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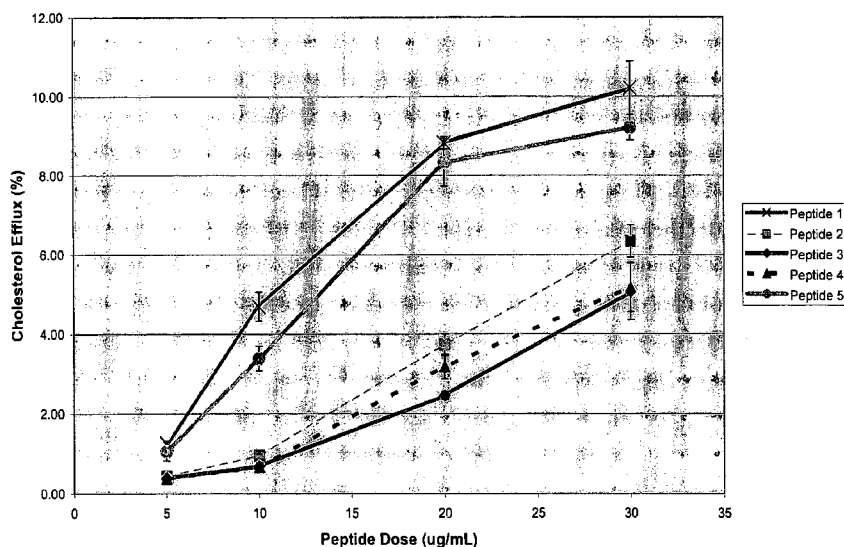
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(54) Title: NOVEL PEPTIDES THAT PROMOTE LIPID EFFLUX

ABCA1-dependent Cholesterol Efflux



(57) Abstract: Disclosed herein are peptides with domains that promote lipid efflux from cells and optionally possess at least one anti-inflammatory domain and/or a domain that stimulates LCAT activity. The present invention provides the use of the peptides disclosed herein in the preparation of a medicament. Provided herein are methods of using the peptides to treat or inhibit diseases including dyslipidemic disorders, stroke and myocardial infarction. Also provided are methods of detecting plaque in vessels using the labeled peptides of the present invention.

WO 2007/149355 A2

NOVEL PEPTIDES THAT PROMOTE LIPID EFFLUX

5 FIELD OF THE INVENTION

This present invention relates to peptides or peptide analogs that contain functional domains and promote lipid efflux. These peptides or peptide analogs optionally contain one or more anti-inflammatory domain and one or more domain that affects lecithin cholesterol acyltransferase (LCAT) activity. The disclosure further relates to methods for administering
10 these peptides in the treatment and prevention of dyslipidemic and vascular disorders. The disclosure further relates to methods for using these peptides in assays and in methods of imaging sites of association of these peptides with receptors and with sites of lipid deposition.

BACKGROUND OF THE INVENTION

15 Clearance of excess cholesterol from cells by high density lipoproteins (HDL) is facilitated by the interaction of HDL apolipoprotein with cell-surface binding sites or receptors. Research has demonstrated an inverse correlation between the occurrence of atherosclerosis events and levels of HDL and its most abundant protein constituent, apolipoprotein A-I (apoA-I) (Panagotopoulos *et al.*, *J. Biol. Chem.* 277:39477-39484, 2002). ApoA-I has been shown to
20 promote lipid efflux from ABCA1-transfected cells (Wang *et al.*, *J. Biol. Chem.* 275:33053-33058, 2000; Hamon *et al.*, *Nat. Cell Biol.* 2:399-406, 2000; and Remaley *et al.*, *Biochem. Biophys. Res. Commun.* 280:818-823, 2001). However, the nature of the interaction between apoA-I and ABCA1 is not fully understood.

There exists a need for non-cytotoxic, synthetic peptide mimetics of apolipoproteins that
25 promote specific lipid efflux from cells, perhaps by an ABCA1-dependent pathway, for use in the treatment and prevention of cardiovascular diseases, such as atherosclerosis.

Inflammation is believed to contribute to a variety of disease processes, including vascular disease. Inflammation is believed to contribute to the process of atherosclerosis, and physicians often prescribe anti-inflammatory medicine, such as aspirin, to patients with atherosclerosis, in
30 conjunction with statins, in an attempt to decrease the ongoing inflammatory process that contributes to atherosclerosis and vascular disease. What is needed are compounds that decrease inflammation.

LCAT is the major enzyme involved in the esterification of free cholesterol present in circulating plasma lipoproteins, and a major determinant of plasma HDL concentrations. What is needed are compounds that increase LCAT activity.

35 What is needed are new compositions that promote lipid efflux. What is also needed are new compositions with functional domains that promote lipid efflux and have anti-inflammatory properties and/or activity to modulate LCAT activity, or a combination of domains that have anti-inflammatory properties and the activity to modulate LCAT activity.

40

SUMMARY OF THE INVENTION

The present invention solves these problems by providing novel peptide compositions with functional domains. In several embodiments, these novel peptide compositions promote lipid efflux and have anti-inflammatory properties. In several embodiments, these novel peptide compositions promote lipid efflux and have one or more anti-inflammatory domains. In several embodiments, these novel peptide compositions promote lipid efflux and have one or more domains that affect LCAT activity. In several embodiments, these novel peptide compositions promote lipid efflux and have one or more anti-inflammatory domains and one or more domains that affect LCAT activity.

These novel peptide compositions may be labeled and used in a variety of applications including the visualization of plaque in vessels. These novel peptide compositions also display low toxicity.

The present invention provides for the use of the isolated peptides disclosed herein in the preparation of a medicament. The present invention provides for the use of the isolated peptides disclosed herein in the preparation of a medicament useful for treating a dyslipidemic disorder or a vascular disorder. The present invention provides for the use of the isolated peptides disclosed herein in the preparation of a medicament useful for promoting lipid efflux and providing anti-inflammatory activity.

The peptides of the present invention may be combined with pharmaceutically acceptable carriers and administered to a human or an animal as a composition. Administration may be through any means described herein and includes but is not limited to parenteral and oral administration and also administration on a coated device such as a stent or catheter.

Also described herein is a method of treating dyslipidemic and vascular disorders in an animal or a human, including administering to the animal or the human a therapeutically effective amount of the peptides or peptide analogs thereof presented herein. Dyslipidemic and vascular disorders amenable to treatment with the peptides disclosed herein include, but are not limited to, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, HDL deficiency, apoA-I deficiency, coronary artery disease, atherosclerosis, myocardial infarction, stroke and inflammation secondary to stroke, ischemia, ischemic stroke, thrombotic stroke, peripheral vascular disease including peripheral arterial disease, restenosis, thrombosis, acute coronary syndrome, and reperfusion myocardial injury.

The peptides of the present invention may be labeled with labels known to one of ordinary skill in the art and used for numerous applications, including but not limited to use in imaging applications to visualize atherosclerotic plaque. Labels include but are not limited to colorimetric labels, radiodense labels and radioisotopic labels. Other uses include but are not limited to use in assays, such as ELISAs, Western blots, radioimmunoassays and radioreceptor assays.

The peptides of the present invention may be used to generate antisera using techniques known to one of ordinary skill in the art.

The amino acid sequences disclosed herein are shown using standard three letter codes for amino acids, as defined in 37 C.F.R. 1.822 and as commonly known to one of ordinary skill in the

art. When the three letter designation for an amino acid is shown in three upper case letters, for example SER for serine, the SER is a D amino acid.

Several of the generic formulae described below refer to helical regions 5, 6, and 8 of ApoA-I. Helices 5, 6 and 8 of ApoA-I are as follows wherein each helix number is followed by the amino acid residues associated with that helix: 5:145-162; 6:167-184; 8:222-239. Figure 1 shows the numbered amino acid sequence of ApoA-I.

In one embodiment, the peptides of the present invention are described by the following generic formula I:

I. $(A-B-C)_n$

wherein A comprises helix 5 of ApoA-I, helix 6 of ApoA-I, or a modified form of helix 8 of ApoA-I, C comprises helix 8 of ApoA-I, B is a linking group that forms a loop between A and C and n is an integer from 1 to 10.

In one embodiment, A is helix 5 of ApoA-I and is SEQ ID NO: 1 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His, or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 2 His Thr Arg Leu Ala Asp Val His Ala Arg Ala Arg Asp Arg Met Glu Glu Gly.

In another embodiment, A is helix 6 of ApoA-I and is SEQ ID NO: 3 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn, or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 4 Asn Glu Lys Leu Ala Glu Leu Arg Ala Ala Leu Arg Gln Arg Leu Glu Asp Ser.

