ataagtcggc ttcgtgc 27

<210> SEQ ID NO 168

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 168

Cys Pro Asn Asn Lys Ser Ala Ser Cys
1 5

<210> SEQ ID NO 169

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 169

gaggatccta cgttgaaggt g 21

<210> SEQ ID NO 170

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 170

Glu Asp Pro Thr Leu Lys Val
1 5

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<210> SEQ ID NO 171
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 171

tgtgaggatc ctacgttgaa ggtgtgc

27

<210> SEQ ID NO 172
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 172

Cys Glu Asp Pro Thr Leu Lys Val Cys
1 5

<210> SEQ ID NO 173
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 173

atgtctgcga tgtctcgtca g

21

<210> SEQ ID NO 174
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 174

Met Ser Ala Met Ser Arg Gln
1 5

<210> SEQ ID NO 175
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 175

tgatatgtctg cgatgtctcg tcaagtgc

27

<210> SEQ ID NO 176
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 176

Cys Met Ser Ala Met Ser Arg Gln Cys
1 5

<210> SEQ ID NO 177

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 177

cctgggaaga ttctgcgtag t 21

<210> SEQ ID NO 178

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 178

Pro Gly Lys Ile Ser Arg Ser
1 5

<210> SEQ ID NO 179

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 179

tgtctctggga agatttcgcg tagttgc 27

<210> SEQ ID NO 180

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 180

Cys Pro Gly Lys Ile Ser Arg Ser Cys
1 5

<210> SEQ ID NO 181

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 181

ctgaagctgg ggtcgaagca g 21

<210> SEQ ID NO 182

<211> LENGTH: 7

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 182

Leu Lys Leu Gly Ser Lys Gln
1 5

<210> SEQ ID NO 183
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 183

tgtctgaagc tggggtcgaa gcagtgc 27

<210> SEQ ID NO 184
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 184

Cys Leu Lys Leu Gly Ser Lys Gln Cys
1 5

<210> SEQ ID NO 185
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 185

aagactagtc cggagtctac t 21

<210> SEQ ID NO 186
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 186

Lys Thr Ser Pro Glu Ser Thr
1 5

<210> SEQ ID NO 187
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 187

tgtaagacta gtccggagtc tacttgc 27

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<210> SEQ ID NO 188
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 188

Cys Lys Thr Ser Pro Glu Ser Thr Cys
1 5

<210> SEQ ID NO 189
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 189

acgcttttttc cggggaattc t 21

<210> SEQ ID NO 190
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 190

Thr Leu Phe Pro Gly Asn Ser
1 5

<210> SEQ ID NO 191
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 191

tgtacgcttt ttccggggaa ttcttgc 27

<210> SEQ ID NO 192
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 192

Cys Thr Leu Phe Pro Gly Asn Ser Cys
1 5

<210> SEQ ID NO 193
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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display library.

<400> SEQUENCE: 193

ttgccgtcgt ctacgaggct g 21

<210> SEQ ID NO 194

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 194

Leu Pro Ser Ser Thr Arg Leu

1 5

<210> SEQ ID NO 195

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 195

tgtttgccgt cgtctacgag gctgtgc 27

<210> SEQ ID NO 196

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 196

Cys Leu Pro Ser Ser Thr Arg Leu Cys

1 5

<210> SEQ ID NO 197

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 197

tcgagtcaga ggactcctcc g 21

<210> SEQ ID NO 198

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 198

Ser Ser Gln Arg Thr Pro Pro

1 5

<210> SEQ ID NO 199

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<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 199

tggttcgagtc agaggactcc tccgtgc 27

<210> SEQ ID NO 200
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 200

Cys Ser Ser Gln Arg Thr Pro Pro Cys
1 5

<210> SEQ ID NO 201
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 201

ctgcctacga tgacgccgac g 21

<210> SEQ ID NO 202
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 202

Leu Pro Thr Met Thr Pro Thr
1 5

<210> SEQ ID NO 203
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 203

tgtctgccta cgatgacgcc gacgtgc 27

<210> SEQ ID NO 204
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 204

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Cys Leu Pro Thr Met Thr Pro Thr Cys
1 5

<210> SEQ ID NO 205
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 205

cttatgacgc cgtcgaagag g 21

<210> SEQ ID NO 206
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 206

Leu Met Thr Pro Ser Lys Arg
1 5

<210> SEQ ID NO 207
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 207

tgtcttatga cgccgtcgaa gaggtgc 27

<210> SEQ ID NO 208
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 208

Cys Leu Met Thr Pro Ser Lys Arg Cys
1 5

<210> SEQ ID NO 209
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 209

gagcattttt ttagtcggtc t 21

<210> SEQ ID NO 210
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 210

Glu His Phe Phe Ser Arg Ser
1 5

<210> SEQ ID NO 211

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 211

tgtgagcatt ttttagtcg gtcttgc 27

<210> SEQ ID NO 212

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 212

Cys Glu His Phe Phe Ser Arg Ser Cys
1 5

<210> SEQ ID NO 213

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 213

acgaatcagt ttttcagca g 21

<210> SEQ ID NO 214

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 214

Thr Asn Gln Phe Leu Gln Gln
1 5

<210> SEQ ID NO 215

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 215

tgtagcaatc agtttttgca gcagtgc 27

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<210> SEQ ID NO 216
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 216

Cys Thr Asn Gln Phe Leu Gln Gln Cys
1 5

<210> SEQ ID NO 217
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 217

cctgcgaata agtcttcggtt t 21

<210> SEQ ID NO 218
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 218

Pro Ala Asn Lys Ser Ser Phe
1 5

<210> SEQ ID NO 219
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 219

tgtcctgcga ataagtccttc gttttgc 27

<210> SEQ ID NO 220
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 220

Cys Pro Ala Asn Lys Ser Ser Phe Cys
1 5

<210> SEQ ID NO 221
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

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<400> SEQUENCE: 221

agtacgacgc agtctagttg g 21

<210> SEQ ID NO 222

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 222

Ser Thr Thr Gln Ser Ser Trp
1 5

<210> SEQ ID NO 223

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 223

tgtagtacga cgcagtctag ttggtgc 27

<210> SEQ ID NO 224

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 224

Cys Ser Thr Thr Gln Ser Ser Trp Cys
1 5

<210> SEQ ID NO 225

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 225

gtgactccgg atcggtgac g 21

<210> SEQ ID NO 226

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 226

Val Thr Pro Asp Arg Leu Thr
1 5

<210> SEQ ID NO 227

<211> LENGTH: 27

<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 227

tgtttgactc cggatcggct gacgtgc 27

<210> SEQ ID NO 228
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 228

Cys Val Thr Pro Asp Arg Leu Thr Cys
1 5

<210> SEQ ID NO 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 229

acgtggcaga cttagaggtc g 21

<210> SEQ ID NO 230
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 230

Thr Trp Gln Thr Gln Arg Ser
1 5

<210> SEQ ID NO 231
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 231

tgtacgtggc agacttagag gtcgtgc 27

<210> SEQ ID NO 232
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 232

Cys Thr Trp Gln Thr Gln Arg Ser Cys
1 5

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<210> SEQ ID NO 233
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 233

ccgcatcctg ggactcgtca t 21

<210> SEQ ID NO 234
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 234

Pro His Pro Gly Thr Arg His
1 5

<210> SEQ ID NO 235
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 235

tgtccgcatc ctgggactcg tcattgc 27

<210> SEQ ID NO 236
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 236

Cys Pro His Pro Gly Thr Arg His Cys
1 5

<210> SEQ ID NO 237
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 237

gcgccgaagc cgcagtctca g 21

<210> SEQ ID NO 238
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 238

Ala Pro Lys Pro Gln Ser Gln
1 5

<210> SEQ ID NO 239

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 239

tgtgcgccga agccgcagtc tcagtgc

27

<210> SEQ ID NO 240

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 240

Cys Ala Pro Lys Pro Gln Ser Gln Cys
1 5

<210> SEQ ID NO 241

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 241

agtcaggcgt agattcctgc g

21

<210> SEQ ID NO 242

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 242

Ser Gln Ala Gln Ile Pro Ala
1 5

<210> SEQ ID NO 243

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 243

tgtagtcagg cgtagattcc tgcgtgc

27

<210> SEQ ID NO 244

<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 244

Cys Ser Gln Ala Gln Ile Pro Ala Cys
1 5

<210> SEQ ID NO 245
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 245

ccgcagaata aggggaaggc t 21

<210> SEQ ID NO 246
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 246

Pro Gln Asn Lys Gly Lys Ala
1 5

<210> SEQ ID NO 247
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 247

tgtccgcaga ataaggggaa ggcttgc 27

<210> SEQ ID NO 248
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 248

Cys Pro Gln Asn Lys Gly Lys Ala Cys
1 5

<210> SEQ ID NO 249
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 249

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catactgcgc atccgcggtc t 21

<210> SEQ ID NO 250
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 250

His Thr Ala His Pro Arg Ser
1 5

<210> SEQ ID NO 251
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 251

tgtcatactg cgcacccgcg gtcttgc 27

<210> SEQ ID NO 252
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 252

Cys His Thr Ala His Pro Arg Ser Cys
1 5

<210> SEQ ID NO 253
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 253

aagcagtcgtg gtctgtttc t 21

<210> SEQ ID NO 254
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 254

Lys Gln Ser Gly Pro Val Ser
1 5

<210> SEQ ID NO 255
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 255

tgtaagcagt ctggtcctgt ttcttgc 27

<210> SEQ ID NO 256

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 256

Cys Lys Gln Ser Gly Pro Val Ser Cys
1 5

<210> SEQ ID NO 257

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 257

agtcagtatc cgtcgcgttc t 21

<210> SEQ ID NO 258

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 258

Ser Gln Tyr Pro Ser Arg Ser
1 5

<210> SEQ ID NO 259

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 259

tgtagtcagt atccgtcgcg ttcttgc 27

<210> SEQ ID NO 260

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 260

Cys Ser Gln Tyr Pro Ser Arg Ser Cys
1 5

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<210> SEQ ID NO 261
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 261