In one embodiment, A is a modified form of helix 8 of ApoA-I, also called 8' herein, and is SEQ ID NO: 5 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys, or a conservative substitution thereof. These amino acids may also appear in reverse orientation such that Lys is at the N-terminus and Leu is at the C-terminus as in SEQ ID NO: 6 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu. This modification of helix 8 involves substitutions at positions 4 (Phe to Ala), 8 (Phe to Ala) and 15 (Tyr to Ala). It is to be understood that the present invention encompasses other amino acid substitutions at these locations. At positions 4 and 8, Phe may be substituted with Val, Leu, Gly, Thr, Ser or gamma aminobutyric acid (GABA: GABA is also designated as 4Abu herein). At position 15, Tyr may be substituted with Val, Leu, Gly, Thr, Ser or GABA. While not wanting to be bound by the following statement, it is believed that A, the modified form of helix 8 of ApoA-I, has a lower lipid affinity than C, the unmodified form of helix 8 of ApoA-I.

In one embodiment, B is Pro, SEQ ID NO: 7 Lys Leu Ser Pro Leu, SEQ ID NO: 8 Leu Ser Pro Leu, or SEQ ID NO: 9 Ser Pro Leu, or a conservative substitution thereof. These amino acids may also appear in reverse orientation for example as in SEQ ID NO: 10 Leu Pro Ser Leu Lys, SEQ ID NO: 11 Leu Pro Ser Leu, and SEQ ID NO: 12 Leu Pro Ser.

In one embodiment, C is helix 8 of ApoA-I and is SEQ ID NO: 13 Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys, or a conservative substitution thereof. These amino acids may also appear in reverse orientation such that Lys is at the N-terminus and Leu is

at the C-terminus as SEQ ID NO: 14 Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu.

It is to be understood that A and C may be switched in location as in C-B-A.

5 In a further embodiment, peptides of the present invention are described by the following subgeneric formula II, in which one or more additional elements indicated as variables D, E, F and W, are added to formula I to make subgeneric formula II.

II. D-E-(A-B-C)_n-F-W

(A-B-C)_n are as described in formula I above.

10 D is absent or present and is a peptide as defined in the present specification. In one embodiment, D is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D, namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly
15 may occur as D-amino acids;

E is absent or present and is a group linking D and A and is Pro, SEQ ID NO: 10 Leu Pro Ser Leu Lys, or a conservative substitution thereof, provided that E is present only when D is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 7 Lys Leu Ser Pro Leu. When D is absent, E is absent.

20 F is absent or present and is a group linking C and W and is Pro, SEQ ID NO: 19 Ala Leu Ser Pro Leu, or a conservative substitution thereof, provided that F is present only when W is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 20 Leu Pro Ser Leu Ala. When W is absent, F is absent.

25 W is absent or present and is a peptide as defined in the present specification. In one embodiment, W is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp), or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W peptide may be D amino acids.

30 As stated above, in generic formula II, variables D or W may be absent or present. In one embodiment, D is present and W is absent. In another embodiment, W is present and D is absent. In another embodiment, both D and W are present.

In yet another embodiment, W and D as described in formula III may be switched in location.

III. W-E-(A-B-C)_n-F-D

35 In a further embodiment, peptides of the present invention are described by the following subgeneric formula IV, in which one or more additional elements indicated as variables G and H, are added to formula I to make subgeneric formula IV.

IV. $G-(A-B-C)_n-H$

$(A-B-C)_n$ are as described in formula I above,

G is absent or present and is a peptide as defined in the present specification. In one embodiment, G is SEQ ID NO: 9 Ser Pro Leu or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 12 Leu Pro Ser. It is to be understood that one or more of the amino acids in the G peptide may be D amino acids.

H is absent or present and is a peptide as defined in the present specification. In one embodiment, H is SEQ ID NO: 23 Leu Asn Thr Gln or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 24 Gln Thr Asn Leu. It is to be understood that one or more of the amino acids in the H peptide may be D amino acids.

In a further embodiment, peptides of the present invention are described by the following subgeneric formula V, in which one or more additional elements indicated as variables D, E, F, W, G and H are added to formula I to make subgeneric formula V.

V. $D-E-G-(A-B-C)_n-H-F-W$

$(A-B-C)_n$ are as described in formula I above,

D is absent or present and is a peptide as defined in the present specification. In one embodiment, D is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D, namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

E is absent or present and is a group linking D and A and is Pro, SEQ ID NO: 10 Leu Pro Ser Leu Lys, or a conservative substitution thereof, provided that E is present only when D is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 7 Lys Leu Ser Pro Leu. When D is absent, E is absent.

F is absent or present and is a group linking C and W and is Pro, SEQ ID NO: 19 Ala Leu Ser Pro Leu, or a conservative substitution thereof, provided that F is present only when W is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 20 Leu Pro Ser Leu Ala. When W is absent, F is absent.

W is absent or present and is a peptide as defined in the present specification. In one embodiment, W is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W peptide may be D amino acids.

G is absent or present and is a peptide as defined in the present specification provided that G is present when D is absent. In one embodiment, G is SEQ ID NO: 9 Ser Pro Leu or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO:

12 Leu Pro Ser. It is to be understood that one or more of the amino acids in the G peptide may be D amino acids.

H is absent or present and is a peptide as defined in the present specification provided that H is present when W is absent. In one embodiment, H is SEQ ID NO: 23 Leu Asn Thr Gln or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 24 Gln Thr Asn Leu. It is to be understood that one or more of the amino acids in the H peptide may be D amino acids.

As stated above, in generic formula V, variables D or W may be absent or present. In one embodiment, D is present and W is absent. In another embodiment, W is present and D is absent. In another embodiment, both D and W are present.

In a further embodiment, peptides of the present invention are described by formula VI,
VI. D-I-W

D is a peptide as defined in the present specification. In one embodiment, D is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D, namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

I is a group linking D and W and is GABA, Pro, SEQ ID NO: 7 Lys Leu Ser Pro Leu, SEQ ID NO: 25 Leu Lys Leu Ser Pro Leu, or a conservative substitution thereof, or multiples thereof or combinations thereof. These amino acids may also appear in reverse orientation, for example, SEQ ID NO: 26 Leu Pro Ser Leu Lys Leu.

W is absent or present and is a peptide as defined in the present specification. In one embodiment, W is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W peptide may be D amino acids.

D and W may also be switched in location in D-I-W to form W-I-D.

In another embodiment, the peptides of the present invention are described by the following generic formula VII:

VII $(D-R-S-W-T-N-O-(X_n-Y_z-Z_m)_s-O'-N'-T'-W'-S'-R'-D')_r$

wherein: n is an integer from 1 to 3, m is an integer from 1 to 3, r is an integer from 1 to 10, z is an integer from 1 to 13, and s is an integer from 1 to 5. It is to be understood that the letters in the generic formulae VII-XVIII or in components thereof are defined by the text that follows each letter and do not designate an individual amino acid.

D or D' is individually absent or present and is a peptide as defined in the present specification. In one embodiment, D or D' is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative

substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D or D', namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

5 R or R' is individually absent or present and is a linking group comprised of at least one gamma aminobutyric acid (GABA), or one or more neutral amino acids. Neutral amino acids that may be employed include, but are not limited to, proline, serine, leucine, alanine, valine, polymers thereof and combinations (co-polymers) thereof. For example, poly leucine, poly alanine, poly proline, poly valine, and poly serine may be used. Other substituents for R or R' include SEQ ID
10 NO: 27 (Gly-Pro-Gly-Gly)_x and SEQ ID NO: 28 (Gly₄-Ser)_y, wherein x is an integer from about 1 to about 9 and y is an integer from about 1 to about 8. Suitable linking groups for R or R' may be selected from the following without limitation:

GABA; GABA-GABA; GABA-GABA-GABA; SEQ ID NO: 29 Gly Pro Gly Gly; SEQ ID NO: 30 Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 31 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly
15 Gly; SEQ ID NO: 32 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 33 Gly Gly Gly Gly Ser; SEQ ID NO: 34 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser or SEQ ID NO: 35 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser;

S or S' is individually absent or present and is a linking group comprised of amino acid residues of from 1 to 10 residues in length, wherein the amino acid residues are proline, alanine,
20 leucine, lysine, serine, glycine, polymers thereof or combinations (co-polymers) thereof, or is comprised of an alkyl group (CH₂)_n, wherein n is an integer from 1-20;

W or W' is individually absent or present and is a peptide as defined in the present specification. In one embodiment, W or W' is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof.
25 These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W or W' peptide may be D amino acids;

T or T' is individually absent or present and is a linking group comprised of at least one gamma aminobutyric acid (GABA), or one or more neutral amino acids. Neutral amino acids that
30 may be employed include, but are not limited to, proline, serine, leucine, alanine, valine, polymers thereof and combinations (co-polymers) thereof. For example, poly leucine, poly alanine, poly proline, poly valine, and poly serine may be used. Other substituents for T or T' include SEQ ID NO: 27 (Gly-Pro-Gly-Gly)_x and SEQ ID NO: 28 (Gly₄-Ser)_y, wherein x is an integer from about 1 to about 9 and y is an integer from about 1 to about 8. Suitable linking groups for T or T' may be
35 selected from the following without limitation: GABA; GABA-GABA; GABA-GABA-GABA; SEQ ID NO: 29 Gly Pro Gly Gly; SEQ ID NO: 30 Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 31 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 32 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 33 Gly Gly Gly Gly Ser; SEQ ID NO:

34 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser or SEQ ID NO: 35 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser;

N or N' is individually absent or present and is a linking group comprised of amino acid residues of from 1 to 10 residues in length, wherein the amino acid residues are proline, alanine, leucine, serine, glycine, polymers thereof or combinations (co-polymers) thereof, or is comprised of an alkyl group $(CH_2)_n$, wherein n is an integer from 1-20;

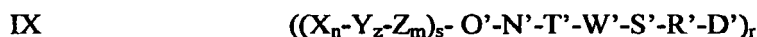
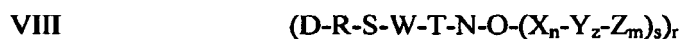
O or O' is individually absent or present and is a linking group comprised of at least one GABA, or one or more neutral amino acids, or combinations thereof. Neutral amino acids that may be employed include, but are not limited to, proline, serine, leucine, alanine, valine, polymers thereof and combinations (co-polymers) thereof. For example, poly leucine, poly alanine, poly proline, poly valine, and poly serine may be used. Other substituents for O or O' include SEQ ID NO: 27 (Gly-Pro-Gly-Gly)_x and SEQ ID NO: 28 (Gly₄-Ser)_y, wherein x is an integer from about 1 to about 9 and y is an integer from about 1 to about 8. Suitable linking groups for O or O' may be selected from the following without limitation: GABA; GABA-GABA; GABA-GABA-GABA; SEQ ID NO: 29 Gly Pro Gly Gly; SEQ ID NO: 30 Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 31 Gly Pro Gly Gly Gly Pro Gly Gly Gly Gly Pro Gly Gly; SEQ ID NO: 32 Gly Pro Gly Gly Gly Gly Pro Gly Gly Gly Gly Pro Gly Gly; SEQ ID NO: 33 Gly Gly Gly Gly Ser; SEQ ID NO: 34 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser or SEQ ID NO: 35 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser;

X is a peptide comprised of from 5 to 25 amino acid residues, provided an amphipathic alpha helix is obtained. Examples of X are provided below in the specification;

Y is absent or present and is a linking group comprised of amino acid(s) of from 1 to 10 residues in length, wherein the amino acid residues are proline, alanine, leucine, serine, glycine, lysine, polymers thereof or combinations (co-polymers) thereof, or is comprised of an alkyl group $(CH_2)_n$, wherein n is an integer from 1-20; z is an integer from 1 to 13 and refers to the number of times Y may be present in $X_n-Y_z-Z_m$ when n or m in $X_n-Y_z-Z_m$ are more than 1 or when s is more than 1;

Z is a peptide comprised of from 5 to 25 amino acids residues, provided an amphipathic alpha helix is obtained. Examples of Z are provided below in the specification, provided that more than one 1 amphipathic alpha helical domain is present when X and Z are taken in combination.

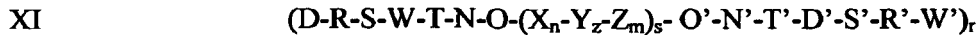
The present invention also provides peptides of the following subgeneric formulae VIII and IX, wherein the variables are as described in formula VII:



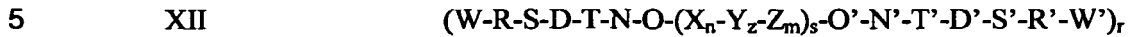
In some embodiments, the D may be placed in the position of W and W may be placed in the position of D in formula VII to yield the following:



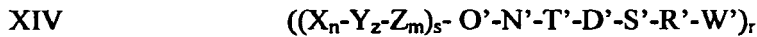
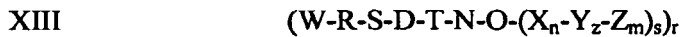
In some embodiments, the D' may be placed in the position of W', and W' may be placed in the position of D' in formula VII to yield the following:



In some embodiments, the D may be placed in the position of W and W may be placed in the position of D in formula VII and D' may be placed in the position of W', and W' may be placed in the position of D' in formula VII to yield the following:



The present invention also provides peptides of the following formulae:



The present invention also includes compositions comprising combinations of individual peptides of the present invention in an acceptable carrier. For example, a mixture of D, W, and $(X_n-Y_z-Z_m)_s$ may be made in an acceptable carrier. These peptides are as defined above and may be labeled or unlabelled. It is to be understood that a mixture of peptides, such as D, W, and $(X_n-Y_z-Z_m)_s$ may include different amounts of the individual peptides. For example, in one embodiment, each peptide component of the combination may be present in a different relative percentage than each other peptide component due to differences in relative efficacy to promote lipid efflux or to provide one or more types of anti-inflammatory activity.

It is to be understood that the letters in the generic formulae I through XVIII or in components thereof are defined by the text that follows each letter and do not designate an individual amino acid.

It is to be understood that in some embodiments, one or more of the amino acids of the peptides of the present invention are D amino acids. In one embodiment, the N-terminal amino acid, the C-terminal amino acid or both are D amino acids. The presence of these D amino acids can help protect against peptide degradation. In another embodiment, all the amino acids of the peptides of the present invention are D amino acids. This embodiment is useful for protection against degradation following oral administration of a pharmaceutical composition comprising the peptides of the present invention.

The N and/or C-terminal amino acids may also be modified by amidation, acetylation or other modifications known to one of ordinary skill in the art. The peptides of the present invention may optionally be acetylated at the N-terminus or the C-terminus using techniques known to one of ordinary skill in the art. The peptides of the present invention may optionally be amidated at the N-terminus or the C-terminus using techniques known to one of ordinary skill in the art. In one embodiment, the peptides of the present invention are acetylated at the N-terminus, amidated at the C-terminus, or both acetylated at the N-terminus and amidated at the C-terminus. In some embodiments, the peptides of the present invention may have both an acetylated N-terminus and a carboxy terminal amide. In the present application, when a peptide is acetylated on an N or C

terminus, the letters Ac are indicated. In the present application, when a peptide is amidated on an N or C terminus, the designation NH₂ is employed.

The present invention also includes compositions comprising one or more individual peptides of the present invention in an acceptable carrier. These peptides are as defined above and may be labeled or unlabelled. It is to be understood that a mixture of peptides, may include different amounts of the individual peptides. For example, in one embodiment, each peptide component of the combination may be present in a different relative percentage than each other peptide component due to differences in relative efficacy to promote lipid efflux or to provide one or more types of anti-inflammatory activity.

Accordingly, it is an object of the present invention to provide novel peptides.

Accordingly, it is an object of the present invention to provide novel peptides that facilitate lipid efflux.

Yet another object of the present invention is to provide novel peptides that facilitate lipid efflux and possess anti-inflammatory biological activity.

Still another object of the present invention is to provide novel peptides that facilitate lipid efflux and stimulate LCAT activity.

Yet another object of the present invention is to provide novel peptides that facilitate lipid efflux, possess anti-inflammatory biological activity, and stimulate LCAT activity.

It is another object of the present invention to provide new methods for visualizing plaque using labeled peptides of the present invention.

It is yet another object of the present invention to provide new methods for the treatment of atherosclerosis, cardiovascular disease and cerebrovascular disease in an animal or a human by administering pharmaceutical compositions comprising one or more peptides of the present invention with a pharmaceutically acceptable carrier, or on a medical device.

These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments and claims.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the amino acid sequence of ApoA-I (SEQ ID NO: 36).

Figure 2 is a schematic illustration of the statistically significant, anti-inflammatory effects of ApoA-I (SEQ ID NO: 36) and peptide 1 (SEQ ID NO: 644), (each at 20 ug/ml) to decrease PMA (1 uM) induced expression of CD11b in human monocytes.

Figure 3 is a schematic illustration of the statistically significant, anti-inflammatory effects of ApoAI and peptide 6 (SEQ ID NO: 155), (each at 20 ug/ml) to decrease PMA (1 uM) induced expression of CD11b in human monocytes.

Figure 4 is a schematic illustration of the dose dependent stimulation of cholesterol efflux from the cells containing the ABCA1 pathway 1=SEQ ID NO: 644, 2=SEQ ID NO: 121, 3=SEQ ID NO: 121, 4=SEQ ID NO: 130, 5=SEQ ID NO: 644.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention provides novel peptides. The present invention solves the problems described above by providing novel peptide compositions with functional domains. In some embodiments, these novel peptide compositions promote lipid efflux. In some embodiments, these novel peptide compositions promote lipid efflux and have anti-inflammatory properties. In other embodiments, these novel peptide compositions promote lipid efflux and have one or more anti-inflammatory domains. In yet other embodiments, these novel peptide compositions promote lipid efflux and have one or more domains that affect LCAT activity. In several embodiments, these novel peptide compositions promote lipid efflux and have one or more anti-inflammatory domains and one or more domain that affects LCAT activity.

Any of the peptides of the present invention may optionally be acetylated at the N-terminus or the C-terminus using techniques known to one of ordinary skill in the art. The peptides of the present invention may optionally be amidated at the N-terminus or the C-terminus using techniques known to one of ordinary skill in the art. In one embodiment, the peptides of the present invention are acetylated at the N-terminus, amidated at the C-terminus, or both acetylated at the N-terminus and amidated at the C-terminus. In some embodiments, the peptides of the present invention may have both an acetylated N-terminus and a carboxy terminal amide. In the present application, when a peptide is acetylated on an N or C terminus, the letters Ac are indicated. In the present application, when a peptide is amidated on an N or C terminus, the designation NH₂ is employed.

The present invention provides for the use of the isolated peptides disclosed herein in the preparation of a medicament. The present invention provides for the use of the isolated peptides disclosed herein in the preparation of a medicament useful for treating a dyslipidemic disorder or a vascular disorder. The present invention provides for the use of the isolated peptides disclosed herein in the preparation of a medicament useful for promoting lipid efflux and providing anti-inflammatory activity.

One or more of these peptides may be combined with an acceptable carrier and administered as compositions to individuals in order to provide lipid efflux and anti-inflammatory activities. These compositions may be administered to treat dyslipidemic and vascular disorders or to delay or prevent the onset or progression of dyslipidemic and vascular disorders. In one embodiment, these compositions may be administered to treat atherosclerosis or to delay or prevent its onset or progression. These novel peptide compositions may be labeled and used in a variety of applications including the visualization of plaque in vessels. These novel peptide compositions also display low toxicity.

I. Abbreviations

ABCA1:	ATP-binding cassette transporter A1
apoA-I:	apolipoprotein A-I
DMPC:	dimyristoyl phosphatidyl choline

HDL:	high-density lipoprotein
HPLC:	high-pressure liquid chromatography
LDL:	low-density lipoprotein
RBC:	red blood cell

5

II. Terms

Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes VII*, published by Oxford University Press, 2000 (ISBN 019879276X); Kendrew *et al.* (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Publishers, 1994 (ISBN 0632021829); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by Wiley, John & Sons, Inc., 1995 (ISBN 0471186341); and other similar references.

As used herein, the singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Also, as used herein, the term "comprises" means "includes." Hence "comprising A or B" means including A, B, or A and B.

In order to facilitate review of the various embodiments of this disclosure, the following explanations of specific terms are provided:

Analog, derivative or mimetic: An analog is a molecule that differs in chemical structure from a parent compound, for example a homolog (differing by an increment in the chemical structure, such as a difference in the length of an alkyl chain), a molecular fragment, a structure that differs by one or more functional groups, a change in ionization. Structural analogs are often found using quantitative structure activity relationships (QSAR), with techniques such as those disclosed in Remington (*The Science and Practice of Pharmacology*, 19th Edition (1995), chapter 28). A derivative is a biologically active molecule derived from the base structure. A mimetic is a molecule that mimics the activity of another molecule, such as a biologically active molecule. Biologically active molecules can include chemical structures that mimic the biological activities of a compound.

Animal: Living multi-cellular vertebrate organisms, a category that includes, for example, mammals and birds. The term mammal includes both human and non-human mammals. Similarly, the term "subject" includes both human and veterinary subjects, for example, humans, non-human primates, dogs, cats, horses, and cows.

Antibody: A protein (or protein complex) that includes one or more polypeptides substantially encoded by immunoglobulin genes or fragments of immunoglobulin genes. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon, and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha,

delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively.

The basic immunoglobulin (antibody) structural unit is generally a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" (about 50-70 kDa) chain. The N- terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms "variable light chain" (V_L) and "variable heavy chain" (V_H) refer, respectively, to these light and heavy chains.

As used herein, the term "antibody" includes intact immunoglobulins as well as a number of well-characterized fragments. For instance, Fabs, Fvs, and single-chain Fvs (SCFvs) that bind to target protein (or epitope within a protein or fusion protein) would also be specific binding agents for that protein (or epitope). These antibody fragments are as follows: (1) Fab, the fragment which contains a monovalent antigen-binding fragment of an antibody molecule produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain; (2) Fab', the fragment of an antibody molecule obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain; two Fab' fragments are obtained per antibody molecule; (3) (Fab')₂, the fragment of the antibody obtained by treating whole antibody with the enzyme pepsin without subsequent reduction; (4) F(ab')₂, a dimer of two Fab' fragments held together by two disulfide bonds; (5) Fv, a genetically engineered fragment containing the variable region of the light chain and the variable region of the heavy chain expressed as two chains; and (6) single chain antibody, a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Methods of making these fragments are routine (see, e.g., Harlow and Lane, *Using Antibodies: A Laboratory Manual*, CSHL, New York, 1999).

Antibodies for use in the methods and compositions of this disclosure can be monoclonal or polyclonal. Merely by way of example, monoclonal antibodies can be prepared from murine hybridomas according to the classical method of Kohler and Milstein (*Nature* 256:495-97, 1975) or derivative methods thereof. Detailed procedures for monoclonal antibody production are described in Harlow and Lane, *Using Antibodies: A Laboratory Manual*, CSHL, New York, 1999.

Domain: A domain of a protein is a part of a protein that shares common structural, physiochemical and functional features; for example hydrophobic, polar, globular, helical domains or properties, for example a DNA binding domain, an ATP binding domain, an anti-inflammatory domain, an LCAT activating domain and the like. Some peptides of the present invention possess a domain or domains that have more than one functional feature, for example both lipid efflux activity and anti-inflammatory activity.

Dyslipidemic disorder: A disorder associated with any altered amount of any or all of the lipids or lipoproteins in the blood. Dyslipidemic disorders include, for example, hyperlipidemia,

hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, HDL deficiency, apoA-I deficiency, and cardiovascular disease (e.g., coronary artery disease, atherosclerosis and restenosis).

5 Efflux: The process of flowing out. As applied to the results described herein, lipid efflux refers to a process whereby lipid, such as cholesterol and phospholipid, is complexed with an acceptor, such as an apolipoprotein or apolipoprotein peptide mimetic, or a peptide of the present invention and removed from vesicles or cells. "ABCA1-dependent lipid efflux" (or lipid efflux by an "ABCA1-dependent pathway") refers to a process whereby apolipoproteins, synthetic peptide mimetics of apolipoproteins, or a peptide of the present invention, bind to a cell and
10 efflux lipid from the cell by a process that is facilitated by the ABCA1 transporter.

 Helix: The molecular conformation of a spiral nature, generated by regularly repeating rotations around the backbone bonds of a macromolecule. Helices 5, 6 and 8 of ApoA-I are as follows wherein each helix number is followed by the amino acid residues associated with that helix: 5:145-162; 6:167-184; 8:222-239. Figure 1 shows the amino acid sequence of ApoA-I
15 (SEQ ID NO: 36).

 Hydrophobic: A hydrophobic (or lipophilic) group is electrically neutral and nonpolar, and thus prefers other neutral and nonpolar solvents or molecular environments. Examples of hydrophobic molecules include alkanes, oils and fats.

 Hydrophilic: A hydrophilic (or lipophobic) group is electrically polarized and capable of
20 H-bonding, enabling it to dissolve more readily in water than in oil or other "non-polar" solvents.

 Inhibiting or treating a disease: Inhibiting the full development of a disease, disorder or condition, for example, in a subject who is at risk for a disease such as atherosclerosis and cardiovascular disease. "Treatment" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. As used herein, the
25 term "ameliorating," with reference to a disease, pathological condition or symptom, refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, a reduction in the number of relapses of the disease, an improvement in the overall health
30 or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease.

 Isolated/purified: An "isolated" or "purified" biological component (such as a nucleic acid, peptide or protein) has been substantially separated, produced apart from, or purified away from other biological components in the cell of the organism in which the component naturally
35 occurs, that is, other chromosomal and extrachromosomal DNA and RNA, and proteins. Nucleic acids, peptides and proteins that have been "isolated" thus include nucleic acids and proteins purified by standard purification methods. The term also embraces nucleic acids, peptides and proteins prepared by recombinant expression in a host cell as well as chemically synthesized nucleic acids or proteins. The term "isolated" or "purified" does not require absolute purity;

rather, it is intended as a relative term. Thus, for example, an isolated biological component is one in which the biological component is more enriched than the biological component is in its natural environment within a cell. Preferably, a preparation is purified such that the biological component represents at least 50%, such as at least 70%, at least 90%, at least 95%, or greater of the total biological component content of the preparation.

Label: A detectable compound or composition that is conjugated directly or indirectly to another molecule to facilitate detection of that molecule. Specific, non-limiting examples of labels include fluorescent tags, colorimetric labels, dyes, beads, enzymatic linkages, radiodense materials, and radioactive isotopes.