tcgagggatg ggaagactac g 21

<210> SEQ ID NO 262
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 262

Ser Arg Asp Gly Lys Thr Thr
1 5

<210> SEQ ID NO 263
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 263

tgttcgaggg atgggaagac tacgtgc 27

<210> SEQ ID NO 264
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 264

Cys Ser Arg Asp Gly Lys Thr Thr Cys
1 5

<210> SEQ ID NO 265
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 265

acgacgctga tgcctaatat t 21

<210> SEQ ID NO 266
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 266

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Thr Thr Leu Met Pro Asn Ile
1 5

<210> SEQ ID NO 267
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 267

tgtacgacgc tgatgcctaa tatttgc 27

<210> SEQ ID NO 268
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 268

Cys Thr Thr Leu Met Pro Asn Ile Cys
1 5

<210> SEQ ID NO 269
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 269

acgaataagc ttgataatac t 21

<210> SEQ ID NO 270
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 270

Thr Asn Lys Leu Asp Asn Thr
1 5

<210> SEQ ID NO 271
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 271

tgtacgaata agcttgataa tacttgc 27

<210> SEQ ID NO 272
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 272

Cys Thr Asn Lys Leu Asp Asn Thr Cys
1 5

<210> SEQ ID NO 273

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 273

actaagatgc ggttgagca g 21

<210> SEQ ID NO 274

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 274

Thr Lys Met Arg Leu Glu Gln
1 5

<210> SEQ ID NO 275

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 275

tgtactaaga tgcggttgga gcagtgc 27

<210> SEQ ID NO 276

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 276

Cys Thr Lys Met Arg Leu Glu Gln Cys
1 5

<210> SEQ ID NO 277

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 277

tcgccgcatc cggtagtaa g 21

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<210> SEQ ID NO 278
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 278

Ser Pro Asp Pro Gly Ser Lys
1 5

<210> SEQ ID NO 279
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 279

tggtcgccgg atccgggtag taagtgc 27

<210> SEQ ID NO 280
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 280

Cys Ser Pro Asp Pro Gly Ser Lys Cys
1 5

<210> SEQ ID NO 281
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 281

gagcattttt ttagtcggtc t 21

<210> SEQ ID NO 282
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 282

Glu His Phe Phe Ser Arg Ser
1 5

<210> SEQ ID NO 283
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 283

tgtgagcatt tttttagtcg gtcttg

27

<210> SEQ ID NO 284

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 284

Cys Glu His Phe Phe Ser Arg Ser Cys

1

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<210> SEQ ID NO 285

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 285

ggggcgccgt ctgatcatgt g

21

<210> SEQ ID NO 286

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 286

Gly Ala Pro Ser Asp His Val

1

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<210> SEQ ID NO 287

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 287

tgtggggcgc cgtctgatca tgtgtgc

27

<210> SEQ ID NO 288

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 288

Cys Gly Ala Pro Ser Asp His Val Cys

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<210> SEQ ID NO 289

<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 289

ccgcatacctg ggactcgtca t 21

<210> SEQ ID NO 290
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 290

Pro His Pro Gly Thr Arg His
1 5

<210> SEQ ID NO 291
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 291

tgtccgcatac ctgggactcg tcattgc 27

<210> SEQ ID NO 292
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 292

Cys Pro His Pro Gly Thr Arg His Cys
1 5

<210> SEQ ID NO 293
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 293

attaagcagt cgctgtctcg t 21

<210> SEQ ID NO 294
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 294

Ile Lys Gln Ser Leu Ser Arg

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1	5
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<210> SEQ ID NO 295
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 295

tgtattaagc agtcgctgtc tcgttgc 27

<210> SEQ ID NO 296
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 296

Cys Ile Lys Gln Ser Leu Ser Arg Cys
1 5

<210> SEQ ID NO 297
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 297

acgacgcata atgcgaagtg g 21

<210> SEQ ID NO 298
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 298

Thr Thr His Asn Ala Lys Trp
1 5

<210> SEQ ID NO 299
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 299

tgtacgacgc ataatgcgaa gtggtgc 27

<210> SEQ ID NO 300
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage

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display library.

<400> SEQUENCE: 300

Cys Thr Thr His Asn Ala Lys Trp Cys
1 5

<210> SEQ ID NO 301

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 301

ctgactacga agcctaggat g 21

<210> SEQ ID NO 302

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 302

Leu Thr Thr Lys Pro Arg Met
1 5

<210> SEQ ID NO 303

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 303

tgtctgacta cgaagcctag gatgtgc 27

<210> SEQ ID NO 304

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 304

Cys Leu Thr Thr Lys Pro Arg Met Cys
1 5

<210> SEQ ID NO 305

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 305

aagctgaagt cggggtcgct g 21

<210> SEQ ID NO 306

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<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 306

Lys Leu Lys Ser Gly Ser Leu
1 5

<210> SEQ ID NO 307
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 307

tgtaagctga agtcgggggc gctgtgc 27

<210> SEQ ID NO 308
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 308

Cys Lys Leu Lys Ser Gly Ser Leu Cys
1 5

<210> SEQ ID NO 309
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 309

cttccgtcga aggtgtctcg g 21

<210> SEQ ID NO 310
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 310

Leu Pro Ser Lys Val Ser Arg
1 5

<210> SEQ ID NO 311
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 311

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tgtgttccgt cgaaggtgtc tcggtgc

27

<210> SEQ ID NO 312
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 312

Cys Leu Pro Ser Lys Val Ser Arg Cys
1 5

<210> SEQ ID NO 313
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 313

gcgcccgggtc cgtctaagag t

21

<210> SEQ ID NO 314
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 314

Ala Pro Gly Pro Ser Lys Ser
1 5

<210> SEQ ID NO 315
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 315

tgtgcgccgg gtccgtctaa gaggtagc

27

<210> SEQ ID NO 316
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 316

Cys Ala Pro Gly Pro Ser Lys Ser Cys
1 5

<210> SEQ ID NO 317
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 317

tctccgctta agtcttcttc g 21

<210> SEQ ID NO 318

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 318

Ser Pro Leu Lys Ser Leu Ser
1 5

<210> SEQ ID NO 319

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 319

tgttctccgc ttaagtctct ttcgtgc 27

<210> SEQ ID NO 320

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 320

Cys Ser Pro Leu Lys Ser Leu Ser Cys
1 5

<210> SEQ ID NO 321

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 321

gcgccggggtc cgtctaagag t 21

<210> SEQ ID NO 322

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 322

Ala Pro Gly Pro Ser Lys Ser
1 5

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<210> SEQ ID NO 323
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 323

tgtgcgccgg gtccgtctaa gagttgc 27

<210> SEQ ID NO 324
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 324

Cys Ala Pro Gly Pro Ser Lys Ser Cys
1 5

<210> SEQ ID NO 325
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 325

ccgtcgggtc ttactaagca g 21

<210> SEQ ID NO 326
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 326

Pro Ser Gly Leu Thr Lys Gln
1 5

<210> SEQ ID NO 327
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 327

tgtccgtcgg gtcttactaa gcagtcg 27

<210> SEQ ID NO 328
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 328

Cys Pro Ser Gly Leu Thr Lys Gln Cys
1 5

<210> SEQ ID NO 329

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 329

aagtcgaata tgctctgag t 21

<210> SEQ ID NO 330

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 330

Lys Ser Asn Met Pro Leu Thr
1 5

<210> SEQ ID NO 331

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 331

tgtaagtcga atatgcctct gagttgc 27

<210> SEQ ID NO 332

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 332

Cys Lys Ser Asn Met Pro Leu Thr Cys
1 5

<210> SEQ ID NO 333

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 333

aatcagcggc attagatgtc t 21

<210> SEQ ID NO 334

<211> LENGTH: 7

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 334

Asn Gln Arg His Gln Met Ser
1 5

<210> SEQ ID NO 335
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 335

tgtaatcagc ggcattagat gtcttgc 27

<210> SEQ ID NO 336
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 336

Cys Asn Gln Arg His Gln Met Ser Cys
1 5

<210> SEQ ID NO 337
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 337

cagcgggagg atcagaagca g 21

<210> SEQ ID NO 338
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 338

Gln Arg Ala Asp Gln Lys Gln
1 5

<210> SEQ ID NO 339
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 339

tgtcagcggg cggatcagaa gcagtgc 27

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<210> SEQ ID NO 340
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 340