Linker: A molecule that joins two other molecules, either covalently, or through ionic, van der Waals or hydrogen bonds.

Lipid: A class of water-insoluble, or partially water insoluble, oily or greasy organic substances, that are extractable from cells and tissues by nonpolar solvents, such as chloroform or ether. Types of lipids include triglycerides (*e.g.*, natural fats and oils composed of glycerin and fatty acid chains), glycolipids, phospholipids (*e.g.*, phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, and phosphatidylinositol), sphingolipids (*e.g.*, sphingomyelin, cerebroside and gangliosides), and sterols (*e.g.*, cholesterol).

Lipid affinity: A measurement of the relative binding affinity of an amphipathic α -helix for lipids. In some embodiments, the lipid affinity of an amphipathic α -helix is determined by one or more functional tests. Specific, non-limiting examples of functional tests include: retention time on reverse phase HPLC, surface monolayer exclusion pressure (Palgunachari *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 16:328-338, 1996), binding affinity to phospholipid vesicles (Palgunachari *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 16:328-338, 1996), and DMPC vesicle solubilization (Remaley *et al.*, *J. Lipid Res.* 44:828-836, 2003).

Further non-limiting examples of alternative methods of calculating the lipid affinity of an amphipathic α -helix include: total hydrophobic moment, total peptide hydrophobicity, total peptide hydrophobicity per residue, hydrophobicity of amino acids on the hydrophobic face, hydrophobicity per residue of amino acids on the hydrophobic face, and calculated lipid affinity based on predicted peptide penetration into phospholipid bilayers (Palgunachari *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 16:328-338, 1996).

Non-cytotoxic: A non-cytotoxic compound is one that does not substantially affect the viability or growth characteristics of a cell at a dosage normally used to treat the cell or a subject. Furthermore, the percentage of cells releasing intracellular contents, such as LDH or hemoglobin, is low (*e.g.*, about 10% or less) in cells treated with a non-cytotoxic compound. Lipid efflux from a cell that occurs by a non-cytotoxic compound results in the removal of lipid from a cell by a process that maintains the overall integrity of the cell membrane and does not lead to significant cell toxicity.

Non-polar: A non-polar compound is one that does not have concentrations of positive or negative electric charge. Non-polar compounds, such as, for example, oil, are not well soluble in water.

5 Peptide: A polymer in which the monomers are amino acid residues which are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used. The amino acid sequences disclosed herein are shown using three letter codes for amino acids, as defined in 37 C.F.R. 1.822 and as commonly known to one of ordinary skill in the art. When the three letter designation for an amino acid, for example Ser for serine is shown in upper case, SER, the serine is a D amino acid. The terms
10 "peptide" or "polypeptide" as used herein are intended to encompass any amino acid sequence and include modified sequences such as glycoproteins. The term "peptide" is specifically intended to cover naturally occurring peptides, as well as those which are recombinantly or synthetically produced. The term "residue" or "amino acid residue" includes reference to an amino acid that is incorporated into a peptide, polypeptide, or protein. As known to one of skill
15 in the art, the peptides presented herein are read from the N to the C terminus i.e., from left to right. Accordingly, the N terminal amino acid in Leu Glu Lys is Leu and the C-terminal amino acid is Lys. Peptides of the present invention include conservatively substituted peptides, wherein these conservative substitutions occur at 1%, 3%, 5%, 7%, 10%, 15%, 20%, 25%, 30%, 40%, or 50% of the amino acid residues. Peptides of the present invention include peptides that
20 are homologous at 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% of the entire sequence of the peptide.

Pharmaceutically acceptable carriers: The pharmaceutically acceptable carriers (vehicles) useful in this disclosure are conventional. *Remington's Pharmaceutical Sciences*, by E. W. Martin, Mack Publishing Co., Easton, PA, 15th Edition (1975), describes compositions and
25 formulations suitable for pharmaceutical delivery of one or more therapeutic compounds or molecules, such as one or more peptides or peptide analogs and additional pharmaceutical agents.

In general, the nature of the carrier will depend on the particular mode of administration being employed. For instance, parenteral formulations usually comprise injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological
30 saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (e.g., powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or
35 emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

Phospholipid: A phospholipid consists of a water-soluble polar head, linked to two water-insoluble non-polar tails (by a negatively charged phosphate group). Both tails consist of a fatty acid, each about 14 to about 24 carbon groups long. When placed in an aqueous environment,

phospholipids form a bilayer or micelle, where the hydrophobic tails line up against each other. This forms a membrane with hydrophilic heads on both sides. A phospholipid is a lipid that is a primary component of animal cell membranes.

Polar: A polar molecule is one in which the centers of positive and negative charge distribution do not converge. Polar molecules are characterized by a dipole moment, which measures their polarity, and are soluble in other polar compounds and virtually insoluble in nonpolar compounds.

Recombinant nucleic acid: A sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, for example, by genetic engineering techniques such as those described in Sambrook *et al.* (ed.), *Molecular Cloning: A Laboratory Manual*, 2nd ed., vol. 1-3, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid.

Therapeutically effective amount: A quantity of a specified agent sufficient to achieve a desired effect in a subject being treated with that agent. For example, this can be the amount of a peptide or peptide analog useful in preventing, ameliorating, and/or treating a dyslipidemic disorder (*e.g.*, atherosclerosis) in a subject. Ideally, a therapeutically effective amount of an agent is an amount sufficient to prevent, ameliorate, and/or treat a dyslipidemic disorder (*e.g.*, atherosclerosis) in a subject without causing a substantial cytotoxic effect (*e.g.*, membrane microsolubilization) in the subject. The effective amount of an agent useful for preventing, ameliorating, and/or treating a dyslipidemic disorder (*e.g.*, atherosclerosis) in a subject will be dependent on the subject being treated, the severity of the disorder, and the manner of administration of the therapeutic composition.

Transformed: A "transformed" cell is a cell into which has been introduced a nucleic acid molecule by molecular biology techniques. The term encompasses all techniques by which a nucleic acid molecule might be introduced into such a cell, including transfection with viral vectors, transformation with plasmid vectors, and introduction of naked DNA by electroporation, lipofection, and particle gun acceleration.

III. *Peptides of the Present Invention and Analogs Thereof*

In one embodiment, the peptides of the present invention are described by the following generic formula I:

I. (A-B-C)_n

In one embodiment, A is helix 5 of ApoA-I and is SEQ ID NO: 1 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His, or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 2 His Thr Arg Leu Ala Asp Val His Ala Arg Ala Arg Asp Arg Met Glu Glu Gly.

In another embodiment, A is helix 6 of ApoA-I and is SEQ ID NO: 3 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn, or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 4 Asn Glu Lys Leu Ala Glu Leu Arg Ala Ala Leu Arg Gln Arg Leu Glu Asp Ser.

5 In one embodiment, A is a modified form of helix 8 of ApoA-I, also called 8' herein, and is SEQ ID NO: 5 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys, or a conservative substitution thereof. These amino acids may also appear in reverse orientation such that Lys is at the N-terminus and Leu is at the C-terminus as in SEQ ID NO: 6 Lys Lys Thr Ala
10 Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu. This modification of helix 8 involves substitutions at positions 4 (Phe to Ala), 8 (Phe to Ala) and 15 (Tyr to Ala). It is to be understood that the present invention encompasses other amino acid substitutions at these locations. At positions 4 and 8, Phe may be substituted with Val, Leu, Gly, Thr, Ser or gamma
15 aminobutyric acid (GABA). At position 15, Tyr may be substituted with Val, Leu, Gly, Thr, Ser or GABA. While not wanting to be bound by the following statement, it is believed that A, the modified form of helix 8 of ApoA-I, has a lower lipid affinity than C, the unmodified form of helix 8 of ApoA-I.

In one embodiment, B is Pro, SEQ ID NO: 7 Lys Leu Ser Pro Leu, SEQ ID NO: 8 Leu Ser Pro Leu, or SEQ ID NO: 9 Ser Pro Leu, or a conservative substitution thereof. These amino acids may also appear in reverse orientation for example as in SEQ ID NO: 10 Leu Pro Ser Leu Lys,
20 SEQ ID NO: 11 Leu Pro Ser Leu, and SEQ ID NO: 12 Leu Pro Ser.

In one embodiment, C is helix 8 of ApoA-I and is SEQ ID NO: 13 Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys, or a conservative substitution thereof. These amino acids may also appear in reverse orientation such that Lys is at the N-terminus and Leu is at the C-terminus as SEQ ID NO: 14 Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys
25 Phe Ser Glu Leu. It is to be understood that A and C may be switched in location as in C-B-A. Specific embodiments of peptides represented by generic formula I are:

Wherein A is 5 and C is 8

SEQ ID NO: 37 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys
30 Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;
SEQ ID NO: 38 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

Wherein A is 6 and C is 8

SEQ ID NO: 39 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys
35 Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;
SEQ ID NO: 40 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

Wherein A is 8' and C is 8

SEQ ID NO: 41 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 42 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro
5 Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 43 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys
Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 44 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro
Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

10 SEQ ID NO: 45 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 46 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

15 SEQ ID NO: 47 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 48 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 49 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Leu
Pro Ser Leu Lys Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

20 SEQ ID NO: 50 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Pro Lys
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 51 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Leu
Pro Ser Leu Lys Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

25 SEQ ID NO: 52 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Pro Lys
Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 53 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Leu
Pro Ser Leu Lys Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 54 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Leu
Pro Ser Leu Lys Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys; and,

30 SEQ ID NO: 55 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

Wherein A is 8 and C is 8'

35 SEQ ID NO: 56 Leu Glu Ser Phe Leu Val Ser Phe Lys Ser Ala Leu Glu Glu Tyr Phe Glu Lys Lys
Leu Ser Pro Leu Leu Glu Ser Ala Ala Val Ser Ala Lys Ser Ala Leu Glu Glu Tyr Ala Glu Lys;

In a further embodiment, peptides of the present invention are described by the following subgeneric formula II, in which one or more additional elements indicated as variables D, E, F and W, are added to formula I to make subgeneric formula II.

II. D-E-(A-B-C)_n-F-W

(A-B-C)_n are as described in formula I above.

D is absent or present and is a peptide as defined in the present specification. In one embodiment, D is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D, namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

E is absent or present and is a group linking D and A and is Pro, SEQ ID NO: 10 Leu Pro Ser Leu Lys, or a conservative substitution thereof, provided that E is present only when D is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 7 Lys Leu Ser Pro Leu. When D is absent, E is absent.

F is absent or present and is a group linking C and W and is Pro, SEQ ID NO: 19 Ala Leu Ser Pro Leu, or a conservative substitution thereof, provided that F is present only when W is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 20 Leu Pro Ser Leu Ala. When W is absent, F is absent.

W is absent or present and is a peptide as defined in the present specification. In one embodiment, W is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp), or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W peptide may be D amino acids.

As stated above, in generic formula II, variables D or W may be absent or present. In one embodiment, D is present and W is absent. In another embodiment, W is present and D is absent. In another embodiment, both D and W are present.

Specific embodiments of peptides represented by generic formula II are:

Wherein A is 5 or 6 and C is 8

SEQ ID NO: 57 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 58 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 59 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 60 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

- 5 SEQ ID NO: 61 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 62 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

- 10 SEQ ID NO: 63 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

- 15 SEQ ID NO: 64 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 65 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

- 20 SEQ ID NO: 66 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 67 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

- 25 or,
SEQ ID NO: 68 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp

- 30 Wherein A is 8' and C is 8

SEQ ID NO: 69 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

- 35 SEQ ID NO: 70 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 71 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala
Leu Ser Pro Leu Trp Arg Trp Trp Trp;

5 SEQ ID NO: 72 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys
Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp
Trp;

10 SEQ ID NO: 73 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys
Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 74 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala
Leu Ser Pro Leu Trp Arg Trp Trp Trp;

15 SEQ ID NO: 75 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu
Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp
Trp;

20 SEQ ID NO: 76 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu
Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 77 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Trp
Arg Trp Trp Trp;

25 SEQ ID NO: 78 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys
Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu
Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 79 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys
Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu
Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

30 SEQ ID NO: 80 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu
Trp Arg Trp Trp Trp;

35 SEQ ID NO: 81 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu
Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 82 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu
Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 83 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu
Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 84 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
5 Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Pro Lys Thr Tyr Glu Glu Leu Ala Ser
Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 85 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser
Leu Phe Ser Val Lys Phe Ser Glu Leu;

10 SEQ ID NO: 86 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Trp Arg Trp Trp Trp
Trp; and,

SEQ ID NO: 87 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu
Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser
15 Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

In yet another embodiment, W and D as described in formula III may be switched in
location.

III. W-E-(A-B-C)_n-F-D

20 Specific embodiments of peptides represented by generic formula III are as follows:

Wherein A is 5 or 6 and C is 8

SEQ ID NO: 88 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala
Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe
25 Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val
Thr;

SEQ ID NO: 89 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala
Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

30 SEQ ID NO: 90 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala
Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe
Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 91 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu
Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe
35 Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val
Thr;

SEQ ID NO: 92 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala
Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 93 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 94 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 95 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 96 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 97 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 98 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr; or,

SEQ ID NO: 99 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys.

Wherein A is 8' and C is 8

SEQ ID NO: 100 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 101 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 102 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 103 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 104 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala
Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

5 SEQ ID NO: 105 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala
Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe
Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

10 SEQ ID NO: 106 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala
Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala
Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val
Thr;

SEQ ID NO: 107 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala
Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

15 SEQ ID NO: 108 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala
Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala
Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 109 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala
Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu
Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

20 SEQ ID NO: 110 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu
Pro Arg Gly Gly Ser Val Leu Val Thr;

25 SEQ ID NO: 111 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala
Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu
Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 112 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala
Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu
Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

30 SEQ ID NO: 113 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu
Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 114 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala
Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu
Glu Glu Tyr Thr Lys Lys;

35 SEQ ID NO: 115 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala
Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser
Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 116 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr; and,

5 SEQ ID NO: 117 Trp Arg Trp Trp Trp Trp Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu

10 In a further embodiment, peptides of the present invention are described by the following subgeneric formula IV, in which one or more additional elements indicated as variables G and H, are added to formula I to make subgeneric formula IV.

IV. $G-(A-B-C)_n-H$

$(A-B-C)_n$ are as described in formula I above,

15 G is absent or present and is a peptide as defined in the present specification. In one embodiment, G is SEQ ID NO: 9 Ser Pro Leu or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 10 Leu Pro Ser. It is to be understood that one or more of the amino acids in the G peptide may be D amino acids.

20 H is absent or present and is a peptide as defined in the present specification. In one embodiment, H is SEQ ID NO: 23 Leu Asn Thr Gln or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 24 Gln Thr Asn Leu. It is to be understood that one or more of the amino acids in the H peptide may be D amino acids.

Specific embodiments of peptides represented by generic formula IV are as follows:

Wherein A is 5 or 6 and C is 8

25 SEQ ID NO: 118 Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 119 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

30 SEQ ID NO: 120 Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 121 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

35 SEQ ID NO: 122 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 123 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys
Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr
Lys Lys;

5 SEQ ID NO: 124 Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg
Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn
Thr Gln;

SEQ ID NO: 125 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

10 SEQ ID NO: 126 Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg
Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 127 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys
Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn
Thr Gln;

15 SEQ ID NO: 128 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro
Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln; and,

SEQ ID NO: 129 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys
Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys.

Wherein A is 8' and C is 8

20 SEQ ID NO: 130 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr
Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr
Lys Lys Leu Asn Thr Gln;

25 SEQ ID NO: 131 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu
Asn Thr Gln;

SEQ ID NO: 132 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr
Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr
Lys Lys;

30 SEQ ID NO: 133 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser
Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr
Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 134 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu
Asn Thr Gln;

35 SEQ ID NO: 135 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser
Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr
Lys Lys;

SEQ ID NO: 136 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 137 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys
5 Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 138 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

10 SEQ ID NO: 139 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 140 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu
15 Asn Thr Gln;

SEQ ID NO: 141 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 142 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr
20 Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 143 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 144 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr
25 Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 145 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 146 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro
30 Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 147 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys;

SEQ ID NO: 148 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn
35 Thr Gln;

SEQ ID NO: 149 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 150 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu;

SEQ ID NO: 151 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 152 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln; and,

SEQ ID NO: 153 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu.

In a further embodiment, peptides of the present invention are described by the following subgeneric formula V, in which one or more additional elements indicated as variables D, E, F, W, G and H are added to formula I to make subgeneric formula V.

V. D-E-G-(A-B-C)_n-H-F-W

(A-B-C)_n are as described in formula I above,

D is absent or present and is a peptide as defined in the present specification. In one embodiment, D is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D, namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

E is absent or present and is a group linking D and A and is Pro, SEQ ID NO: 10 Leu Pro Ser Leu Lys, or a conservative substitution thereof, provided that E is present only when D is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 7 Lys Leu Ser Pro Leu. When D is absent, E is absent.

F is absent or present and is a group linking C and W and is Pro, SEQ ID NO: 19 Ala Leu Ser Pro Leu, or a conservative substitution thereof, provided that F is present only when W is present. These amino acids may also appear in reverse orientation as in SEQ ID NO: 20 Leu Pro Ser Leu Ala. When W is absent, F is absent.

W is absent or present and is a peptide as defined in the present specification. In one embodiment, W is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W peptide may be D amino acids.

G is absent or present and is a peptide as defined in the present specification provided that G is present when D is absent. In one embodiment, G is SEQ ID NO: 9 Ser Pro Leu or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 12 Leu Pro Ser. It is to be understood that one or more of the amino acids in the G peptide may be D amino acids.