Cys Gln Arg Ala Asp Gln Lys Gln Cys
1 5

<210> SEQ ID NO 341
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 341

aatcatcggt atatgcagat g 21

<210> SEQ ID NO 342
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 342

Asn His Arg Tyr Met Gln Met
1 5

<210> SEQ ID NO 343
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 343

tgtaatcatc ggtatatgca gatgtgc 27

<210> SEQ ID NO 344
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 344

Cys Asn His Arg Tyr Met Gln Met Cys
1 5

<210> SEQ ID NO 345
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage

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display library.

<400> SEQUENCE: 345

attactccta tgtctcgtag t

21

<210> SEQ ID NO 346

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 346

Ile Thr Pro Met Ser Arg Thr

1

5

<210> SEQ ID NO 347

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 347

tgtattactc ctatgtctcg tacttgc

27

<210> SEQ ID NO 348

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 348

Cys Ile Thr Pro Met Ser Arg Thr Cys

1

5

<210> SEQ ID NO 349

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 349

agtcctacga ttgggcagaa g

21

<210> SEQ ID NO 350

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 350

Ser Pro Thr Ile Gly Gln Lys

1

5

<210> SEQ ID NO 351

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<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 351

tgtagtccta cgattgggca gaagtgc 27

<210> SEQ ID NO 352
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 352

Cys Ser Pro Thr Ile Gly Gln Lys Cys
1 5

<210> SEQ ID NO 353
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 353

tctaattatt cgctgggtat g 21

<210> SEQ ID NO 354
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 354

Ser Asn Tyr Ser Leu Gly Met
1 5

<210> SEQ ID NO 355
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 355

tgttctaatt attcgctggg tatgtgc 27

<210> SEQ ID NO 356
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 356

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Cys Ser Asn Tyr Ser Leu Gly Met Cys
1 5

<210> SEQ ID NO 357
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 357

acgaatacgg ggcataaggca t 21

<210> SEQ ID NO 358
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 358

Thr Asn Thr Gly His Arg His
1 5

<210> SEQ ID NO 359
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 359

tgtacgaata cggggcatag gcattgc 27

<210> SEQ ID NO 360
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 360

Cys Thr Asn Thr Gly His Arg His Cys
1 5

<210> SEQ ID NO 361
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 361

actatgcgta ctaattctag t 21

<210> SEQ ID NO 362
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 362

Thr Met Arg Thr Asn Ser Ser
1 5

<210> SEQ ID NO 363

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 363

tgtactatgc gtactaatc tagttgc 27

<210> SEQ ID NO 364

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 364

Cys Thr Met Arg Thr Asn Ser Ser Cys
1 5

<210> SEQ ID NO 365

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 365

acggcgccgt tggagcggag g 21

<210> SEQ ID NO 366

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 366

Thr Ala Pro Leu Glu Arg Arg
1 5

<210> SEQ ID NO 367

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 367

tgtagcgcg cgttgagcg gaggtgc 27

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<210> SEQ ID NO 368
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 368

Cys Thr Ala Pro Leu Glu Arg Arg Cys
1 5

<210> SEQ ID NO 369
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 369

ctgcttgagg agcctcgac t 21

<210> SEQ ID NO 370
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 370

Leu Leu Gly Glu Pro Arg Thr
1 5

<210> SEQ ID NO 371
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 371

tgtctgcttg gggagcctcg gacttgc 27

<210> SEQ ID NO 372
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 372

Cys Leu Leu Gly Glu Pro Arg Thr Cys
1 5

<210> SEQ ID NO 373
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 373

tctcgtgcta gtactaatga t 21

<210> SEQ ID NO 374

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 374

Ser Arg Ala Ser Thr Asn Asp
1 5

<210> SEQ ID NO 375

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 375

tgttctcgtg ctagtactaa tgattgc 27

<210> SEQ ID NO 376

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 376

Cys Ser Arg Ala Ser Thr Asn Asp Cys
1 5

<210> SEQ ID NO 377

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 377

aataagtcga ataaggagtt t 21

<210> SEQ ID NO 378

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 378

Asn Lys Ser Asn Lys Glu Phe
1 5

<210> SEQ ID NO 379

<211> LENGTH: 27

<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 379

tgtaataagt cgaataagga gttttgc 27

<210> SEQ ID NO 380
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 380

Cys Asn Lys Ser Asn Lys Glu Phe Cys
1 5

<210> SEQ ID NO 381
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 381

catgcgcggg tgccgctggt t 21

<210> SEQ ID NO 382
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 382

His Ala Arg Val Pro Leu Val
1 5

<210> SEQ ID NO 383
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 383

tgtcatgcgc gggtgccgct ggtttgc 27

<210> SEQ ID NO 384
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 384

Cys His Ala Arg Val Pro Leu Val Cys
1 5

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<210> SEQ ID NO 385
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 385

cttaataatt ctcaggctca t 21

<210> SEQ ID NO 386
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 386

Leu Asn Asn Ser Gln Ala His
1 5

<210> SEQ ID NO 387
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 387

tgtcttaata attctcaggc tcattgc 27

<210> SEQ ID NO 388
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 388

Cys Leu Asn Asn Ser Gln Ala His Cys
1 5

<210> SEQ ID NO 389
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 389

aatccgctgc gttctacgctc g 21

<210> SEQ ID NO 390
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 390

Asn Pro Ser Arg Ser Thr Ser
1 5

<210> SEQ ID NO 391

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 391

tgtaatccgt cgcgttctac gtcgtgc

27

<210> SEQ ID NO 392

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 392

Cys Asn Pro Ser Arg Ser Thr Ser Cys
1 5

<210> SEQ ID NO 393

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 393

acgccgactt agaagagttt g

21

<210> SEQ ID NO 394

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 394

Thr Pro Thr Gln Lys Ser Leu
1 5

<210> SEQ ID NO 395

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 395

tgtacgccga cttagaagag tttgtgc

27

<210> SEQ ID NO 396

<211> LENGTH: 9

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 396

Cys Thr Pro Thr Gln Lys Ser Leu Cys
1 5

<210> SEQ ID NO 397
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 397

tcgcagcggc ctgttcagat g 21

<210> SEQ ID NO 398
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 398

Ser Gln Arg Pro Val Gln Met
1 5

<210> SEQ ID NO 399
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 399

tgttcgcagc ggccgtgttca gatgtgc 27

<210> SEQ ID NO 400
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 400

Cys Ser Gln Arg Pro Val Gln Met Cys
1 5

<210> SEQ ID NO 401
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 401

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gcgccgggtc cgtctaagag t

21

<210> SEQ ID NO 402

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 402

Ala Pro Gly Pro Ser Lys Ser

1

5

<210> SEQ ID NO 403

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 403

tgtgcgccgg gtccgtctaa gagttgc

27

<210> SEQ ID NO 404

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 404

Cys Ala Pro Gly Pro Ser Lys Ser Cys

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5

<210> SEQ ID NO 405

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 405

aaggggtcgt ctattcttaa t

21

<210> SEQ ID NO 406

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 406

Lys Gly Ser Ser Ile Leu Asn

1

5

<210> SEQ ID NO 407

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 407

tgtaaggggt cgtctattct taattgc

27

<210> SEQ ID NO 408

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 408

Cys Lys Gly Ser Ser Ile Leu Asn Cys

1

5

<210> SEQ ID NO 409

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 409

gttaatcgga gtgatgggat g

21

<210> SEQ ID NO 410

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 410

Val Asn Arg Ser Asp Gly Met

1

5

<210> SEQ ID NO 411

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 411

tgtgttaatc ggagtgatgg gatgtgc

27

<210> SEQ ID NO 412

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 412

Cys Val Asn Arg Ser Asp Gly Met Cys

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<210> SEQ ID NO 413
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 413

ccgcatcctg ggactcgtca t 21

<210> SEQ ID NO 414
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 414

Pro His Pro Gly Thr Arg His
1 5

<210> SEQ ID NO 415
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 415

tgtccgcatc ctgggactcg tcattgc 27

<210> SEQ ID NO 416
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 416

Cys Pro His Pro Gly Thr Arg His Cys
1 5

<210> SEQ ID NO 417
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 417

atgaatcagc gggttcagaa t 21

<210> SEQ ID NO 418
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 418

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Met Asn Gln Arg Val Gln Asn
1 5