H is absent or present and is a peptide as defined in the present specification provided that H is present when W is absent. In one embodiment, H is SEQ ID NO: 23 Leu Asn Thr Gln or a conservative substitution thereof. These amino acids may also appear in reverse orientation as in SEQ ID NO: 24 Gln Thr Asn Leu. It is to be understood that one or more of the amino acids in the H peptide may be D amino acids.

As stated above, in generic formula V, variables D or W may be absent or present. In one embodiment, D is present and W is absent. In another embodiment, W is present and D is absent. In another embodiment, both D and W are present.

Specific embodiments of peptides represented by generic formula V are:

Wherein A is 5 or 6 and C is 8

SEQ ID NO: 154 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 155 Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 156 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 157 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 158 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 159 Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 160 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln; or,

SEQ ID NO: 161 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp.

Wherein A is 8' and C is 8

SEQ ID NO: 162 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

5 SEQ ID NO: 163 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 164 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

10 SEQ ID NO: 165 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 166 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 167 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

20 SEQ ID NO: 168 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 169 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

25 SEQ ID NO: 170 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

SEQ ID NO: 171 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 172 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln;

35 SEQ ID NO: 173 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 174 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln;

SEQ ID NO: 175 Ser Pro Leu Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp;

SEQ ID NO: 176 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Leu Asn Thr Gln; and

SEQ ID NO: 177 Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Pro Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp

In a further embodiment, peptides of the present invention are described by formula VI,

VI. D-I-W

D is a peptide as defined in the present specification. In one embodiment, D is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D, namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

I is a group linking D and W and is GABA, Pro, SEQ ID NO: 7 Lys Leu Ser Pro Leu, SEQ ID NO: 25 Leu Lys Leu Ser Pro Leu, or a conservative substitution thereof, or multiples thereof or combinations thereof. These amino acids may also appear in reverse orientation, for example, SEQ ID NO: 26 Leu Pro Ser Leu Lys Leu.

W is absent or present and is a peptide as defined in the present specification. In one embodiment, W is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W peptide may be D amino acids.

D and W may also be switched in location in D-I-W to form W-I-D. Specific embodiments of peptides represented by formula VI are:

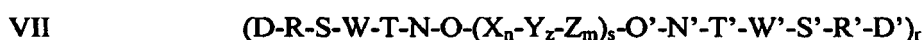
SEQ ID NO: 178 Pro Arg Gly Gly Ser Val Leu Val Thr Leu Lys Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 179 Trp Arg Trp Trp Trp Trp Leu Lys Leu Ser Pro Leu Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 180 Pro Arg Gly Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp Trp;

- SEQ ID NO: 181 Pro Arg Gly Gly Ser Val Leu Val Thr -(GABA-GABA) Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 182 Pro Arg Gly Gly Ser Val Leu Val Thr -(GABA-GABA-GABA)-Pro Trp Arg Trp Trp Trp Trp;
- 5 SEQ ID NO: 183 Pro Arg Gly Gly Ser Val Leu Val Thr -(GABA-GABA-GABA-GABA) Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 184 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 185 PRO Arg Gly Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp Trp;
- 10 SEQ ID NO: 186 Pro ARG Gly Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 187 Pro Arg GLY Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 188 Pro Arg Gly GLY Ser Val Leu Val Thr -(GABA)-Pro Trp Arg Trp Trp Trp Trp;
- 15 SEQ ID NO: 189 Pro Arg Gly Gly SER Val Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 190 Pro Arg Gly Gly Ser VAL Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 191 PRO Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- 20 SEQ ID NO: 192 Pro ARG Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 193 Pro Arg GLY Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 194 Pro Arg Gly GLY Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 195 Pro Arg Gly Gly SER Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 196 Pro Arg Gly Gly Ser VAL Leu Val Thr Pro Trp Arg Trp Trp Trp Trp;
- 25 SEQ ID NO: 197 PRO Arg Gly Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Arg Trp Trp Trp TRP;
- SEQ ID NO: 198 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 199 PRO ARG GLY GLY SER VAL LEU VAL THR PRO TRP TRP TRP TRP ARG TRP;
- 30 SEQ ID NO: 200 PRO Arg Gly Gly Ser Val Leu Val Thr Pro Trp Trp Trp Trp Arg TRP;
- SEQ ID NO: 201 Pro Arg Gly Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 202 PRO Arg Gly Gly Ser Val Leu Val Thr -(GABA)- Pro Trp Trp Trp Trp Arg TRP; and
- SEQ ID NO: 203 PRO ARG GLY GLY SER VAL LEU VAL THR -(gaba)- PRO TRP TRP TRP TRP ARG TRP.
- 35

In another embodiment, the peptides of the present invention are described by the following generic formula VII:



wherein: n is an integer from 1 to 3, m is an integer from 1 to 3, r is an integer from 1 to 10,

z is an integer from 1 to 13, and s is an integer from 1 to 5. It is to be understood that the letters in the generic formulae VII-XVIII or in components thereof are defined by the text that follows each letter and do not designate an individual amino acid.

D or D' is individually absent or present and is a peptide as defined in the present specification. In one embodiment, D or D' is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D or D', namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser Gly may occur as D-amino acids;

R or R' is individually absent or present and is a linking group comprised of at least one gamma aminobutyric acid (GABA), or one or more neutral amino acids. Neutral amino acids that may be employed include, but are not limited to, proline, serine, leucine, alanine, valine, polymers thereof and combinations (co-polymers) thereof. For example, poly leucine, poly alanine, poly proline, poly valine, and poly serine may be used. Other substituents for R or R' include SEQ ID NO: 27 (Gly-Pro-Gly-Gly)_x and SEQ ID NO: 28 (Gly₄-Ser)_y, wherein x is an integer from about 1 to about 9 and y is an integer from about 1 to about 8. Suitable linking groups for R or R' may be selected from the following without limitation:

GABA; GABA-GABA; GABA-GABA-GABA; SEQ ID NO: 29 Gly Pro Gly Gly; SEQ ID NO: 30 Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 31 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 32 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 33 Gly Gly Gly Gly Ser; SEQ ID NO: 34 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser or SEQ ID NO: 35 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser;

S or S' is individually absent or present and is a linking group comprised of amino acid residues of from 1 to 10 residues in length, wherein the amino acid residues are proline, alanine, leucine, lysine, serine, glycine, polymers thereof or combinations (co-polymers) thereof, or is comprised of an alkyl group (CH₂)_n, wherein n is an integer from 1-20;

W or W' is individually absent or present and is a peptide as defined in the present specification. In one embodiment, W or W' is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W or W' peptide may be D amino acids;

T or T' is individually absent or present and is a linking group comprised of at least one gamma aminobutyric acid (GABA), or one or more neutral amino acids. Neutral amino acids that may be employed include, but are not limited to, proline, serine, leucine, alanine, valine, polymers thereof and combinations (co-polymers) thereof. For example, poly leucine, poly alanine, poly proline, poly valine, and poly serine may be used. Other substituents for T or T' include SEQ ID NO: 27 (Gly-Pro-Gly-Gly)_x and SEQ ID NO: 28 (Gly₄-Ser)_y, wherein x is an integer from about 1 to

about 9 and y is an integer from about 1 to about 8. Suitable linking groups for T or T' may be selected from the following without limitation: GABA; GABA-GABA; GABA-GABA-GABA; SEQ ID NO: 29 Gly Pro Gly Gly; SEQ ID NO: 30 Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 31 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 32 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 33 Gly Gly Gly Gly Ser; SEQ ID NO: 34 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser or SEQ ID NO: 35 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser;

N or N' is individually absent or present and is a linking group comprised of amino acid residues of from 1 to 10 residues in length, wherein the amino acid residues are proline, alanine, leucine, serine, glycine, polymers thereof or combinations (co-polymers) thereof, or is comprised of an alkyl group $(CH_2)_n$, wherein n is an integer from 1-20;

O or O' is individually absent or present and is a linking group comprised of at least one GABA, or one or more neutral amino acids, or combinations thereof. Neutral amino acids that may be employed include, but are not limited to, proline, serine, leucine, alanine, valine, polymers thereof and combinations (co-polymers) thereof. For example, poly leucine, poly alanine, poly proline, poly valine, and poly serine may be used. Other substituents for O or O' include SEQ ID NO: 27 (Gly-Pro-Gly-Gly)_x and SEQ ID NO: 28 (Gly₄-Ser)_y, wherein x is an integer from about 1 to about 9 and y is an integer from about 1 to about 8. Suitable linking groups for O or O' may be selected from the following without limitation: GABA; GABA-GABA; GABA-GABA-GABA; SEQ ID NO: 29 Gly Pro Gly Gly; SEQ ID NO: 30 Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 31 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 32 Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly Gly Pro Gly Gly; SEQ ID NO: 33 Gly Gly Gly Gly Ser; SEQ ID NO: 34 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser or SEQ ID NO: 35 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser;

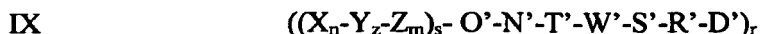
X is a peptide comprised of from 5 to 25 amino acid residues, provided an amphipathic alpha helix is obtained. Examples of X are provided below in the specification;

Y is absent or present and is a linking group comprised of amino acid(s) of from 1 to 10 residues in length, wherein the amino acid residues are proline, alanine, leucine, serine, glycine, lysine, polymers thereof or combinations (co-polymers) thereof, or is comprised of an alkyl group $(CH_2)_n$ wherein n is an integer from 1-20; z is an integer from 1 to 13 and refers to the number of times Y may be present in $X_n-Y_z-Z_m$ when n or m in $X_n-Y_z-Z_m$ are more than 1 or when s is more than 1;

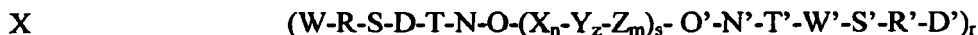
Z is a peptide comprised of from 5 to 25 amino acids residues, provided an amphipathic alpha helix is obtained. Examples of Z are provided below in the specification, provided that more than one 1 amphipathic alpha helical domain is present when X and Z are taken in combination.