<210> SEQ ID NO 419
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 419

tgtatgaatc agcgggttca gaattgc 27

<210> SEQ ID NO 420
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 420

Cys Met Asn Gln Arg Val Gln Asn Cys
1 5

<210> SEQ ID NO 421
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 421

aatcagtga agtcggtgtc t 21

<210> SEQ ID NO 422
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 422

Asn Gln Trp Lys Ser Val Ser
1 5

<210> SEQ ID NO 423
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 423

tgtaatcagt ggaagtcggt gtcttgc 27

<210> SEQ ID NO 424
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 424

Cys Asn Gln Trp Lys Ser Val Ser Cys
1 5

<210> SEQ ID NO 425

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 425

cagacgcacg ctcggcatgt t 21

<210> SEQ ID NO 426

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 426

Gln Thr His Ala Arg His Val
1 5

<210> SEQ ID NO 427

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 427

tgtcagacgc atgctcggca tgtttgc 27

<210> SEQ ID NO 428

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 428

Cys Gln Thr His Ala Arg His Val Cys
1 5

<210> SEQ ID NO 429

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 429

tttcagaatc gtcagccgat g 21

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<210> SEQ ID NO 430
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 430

Phe Gln Asn Arg Gln Pro Met
1 5

<210> SEQ ID NO 431
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 431

tgttttcaga atcgtcagcc gatgtgc 27

<210> SEQ ID NO 432
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 432

Cys Phe Gln Asn Arg Gln Pro Met Cys
1 5

<210> SEQ ID NO 433
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 433

agggtcttgg atacggcgaa t 21

<210> SEQ ID NO 434
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 434

Arg Ala Leu Asp Thr Ala Asn
1 5

<210> SEQ ID NO 435
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

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<400> SEQUENCE: 435

tgtagggctc tggatacggc gaattgc

27

<210> SEQ ID NO 436

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 436

Cys Arg Ala Leu Asp Thr Ala Asn Cys

1

5

<210> SEQ ID NO 437

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 437

caggagccga cgcggctgaa g

21

<210> SEQ ID NO 438

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 438

Gln Glu Pro Thr Arg Leu Lys

1

5

<210> SEQ ID NO 439

<211> LENGTH: 27

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 439

tgtcaggagc cgacgcggct gaagtgc

27

<210> SEQ ID NO 440

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 440

Cys Gln Glu Pro Thr Arg Leu Lys Cys

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<210> SEQ ID NO 441

<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 441

aaggagccta cgaaggcgca t 21

<210> SEQ ID NO 442
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 442

Lys Glu Pro Thr Lys Ala His
1 5

<210> SEQ ID NO 443
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 443

tgtaaggagc ctacgaaggc gcattgc 27

<210> SEQ ID NO 444
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 444

Cys Lys Glu Pro Thr Lys Ala His Cys
1 5

<210> SEQ ID NO 445
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 445

aatggttaagg ctaattggaa g 21

<210> SEQ ID NO 446
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 446

Asn Gly Lys Ala Asn Trp Lys

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1 5

<210> SEQ ID NO 447
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 447

tgtaatggta aggctaattg gaagtgc 27

<210> SEQ ID NO 448
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 448

Cys Asn Gly Lys Ala Asn Trp Lys Cys
1 5

<210> SEQ ID NO 449

<400> SEQUENCE: 449

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<210> SEQ ID NO 450
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic region of similarity between SEQ ID
NO:8 and SEQ ID NO:12.

<400> SEQUENCE: 450

Glu Pro Thr Arg
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<210> SEQ ID NO 451

<400> SEQUENCE: 451

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<210> SEQ ID NO 452
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 452

Cys Ile Lys Arg Ser Asp Gly Ser Cys
1 5

<210> SEQ ID NO 453

<400> SEQUENCE: 453

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<210> SEQ ID NO 454
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 454

Asn Gln Arg Tyr Gln Met Gly Cys
1 5

<210> SEQ ID NO 455

<400> SEQUENCE: 455

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<210> SEQ ID NO 456
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
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<400> SEQUENCE: 456

Asn His Arg Tyr Gln Met Gly Cys
1 5

<210> SEQ ID NO 457

<400> SEQUENCE: 457

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<210> SEQ ID NO 458
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
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<400> SEQUENCE: 458

Cys Ala Pro Gly Pro Ser
1 5

<210> SEQ ID NO 459

<400> SEQUENCE: 459

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<210> SEQ ID NO 460
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
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<400> SEQUENCE: 460

-continued

Gly Pro Ser Lys Ser Cys
1 5

<210> SEQ ID NO 461

<400> SEQUENCE: 461

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<210> SEQ ID NO 462

<211> LENGTH: 6

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 462

Ala Pro Gly Pro Ser Lys
1 5

<210> SEQ ID NO 463

<400> SEQUENCE: 463

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<210> SEQ ID NO 464

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage display library.

<400> SEQUENCE: 464

Cys Tyr Asn Arg Ser Asp Gly Met Cys
1 5

<210> SEQ ID NO 465

<400> SEQUENCE: 465

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<210> SEQ ID NO 466

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: A synthetic control peptide.

<400> SEQUENCE: 466

Ala Cys Val Asn Arg Ser Asp Gly Met Cys
1 5 10

<210> SEQ ID NO 467

<400> SEQUENCE: 467

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<210> SEQ ID NO 468

<211> LENGTH: 15

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 468

Ala Cys Ala Pro Gly Pro Ser Lys Ser Cys Gly Gly Ser Tyr Lys
1 5 10 15

<210> SEQ ID NO 469

<400> SEQUENCE: 469

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<210> SEQ ID NO 470
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 470

Ala Cys Asn His Arg Tyr Met Gln Met Cys Gly Gly Ser Tyr Lys
1 5 10 15

<210> SEQ ID NO 471

<400> SEQUENCE: 471

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<210> SEQ ID NO 472
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

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1 5 10 15

<210> SEQ ID NO 473

<400> SEQUENCE: 473

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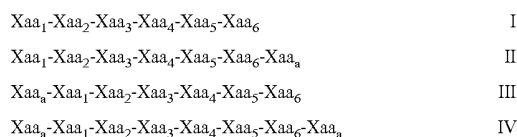
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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: A synthetic sequence from a combinatorial phage
display library.

<400> SEQUENCE: 474

Ala Cys Val Asn Arg Ser Asp Gly Met Cys Gly Gly Ser Tyr Lys
1 5 10 15

What is claimed:

1. An isolated peptide having any one of formulae I-IV:



wherein Xaa₁ is an aliphatic amino acid;

wherein Xaa₂, Xaa₃ and Xaa₄ are separately each an apolar amino acid;

wherein Xaa₅ and Xaa₆ are separately each a polar amino acid;

wherein Xaa₆ is a basic amino acid;

wherein Xaa_a is a cysteine-like amino acid; and

wherein the peptides can bind with specificity to a biomolecule or tissue in vivo.

2. The isolated peptide of claim 1 wherein the aliphatic amino acid is alanine, valine, leucine, isoleucine, norleucine, t-butylalanine, t-butylglycine, alanine, N-methylisoleucine, N-methylvaline, cyclohexylalanine, β -alanine, N-methylglycine, or α -aminoisobutyric acid.

3. The isolated peptide of claim 1 wherein the apolar amino acid is methionine, glycine, proline or cyclohexylalanine.

4. The isolated peptide of claim 1 wherein the polar amino acid is asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide or homoserine.

5. The isolated peptide of claim 1 wherein the basic amino acid is arginine, lysine, histidine, ornithine, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid or homoarginine.

6. The isolated peptide of claim 1 wherein the cysteine-like amino acid is cysteine, homocysteine, penicillamine, or β -methyl-cysteine.

7. An isolated peptide comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID

NO:176, SEQ ID NO:178, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:188, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:212, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, SEQ ID NO:230, SEQ ID NO:232, SEQ ID NO:234, SEQ ID NO:236, SEQ ID NO:238, SEQ ID NO:240, SEQ ID NO:242, SEQ ID NO:244, SEQ ID NO:246, SEQ ID NO:248, SEQ ID NO:250, SEQ ID NO:252, SEQ ID NO:254, SEQ ID NO:256, SEQ ID NO:258, SEQ ID NO:260, SEQ ID NO:262, SEQ ID NO:264, SEQ ID NO:266, SEQ ID NO:268, SEQ ID NO:270, SEQ ID NO:272, SEQ ID NO:274, SEQ ID NO:276, SEQ ID NO:278, SEQ ID NO:280, SEQ ID NO:282, SEQ ID NO:284, SEQ ID NO:286, SEQ ID NO:288, SEQ ID NO:290, SEQ ID NO:292, SEQ ID NO:294, SEQ ID NO:296, SEQ ID NO:298, SEQ ID NO:300, SEQ ID NO:302, SEQ ID NO:304, SEQ ID NO:306, SEQ ID NO:308, SEQ ID NO:310, SEQ ID NO:312, SEQ ID NO:314, SEQ ID NO:316, SEQ ID NO:318, SEQ ID NO:320, SEQ ID NO:322, SEQ ID NO:324, SEQ ID NO:326, SEQ ID NO:328, SEQ ID NO:330, SEQ ID NO:332, SEQ ID NO:334, SEQ ID NO:336, SEQ ID NO:338, SEQ ID NO:340, SEQ ID NO:342, SEQ ID NO:344, SEQ ID NO:346, SEQ ID NO:348, SEQ ID NO:350, SEQ ID NO:352, SEQ ID NO:354, SEQ ID NO:356, SEQ ID NO:358, SEQ ID NO:360, SEQ ID NO:362, SEQ ID NO:364, SEQ ID NO:366, SEQ ID NO:368, SEQ ID NO:370, SEQ ID NO:372, SEQ ID NO:374, SEQ ID NO:376, SEQ ID NO:378, SEQ ID NO:380, SEQ ID NO:382, SEQ ID NO:384, SEQ ID NO:386, SEQ ID NO:388, SEQ ID NO:390, SEQ ID NO:392, SEQ ID NO:394, SEQ ID NO:396, SEQ ID NO:398, SEQ ID NO:400, SEQ ID NO:402, SEQ ID NO:404, SEQ ID NO:406, SEQ ID NO:408, SEQ ID NO:410, SEQ ID NO:412, SEQ ID NO:414, SEQ ID NO:416, SEQ ID NO:418, SEQ ID NO:420, SEQ ID NO:422, SEQ ID NO:424, SEQ ID NO:426, SEQ ID NO:428, SEQ ID NO:430, SEQ ID NO:432, SEQ ID NO:434, SEQ ID NO:436, SEQ ID NO:438, SEQ ID NO:440, SEQ ID NO:442, SEQ ID NO:444, SEQ ID NO:446, SEQ ID NO:448, SEQ ID NO:450, SEQ ID NO:452, SEQ ID NO:454, SEQ ID NO:456, SEQ ID NO:458, SEQ ID NO:460, SEQ ID NO:462, SEQ ID NO:464, SEQ ID NO:468, SEQ ID NO:470, SEQ ID NO:472, or SEQ ID NO:474, which is capable of binding to an atherosclerotic lesion in a mammal.

8. An isolated peptide comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 or SEQ ID NO:464, which is capable of binding to an atherosclerotic lesion in a mammal.

9. An isolated peptide wherein the amino acid sequence of the peptide is identical to any one of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 or SEQ ID NO:464 at four amino acid positions, which is capable of binding to an atherosclerotic lesion in a mammal.

10. The isolated peptide according to any one of claims 1 to 9 wherein the peptide is conjugated to a therapeutic agent or a reporter molecule.

11. A method of treating atherosclerosis in a mammal that comprises administering a therapeutically effective amount of a peptide according to claim 10.

12. The isolated peptide according to claim 10 wherein the therapeutic agent is:

- a) an agent that can modulate lipid levels in mammalian serum selected from the group consisting of an HMG-CoA reductase inhibitor, a thymomimetic, a fibrate, and an agonist of peroxisome proliferator-activated receptors (PPAR);
- b) an agent that can modulate an oxidative process in a mammal;
- c) an agent that can modulate insulin resistance or glucose metabolism in a mammal selected from the group consisting of PPAR-alpha, PPAR-gamma, PPAR-delta, a modifier of DPP-IV, and a modifier of a glucocorticoid receptor;
- d) an agent that can modulate expression of an endothelial cell receptor, an endothelial cell adhesion molecule, an endothelial cell integrin, a smooth muscle cell receptor, a smooth muscle cell adhesion molecule or a smooth muscle cell integrin;
- e) an agent that can modulate the proliferation of an endothelial cell or a smooth muscle cell in a mammalian blood vessel;
- f) an agent that can modulate an inflammation associated receptor selected from the group consisting of a chemokine receptor, a RAGE receptor, a toll-like receptor, an angiotensin receptor, a TGF receptor, an interleukin receptor, a TNF receptor, a C-reactive protein receptor, and a receptor that can activate NF-kb;
- g) an agent that can modulate proliferation, apoptosis or necrosis of endothelial cells, vascular smooth muscle cells, lymphocytes, monocytes, or neutrophils;
- h) an agent that can modulate production, degradation, or cross-linking of an extracellular matrix protein selected from the group consisting of a collagen, an elastin, and a proteoglycan;
- i) an agent that can modulate activation, secretion or lipid loading of a cell within a mammalian blood vessel;
- j) an agent that can modulate activation or proliferation of a dendritic cell within a mammalian blood vessel;
- k) an agent that can modulate activation or adhesion of a platelet at a mammalian blood vessel wall;
- l) an agent consisting of a nucleic acid that encodes a protein therapeutic agent, wherein the protein therapeutic agent has an in vivo activity that is beneficial to a mammal suffering from an atherosclerotic lesion.

13. A pharmaceutical composition comprising the peptide according to claims 1 to 12 and a pharmaceutically acceptable carrier.

14. A method of treating atherosclerosis in a mammal comprising administering a therapeutically effective amount of a composition according to claim 13.

15. An isolated nucleic acid encoding a peptide comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, SEQ ID NO:178, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:188, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:212, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, SEQ ID NO:230, SEQ ID NO:232, SEQ ID NO:234, SEQ ID NO:236, SEQ ID NO:238, SEQ ID NO:240, SEQ ID NO:242, SEQ ID NO:244, SEQ ID NO:246, SEQ ID NO:248, SEQ ID NO:250, SEQ ID NO:252, SEQ ID NO:254, SEQ ID NO:256, SEQ ID NO:258, SEQ ID NO:260, SEQ ID NO:262, SEQ ID NO:264, SEQ ID NO:266, SEQ ID NO:268, SEQ ID NO:270, SEQ ID NO:272, SEQ ID NO:274, SEQ ID NO:276, SEQ ID NO:278, SEQ ID NO:280, SEQ ID NO:282, SEQ ID NO:284, SEQ ID NO:286, SEQ ID NO:288, SEQ ID NO:290, SEQ ID NO:292, SEQ ID NO:294, SEQ ID NO:296, SEQ ID NO:298, SEQ ID NO:300, SEQ ID NO:302, SEQ ID NO:304, SEQ ID NO:306, SEQ ID NO:308, SEQ ID NO:310, SEQ ID NO:312, SEQ ID NO:314, SEQ ID NO:316, SEQ ID NO:318, SEQ ID NO:320, SEQ ID NO:322, SEQ ID NO:324, SEQ ID NO:326, SEQ ID NO:328, SEQ ID NO:330, SEQ ID NO:332, SEQ ID NO:334, SEQ ID NO:336, SEQ ID NO:338, SEQ ID NO:340, SEQ ID NO:342, SEQ ID NO:344, SEQ ID NO:346, SEQ ID NO:348, SEQ ID NO:350, SEQ ID NO:352, SEQ ID NO:354, SEQ ID NO:356, SEQ ID NO:358, SEQ ID NO:360, SEQ ID NO:362, SEQ ID NO:364, SEQ ID NO:366, SEQ ID NO:368, SEQ ID NO:370, SEQ ID NO:372, SEQ ID NO:374, SEQ ID NO:376, SEQ ID NO:378, SEQ ID NO:380, SEQ ID NO:382, SEQ ID NO:384, SEQ ID NO:386, SEQ ID NO:388, SEQ ID NO:390, SEQ ID NO:392, SEQ ID

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16. An isolated nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:111, SEQ ID NO:113, SEQ ID NO:115, SEQ ID NO:117, SEQ ID NO:119, SEQ ID NO:121, SEQ ID NO:123, SEQ ID NO:125, SEQ ID NO:127, SEQ ID NO:129, SEQ ID NO:131, SEQ ID NO:133, SEQ ID NO:135, SEQ ID NO:137, SEQ ID NO:139, SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, SEQ ID NO:149, SEQ ID NO:151, SEQ ID NO:153, SEQ ID NO:155, SEQ ID NO:157, SEQ ID NO:159, SEQ ID NO:161, SEQ ID NO:163, SEQ ID NO:165, SEQ ID NO:167, SEQ ID NO:169, SEQ ID NO:171, SEQ ID NO:173, SEQ ID NO:175, SEQ ID NO:177, SEQ ID NO:179, SEQ ID NO:181, SEQ ID NO:183, SEQ ID NO:185, SEQ ID NO:187, SEQ ID NO:189, SEQ ID NO:191, SEQ ID NO:193, SEQ ID NO:195, SEQ ID NO:197, SEQ ID NO:199, SEQ ID NO:201, SEQ ID NO:203, SEQ ID NO:205, SEQ ID NO:207, SEQ ID NO:209, SEQ ID NO:211, SEQ ID NO:213, SEQ ID NO:215, SEQ ID NO:217, SEQ ID NO:219, SEQ ID NO:221, SEQ ID NO:223, SEQ ID NO:225, SEQ ID NO:227, SEQ ID NO:229, SEQ ID NO:231, SEQ ID NO:233, SEQ ID NO:235, SEQ ID NO:237, SEQ ID NO:239, SEQ ID NO:241, SEQ ID NO:243, SEQ ID NO:245, SEQ ID NO:247, SEQ ID NO:249, SEQ ID NO:251, SEQ ID NO:253, SEQ ID NO:255, SEQ ID NO:257, SEQ ID NO:259, SEQ ID NO:261, SEQ ID NO:263, SEQ ID NO:265, SEQ ID NO:267, SEQ ID NO:269, SEQ ID NO:271, SEQ ID NO:273, SEQ ID NO:275, SEQ ID NO:277, SEQ ID NO:279, SEQ ID NO:281, SEQ ID NO:283, SEQ ID NO:285, SEQ ID NO:287, SEQ ID NO:289, SEQ ID NO:291, SEQ ID NO:293, SEQ ID NO:295, SEQ ID NO:297, SEQ ID NO:299, SEQ ID NO:301, SEQ ID NO:303, SEQ ID

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17. An isolated nucleic acid capable of hybridizing under stringent conditions to the isolated nucleic acid of claim 15, wherein the stringent hybridization conditions comprise hybridization in 6×SSC and at 55° C.

18. A method of identifying a peptide capable of binding to mammalian vascular tissues that comprises:

- (a) circulating a phage display library through the vascular tissues of a mammal;
- (b) isolating a first selected phage that selectively adheres to the vascular tissues of the mammal; and
- (c) identifying a peptide displayed on the first selected phage, wherein the peptide is capable of binding to the vascular tissues of the mammal.

19. The method of claim 18 that further comprises:

- (d) amplifying the first selected phage to provide a first population of phage that selectively adhere to the vascular tissues of the mammal;
- (e) circulating the first population of phage through the vascular tissues of a mammal;
- (f) isolating a second selected phage that selectively adheres to the vascular tissues of the mammal; and
- (g) identifying a peptide displayed on the second selected phage, wherein the peptide is capable of binding to the vascular tissues of the mammal.

20. A method of identifying a peptide capable of binding to an atherosclerotic lesion in a mammal that comprises:

- (a) circulating a phage display library through the vascular tissues of a mammal;
- (b) isolating a first selected phage that selectively adheres to an atherosclerotic lesion in the mammal; and
- (c) identifying a peptide displayed on the first selected phage;

wherein the peptide is capable of binding to an atherosclerotic lesion of the mammal.

21. The method of claim 20 that further comprises:

- (d) amplifying the first selected phage to provide a population of phage that selectively adhere to an atherosclerotic lesion in the mammal;
- (e) circulating the population of phage through the vascular tissues of a mammal; and
- (f) isolating a second selected phage that selectively adheres to an atherosclerotic lesion in the mammal; and
- (g) identifying a peptide displayed on the second selected phage;

wherein the peptide is capable of binding to an atherosclerotic lesion in the mammal.

22. A method of identifying a protein bound by a peptide that comprises:

- (a) obtaining a mixture of proteins from the vascular tissues of a mammal;
- (b) contacting the mixture of proteins with a peptide that is capable of binding to the vascular tissues of the mammal; and
- (c) identifying a protein that binds the peptide.

23. A method of identifying a protein bound by a peptide that comprises:

- (a) obtaining a mixture of proteins from at least one atherosclerotic lesion of a mammal;
- (b) contacting the mixture of proteins with a peptide that is capable of binding to an atherosclerotic lesion of the mammal; and
- (c) identifying a protein that binds the peptide.

24. The method of claim 22 or 23 wherein the mixture of proteins is separated prior to contacting the mixture of proteins with a peptide.

25. The method of claim 22 or 23 wherein the peptide comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID

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26. The method of claim 22 or 23 wherein the peptide comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 or SEQ ID NO:464.

27. A method of identifying a location of an atherosclerotic lesion in a mammal that comprises:

- (a) administering a peptide conjugated to a reporter molecule to the vascular system of a mammal; and
- (b) observing the location of the reporter molecule within the mammal;

wherein the peptide can bind to an atherosclerotic lesion in a mammal.

28. A method of identifying the severity of an atherosclerotic lesion in a mammal that comprises:

- (a) administering a peptide conjugated to a reporter molecule to the vascular system of a mammal; and
- (b) observing the amount, localization, shape, density, or relative distribution of reporter molecules on an atherosclerotic lesion in the mammal;

wherein the peptide can bind to an atherosclerotic lesion in a mammal.

29. The method of claim 27 or 28 wherein the peptide can bind to the atherosclerotic lesion in a mammal through a specific target biomolecule.

30. The method of claim 29 wherein peptide binding permits visualization of the amount, localization, shape, density, or relative distribution of a target biomolecule on the atherosclerotic lesion.

31. The method of claim 27 or 28 wherein the peptide comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID NO:122, SEQ ID NO:124, SEQ ID NO:126, SEQ ID NO:128, SEQ ID NO:130, SEQ ID NO:132, SEQ ID NO:134, SEQ ID NO:136, SEQ ID NO:138, SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, SEQ ID NO:148, SEQ ID NO:150, SEQ ID NO:152, SEQ ID NO:154, SEQ ID NO:156, SEQ ID NO:158, SEQ ID NO:160, SEQ ID NO:162, SEQ ID NO:164, SEQ ID NO:166, SEQ ID NO:168, SEQ ID NO:170, SEQ ID NO:172, SEQ ID NO:174, SEQ ID NO:176, SEQ ID NO:178, SEQ ID NO:180, SEQ ID NO:182, SEQ ID NO:184, SEQ ID NO:186, SEQ ID NO:188, SEQ ID NO:190, SEQ ID NO:192, SEQ ID NO:194, SEQ ID NO:196, SEQ ID NO:198, SEQ ID NO:200, SEQ ID NO:202, SEQ ID NO:204, SEQ ID NO:206, SEQ ID NO:208, SEQ ID NO:210, SEQ ID NO:212, SEQ ID NO:214, SEQ ID NO:216, SEQ ID NO:218, SEQ ID NO:220, SEQ ID NO:222, SEQ ID NO:224, SEQ ID NO:226, SEQ ID NO:228, SEQ ID NO:230, SEQ ID NO:232, SEQ ID NO:234, SEQ ID NO:236, SEQ ID NO:238, SEQ ID NO:240, SEQ ID NO:242, SEQ ID NO:244, SEQ ID NO:246, SEQ ID NO:248, SEQ ID NO:250, SEQ ID NO:252, SEQ ID NO:254, SEQ ID NO:256, SEQ ID NO:258, SEQ ID NO:260, SEQ ID NO:262, SEQ ID NO:264, SEQ ID NO:266, SEQ ID NO:268, SEQ ID NO:270, SEQ ID NO:272, SEQ ID NO:274, SEQ ID NO:276, SEQ ID

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32. The method of claim 27 or 28 wherein the peptide comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 or SEQ ID NO:464.

33. A method of treating atherosclerosis in a mammal that comprises administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent to a mammal, wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can reduce or control the size of an atherosclerotic lesion.

34. The method of claim 33, wherein the atherosclerosis causes stroke, angina, thrombosis, myocardial infarction, ischemic heart disease, peripheral artery disease, congestive heart failure, retinopathy, neuropathy, nephropathy, plaque rupture, restenosis after balloon angioplasty, restenosis after insertion of a stent, transplantation-induced sclerosis, or intermittent claudication.

35. The method of claim 33, wherein the atherosclerosis is associated with diabetes.

36. The method of claim 35, wherein the diabetes leads to ischemic heart disease, peripheral artery disease, congestive heart failure, retinopathy, neuropathy, nephropathy, or thrombosis.

37. The method of claim 33, wherein the therapeutic agent is streptokinase, tissue plasminogen activator, plasmin and urokinase, a tissue factor protease inhibitor, a nematode-extracted anticoagulant protein, a metalloproteinase inhibitor, an anti-inflammatory agent.

38. The method of claim 37 wherein the therapeutic agent is within a liposome.

39. The method of claim 33 wherein the therapeutic agent is:

- (a) an agent that can modulate lipid levels in mammalian serum selected from the group consisting of an HMG-CoA reductase inhibitor, a thyromimetic, a fibrate, and an agonist of peroxisome proliferator-activated receptors (PPAR);
- (b) an agent that can modulate an oxidative process in a mammal;
- (c) an agent that can modulate insulin resistance or glucose metabolism selected from the group consisting of PPAR-alpha, PPAR-gamma, PPAR-delta, a modifier of DPP-IV, and a modifier of a glucocorticoid receptor;
- (d) an agent that can modulate expression of an endothelial cell or smooth muscle cell receptor, adhesion molecule or integrin;
- (e) an agent that can modulate the proliferation of an endothelial cell or a smooth muscle cell in a mammalian blood vessel;
- (f) an agent that can modulate an inflammation associated receptor selected from the group consisting of a chemokine receptor, a RAGE receptor, a toll-like receptor, an angiotensin receptor, a TGF receptor, an interleukin receptor, a TNF receptor, a C-reactive protein receptor, and a receptor that can activate NF-kb;
- (g) an agent that can modulate proliferation, apoptosis or necrosis of endothelial cells, vascular smooth muscle cells, lymphocytes, monocytes, or neutrophils;
- (h) an agent that can modulate production, degradation, or cross-linking of an extracellular matrix protein selected from the group consisting of a collagen, an elastin, and a proteoglycan;
- (i) an agent that can modulate activation, secretion or lipid loading of a cell within a mammalian blood vessel;
- (j) an agent that can modulate activation or proliferation of a dendritic cell within a mammalian blood vessel;
- (k) an agent that can modulate activation or adhesion of a platelet at a mammalian blood vessel wall; or
- (l) an agent consisting of a nucleic acid that encodes a protein therapeutic agent, wherein the protein therapeutic agent has an in vivo activity that is beneficial to a mammal suffering from an atherosclerotic lesion.

40. A method of preventing heart attack in a mammal that comprises administering a therapeutically effective amount of a peptide conjugated to a therapeutic agent wherein the peptide can bind to an atherosclerotic lesion in the mammal and the therapeutic agent can prevent heart attack.

41. The method of claim 40, wherein the therapeutic agent is streptokinase, tissue plasminogen activator, plasmin, urokinase, a tissue factor protease inhibitor, a nematode-extracted anticoagulant protein, a metalloproteinase inhibitor, or an anti-inflammatory agent.

42. The method of claim 40 wherein the therapeutic agent is:

- (a) an agent that can modulate lipid levels in mammalian serum selected from the group consisting of an HMG-

CoA reductase inhibitor, a thyromimetic, a fibrate, and an agonist of peroxisome proliferator-activated receptors (PPAR);

- (b) an agent that can modulate an oxidative process in a mammal;
- (c) an agent that can modulate insulin resistance or glucose metabolism selected from the group consisting of PPAR-alpha, PPAR-gamma, PPAR-delta, a modifier of DPP-IV, and a modifier of a glucocorticoid receptor;
- (d) an agent that can modulate expression of an endothelial cell or smooth muscle cell receptor, adhesion molecule or integrin;
- (e) an agent that can modulate the proliferation of an endothelial cell or a smooth muscle cell in a mammalian blood vessel;
- (f) an agent that can modulate an inflammation associated receptor selected from the group consisting of a chemokine receptor, a RAGE receptor, a toll-like receptor, an angiotensin receptor, a TGF receptor, an interleukin receptor, a TNF receptor, a C-reactive protein receptor, and a receptor that can activate NF-kb;
- (g) an agent that can modulate proliferation, apoptosis or necrosis of endothelial cells, vascular smooth muscle cells, lymphocytes, monocytes, or neutrophils;
- (h) an agent that can modulate production, degradation, or cross-linking of an extracellular matrix protein selected from the group consisting of a collagen, an elastin, and a proteoglycan;
- (i) an agent that can modulate activation, secretion or lipid loading of a cell within a mammalian blood vessel;
- (j) an agent that can modulate activation or proliferation of a dendritic cell within a mammalian blood vessel;
- (k) an agent that can modulate activation or adhesion of a platelet at a mammalian blood vessel wall; or
- (l) an agent consisting of a nucleic acid that encodes a protein therapeutic agent, wherein the protein therapeutic agent has an in vivo activity that is beneficial to a mammal suffering from an atherosclerotic lesion.

43. The method of claim 40, wherein the therapeutic agent is within a liposome.

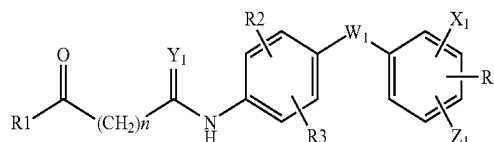
44. The method of claim 33 or 40, wherein the peptide comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:66, SEQ ID NO:68, SEQ ID NO:70, SEQ ID NO:72, SEQ ID NO:74, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:88, SEQ ID NO:90, SEQ ID NO:92, SEQ ID NO:94, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:108, SEQ ID NO:110, SEQ ID NO:112, SEQ ID NO:114, SEQ ID NO:116, SEQ ID NO:118, SEQ ID NO:120, SEQ ID

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 NO:458, SEQ ID NO:460, SEQ ID NO:462, SEQ ID
 NO:464, SEQ ID NO:468, SEQ ID NO:470, SEQ ID
 NO:472, or SEQ ID NO:474.

45. The method of claim 33 or 40, wherein the peptide comprises SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:336, SEQ ID NO:344 or SEQ ID NO:464.

46. The method of claim 33 or 40, wherein the therapeutic agent is an HMG-CoA reductase inhibitor, a fibrate, a thyromimetic, a DPP-IV inhibitor, a PPAR alpha agonist, a PPAR gamma agonist or a PPAR delta agonist.

47. The method of claim 46, wherein the thyromimetic compound is a compound of formula I:



wherein:

W_1 is O, S, S(O) or S(O)₂;

X_1 is —SR₄, —S(O)R₄, —S(O)₂R₄, or —S(O)₂NR₅R₆; or X_1 is —C(O)NR₅R₆ provided that —C(O)NR₅R₆ is located at the 3'-, 4'- or 5'-position;

Y_1 is O or H₂;

Z_1 is hydrogen, halogen, hydroxy, optionally substituted alkoxy, aralkoxy, acyloxy or alkoxy-carbonyloxy;

R₁ is hydroxy, optionally substituted alkoxy, aryloxy, heteroaryloxy, aralkoxy, cycloalkoxy, heteroaralkoxy or —NR₅R₆;

R₂ is hydrogen, halogen or alkyl;

R₃ is halogen or alkyl;

R₄ is optionally substituted alkyl, aryl, aralkyl, heteroaralkyl or heteroaryl;

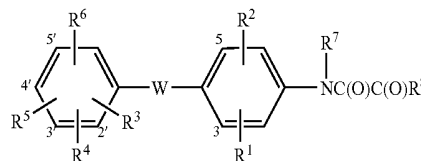
R₅, R₆ and R₇ are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R₅ and R₆ combined are alkylene optionally interrupted by O, S, S(O), S(O)₂ or NR₇ which together with the nitrogen atom to which they are attached form a 5- to 7-membered ring;

R₈ is hydrogen, halogen, trifluoromethyl, lower alkyl or cycloalkyl;

n represents zero or an integer from 1 to 4; and

pharmaceutically acceptable salts thereof.

48. The method of claim 46, wherein the thyromimetic compound is a compound of formula II:



wherein:

R¹, R² and R³ are each independently hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl, —CN, —OCF₃ or —OC₁₋₆ alkyl;

R⁴ is hydrogen, C₁₋₁₂ alkyl optionally substituted with one to three substituents independently selected from

Group Z, C₂₋₁₂ alkenyl, halogen, —CN, aryl, heteroaryl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, —S(O)₂NR⁹R¹⁰, —C(O)NR⁹R¹⁰, —(C₁₋₆ alkyl)-NR⁹R¹⁰, —NR⁹C(O)R¹⁰, —NR⁹C(O)NR⁹R¹⁰, —NR⁹S(O)₂R¹⁰, —(C₁₋₆ alkyl)-OR¹¹, —OR¹¹ or —S(O)_aR¹², provided that, where R⁵ is not fluoro, R⁴ is —S(O)₂NR⁹R¹⁰, —C(O)NR⁹R¹⁰, —(C₁₋₆ alkyl)-NR⁹R¹⁰, —NR⁹C(O)R¹⁰, —NR⁹C(O)NR⁹R¹⁰, —NR⁹S(O)₂R¹⁰, —(C₁₋₆ alkyl)-OR¹¹, —OR¹¹ or —S(O)_aR¹²;

or R³ and R⁴ may be taken together to form a carbocyclic ring A of the formula —(CH₂)_b— or a heterocyclic ring A selected from the group consisting of —Q-(CH₂)_c— and —(CH₂)_j-Q-(CH₂)_k— wherein Q is O, S or NR¹⁷, wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C₁₋₄ alkyl, halide or oxo;

R⁵ is fluoro, hydroxy, C₁₋₄ alkoxy or OC(O)R⁹;

or R⁴ and R⁵ may be taken together to form a heterocyclic ring B selected from the group consisting of —CR⁹=CR¹⁰—NH—, —N=CR⁹—NH—, —CR⁹=CH—O— and —CR⁹=CH—S—;

R⁶ is hydrogen, halogen, C₁₋₄ alkyl or trifluoromethyl;

R⁷ is hydrogen or C₁₋₆ alkyl;

R⁸ is —OR⁹ or —NR¹⁹R²⁰;

R⁹ and R¹⁰ for each occurrence are independently (A) hydrogen, (B) C₁₋₁₂ alkyl optionally substituted with one or more substituents independently selected from Group V, (C) C₂₋₁₂ alkenyl, (D) C₃₋₁₀ cycloalkyl optionally substituted with one or more substituents independently selected from C₁₋₆ alkyl, C₂₋₅ alkynyl, C₃₋₁₀ cycloalkyl, —CN, —NR¹³R¹⁴, oxo, —OR¹⁸, —COOR¹⁸ or aryl optionally substituted with X and Y, (E) aryl optionally substituted with X and Y, or (F) het optionally substituted with X and Y;

or R⁹ and R¹⁰ for any occurrence may be taken together to form a heterocyclic ring C optionally further containing a second heterogroup selected from the group consisting of —O—, —NR¹³— and —S—, and optionally further substituted with one or more substituents independently selected from C₁₋₅ alkyl, oxo, —NR¹³R¹⁴, —OR¹⁸, —C(O)₂R¹⁸, —CN, —C(O)R⁹, aryl optionally substituted with X and Y, het optionally substituted with X and Y, C₅₋₆ spirocycloalkyl, and a carbocyclic ring B selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings, and including any bicyclic group in which said carbocyclic ring B is fused to a carbocyclic ring C selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings;

R¹¹ is C₁₋₁₂ alkyl optionally substituted with one or more substituents independently selected from Group V, C₂₋₁₂ alkenyl, C₃₋₁₀ cycloalkyl, trifluoromethyl, difluoromethyl, monofluoromethyl, aryl optionally substituted with X and Y, het optionally substituted with X and Y, —C(O)NR⁹R¹⁰ or —C(O)R⁹;

R¹² is C₁₋₁₂ alkyl optionally substituted with one or more substituents independently selected from Group V, C₂₋₁₂ alkenyl, C₃₋₁₀ cycloalkyl, aryl optionally substituted with X and Y, or het optionally substituted with X and Y;

R¹³ and R¹⁴ for each occurrence are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, —(C₁₋₆ alkyl)-C₁₋₆ alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, —(C₁₋₄ alkyl)-aryl optionally substituted with X and Y, —(C₁₋₄ alkyl)-heterocycle optionally substituted with X and Y, —(C₁₋₄ alkyl)-hydroxy, —(C₁₋₄ alkyl)-halo, —(C₁₋₄ alkyl)-poly-halo, —(C₁₋₄ alkyl)-CONR¹⁵R¹⁶ or C₃₋₁₀ cycloalkyl;

R¹⁵ and R¹⁶ for each occurrence are independently hydrogen, C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl or aryl optionally substituted with X and Y;

R¹⁷ is hydrogen, alkyl, C₁₋₆ alkyl, —COR⁹ or —SO₂R⁹;

R¹⁸ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, —(C₁₋₆ alkyl)-C₁₋₆ alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, —(C₁₋₄ alkyl)-aryl optionally substituted with X and Y, —(C₁₋₄ alkyl)-heterocycle optionally substituted with X and Y, —(C₁₋₄ alkyl)-hydroxy, —(C₁₋₄ alkyl)-halo, —(C₁₋₄ alkyl)-poly-halo, —(C₁₋₄ alkyl)-CONR¹⁵R¹⁶, —(C₁₋₄ alkyl)-(C₁₋₄ alkoxy) or C₃₋₁₀ cycloalkyl;

R¹⁹ is hydrogen or C₁₋₆ alkyl;

R²⁰ is hydrogen or C₁₋₆ alkyl;

W is O, S(O)_d, CH₂ or NR⁹;

Group Z is C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, —CF₃, —OCF₃, hydroxy, oxo, —CN, aryl, heteroaryl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, —S(O)_aR¹², —S(O)₂NR⁹R¹⁰, —C(O)R⁹R¹⁰, and —NR⁹R¹⁰;

Group V is halogen, —NR¹³R¹⁴, —OCF₃, —OR⁹, oxo, trifluoromethyl, —CN, C₃₋₁₀ cycloalkyl, aryl optionally substituted with X and Y, and het optionally substituted with X and Y;

het for each occurrence is a heterocyclic ring D selected from the group consisting of 4-, 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S, and including any bicyclic group in which said heterocyclic ring D is fused to a benzene ring or a heterocyclic ring E selected from the group consisting of 4-, 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S;

X and Y for each occurrence are independently (A) hydrogen, (B) halogen, (C) trifluoromethyl, (D) —OCF₃, (E) —CN, (F) C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, —OCF₃, —CF₃ and phenyl, (G) C₁₋₆ alkoxy, (H) aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, —OCF₃, —CF₃, C₁₋₄ alkyl and C₁₋₄ alkoxy, (I) —C(O)₂R¹³, (J) —C(O)NR¹³R¹⁴, (K) —C(O)R⁹,

(L) $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$ and (M) $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$; or X and Y for any occurrence in the same variable may be taken together to form (a) a carbocyclic ring D of the formula $-(\text{CH}_2)_e-$ or (b) a heterocyclic ring F selected from the group consisting of $-\text{O}(\text{CH}_2)_f\text{O}-$, $(\text{CH}_2)_g\text{NH}-$ and $-\text{CH}=\text{CHNH}-$;

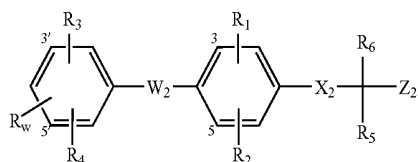
a and d are each independently 0, 1 or 2;

b is 3, 4, 5, 6 or 7;

c, f, g, j and k are each independently 2, 3, 4, 5 or 6; and

e is 3, 4, 5, 6 or 7.

49. The method of claim 46, wherein the thyromimetic compound is a compound of formula III:

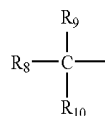


wherein R_w is hydroxy, esterified hydroxy or etherified hydroxy;

R_1 is halogen, trifluoromethyl or lower alkyl;

R_2 is halogen, trifluoromethyl or lower alkyl;

R_3 is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or R_3 is the radical



wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;

R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;

X_2 is $-\text{NR}_7$;

W_2 is O or S;

R_5 and R_6 together represent oxo;

R_7 represents hydrogen or lower alkyl;

Z_2 represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; or

a pharmaceutically acceptable salt thereof.

* * * * *

专利名称(译)	与动脉粥样硬化病变结合的肽		
公开(公告)号	US20070264194A1	公开(公告)日	2007-11-15
申请号	US10/486318	申请日	2002-08-09
[标]申请(专利权)人(译)	斯克里普斯研究学院		
申请(专利权)人(译)	斯克里普斯研究所		
当前申请(专利权)人(译)	斯克里普斯研究所		
[标]发明人	LIU CHENG EDGINGTON THOMAS S PRESCOTT MARGARET FORNEV		
发明人	LIU, CHENG EDGINGTON, THOMAS S. PRESCOTT, MARGARET FORNEV		
IPC分类号	A61K38/08 A61K38/00 A61K49/00 A61P9/00 C07H21/00 C07K1/00 G01N33/53 G01N33/50 A61K9/127 A61K31/19 A61K38/48 A61K45/00 A61P3/10 A61P7/02 A61P9/04 A61P9/10 A61P25/00 A61P25/14 A61P43/00 C07K7/06 C12N15/09 C12Q1/70 G01N33/15		
CPC分类号	C07K7/06 A61K38/00 A61P3/10 A61P25/00 A61P25/14		
优先权	60/311507 2001-08-10 US		
外部链接	Espacenet USPTO		

摘要(译)

本发明提供选择性结合哺乳动物动脉粥样硬化病变的肽。本发明还提供了体内鉴定能够结合生物分子的肽的方法，以及鉴定这种结合部分的靶标的方法。本发明还提供了诊断或治疗涉及动脉粥样硬化病变的病理状况的方法，该方法包括分别向哺乳动物施用与报道分子或治疗剂连接的肽。