The present invention also provides peptides of the following subgeneric formulae VIII and IX, wherein the variables are as described in formula VII:





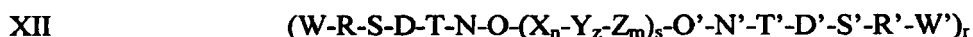
In some embodiments, the D may be placed in the position of W and W may be placed in the position of D in formula VII to yield the following:



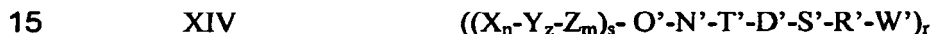
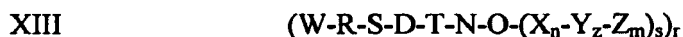
5 In some embodiments, the D' may be placed in the position of W', and W' may be placed in the position of D' in formula VII to yield the following:



10 In some embodiments, the D may be placed in the position of W and W may be placed in the position of D in formula VII and D' may be placed in the position of W', and W' may be placed in the position of D' in formula VII to yield the following:



The present invention also provides peptides of the following formulae:



20

The present invention also includes compositions comprising combinations of individual peptides of the present invention in an acceptable carrier. For example, a mixture of D, W, and $(X_n-Y_z-Z_m)_s$ may be made in an acceptable carrier. These peptides are as defined above and may be labeled or unlabelled. It is to be understood that a mixture of peptides, such as D, W, and $(X_n-Y_z-Z_m)_s$ may include different amounts of the individual peptides. For example, in one embodiment, each peptide component of the combination may be present in a different relative percentage than each other peptide component due to differences in relative efficacy to promote lipid efflux or to provide one or more types of anti-inflammatory activity.

30 *The $X_n-Y_z-Z_m$ Component of Formulae VII-XV and XVIII*

The $X_n-Y_z-Z_m$ component of formula VII-XV and XVIII require that more than one 1 amphipathic alpha helical domain is present when X and Z are taken in combination.

35 While not wanting to be bound by the following statement, it is believed that the $X_n-Y_z-Z_m$ component of formula VII, or formulae VIII-XV or XVIII alone or in combination with the other components of formula VII, or formulae VIII-XV or XVIII facilitate lipid efflux from cells. While not wanting to be bound by the following statement, it is believed that the $X_n-Y_z-Z_m$ component of formula VII, or formulae VIII-XV or XVIII, alone or in combination with the other components of formula VII facilitate lipid efflux from cells through an ABCA1 dependent pathway.

In one embodiment of $X_n-Y_z-Z_m$, $n = 1$, $m = 1$, and $z = 1$, Y is proline, X is SEQ ID NO: 204 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe, and Z is SEQ ID NO: 205 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala, to yield the following peptide,

5 SEQ ID NO: 206 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

It is to be understood that X and Z may be the same or different. In one embodiment, X and Z may be the same or different and may be SEQ ID NO: 204 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe or SEQ ID NO: 205 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala. Y may be Proline (P) and is often shown as -P- in the sequences that follow. Any one or more of the C-terminal six amino acids of Z, specifically SEQ ID NO: 207 Lys Ala Lys Glu Ala Ala may be D amino acids. It is further to be understood that $X_n-Y_z-Z_m$, and the embodiment

10 SEQ ID NO: 206 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala includes the following variations without limitation:

- a) changes in length (N terminal and or C terminal deletions of X and or Z);
- b) multiple repeats;
- c) change in orientation of the X peptide relative to Z peptide in the overall $X_n-Y_z-Z_m$ peptide;
- 20 d) reversal of the N terminal to C terminal orientation of the X peptide;
- e) reversal of the N terminal to C terminal orientation of the Z peptide;
- f) reversal of the N terminal to C terminal orientation of the X peptide, and reversal of the N terminal to C terminal orientation of the Z peptide;
- 25 g) reversal of the N terminal to C terminal orientation of Z and reversal of the N terminal to C terminal orientation of X and change in the order, Z-Y-X;
- h) reversal of the N terminal to C terminal orientation of Z when Z is SEQ ID NO: 204 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe, and X is SEQ ID NO: 205 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala, in the order X-Y-Z;
- 30 i) insertion of D amino acids in the C-terminal six amino acids of Z, specifically SEQ ID NO: 207 Lys Ala Lys Glu Ala Ala; and,
- j) insertion of a D amino acid at the N terminal of X or Z and/or at the C-terminal of X or Z.

The following are specific embodiments of these variations:

- 35 a) changes in length (N terminal and or C terminal deletions of X and or Z),
 SEQ ID NO: 206 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

1. Deletion of residues from the C terminal of X with Z intact:

- SEQ ID NO: 208 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 209 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Pro Asp
Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 5 SEQ ID NO: 210 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 211 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Pro Asp Trp Ala
Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 10 SEQ ID NO: 212 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Pro Asp Trp Ala Lys
Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 213 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Pro Asp Trp Ala Lys Ala
Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
2. Deletion of residues from the C terminal of Z with X intact:
- SEQ ID NO: 214 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
15 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala;
- SEQ ID NO: 215 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu;
- SEQ ID NO: 216 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys;
- 20 SEQ ID NO: 217 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala;
- SEQ ID NO: 218 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys;
- SEQ ID NO: 219 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
25 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu;
- SEQ ID NO: 220 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala;
3. Deletion of residues from the N terminal of X with Z intact:
- SEQ ID NO: 221 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
30 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 222 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp
Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 223 Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 35 SEQ ID NO: 224 Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala
Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 225 Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys
Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 226 Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

4. Deletion of residues from the N terminal of Z with X intact:

SEQ ID NO: 227 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 228 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 229 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 230 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 231 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 232 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

5. Deletion of residues from the N terminal of X and the N terminal of Z:

SEQ ID NO: 233 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 234 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 235 Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 236 Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 237 Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 238 Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

6. Deletion of residues from the C terminal of X and the C terminal of Z:

SEQ ID NO: 239 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala;

SEQ ID NO: 240 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu;

SEQ ID NO: 241 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys;

SEQ ID NO: 242 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala;

SEQ ID NO: 243 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys;

SEQ ID NO: 244 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu;

SEQ ID NO: 245 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala;

5 SEQ ID NO: 246 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala;

7. Deletion of residues from the C terminal of X and the N terminal of Z:

SEQ ID NO: 247 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Pro Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

10 SEQ ID NO: 248 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Pro Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 249 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Pro Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

15 SEQ ID NO: 250 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Pro Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 251 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Pro Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 252 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Pro Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

20 SEQ ID NO: 253 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Pro Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

8. Deletion of residues from the C terminal of Z and the N terminal of X:

SEQ ID NO: 254 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala;

25 SEQ ID NO: 255 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu;

SEQ ID NO: 256 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu;

30 SEQ ID NO: 257 Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala;

SEQ ID NO: 258 Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys;

SEQ ID NO: 259 Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu;

35

b) Multiple Repeats

$(X_n-Y_z-Z_m)_s$

wherein: n is an integer from 1 to 3, m is an integer from 1 to 3, z is an integer from 1 to 13, and s is an integer from 1 to 5, wherein in some embodiment when s is more than 1, Y is optionally present

between repeating units of X-Y-Z, and in some embodiments when n or m is greater than 1, Y is optionally present between repeats of X and/or between repeats of Z and Y or Pro (P).

SEQ ID NO: 260 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp
5 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 261 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp
10 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp
Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 262 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp
15 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp
Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu
Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala
20 Ala;

SEQ ID NO: 263 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 264 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp
25 Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

c) change in orientation of the X peptide relative to Z peptide in the $X_n-Y_z-Z_m$ peptide.

Another embodiment of the $X_n-Y_z-Z_m$ peptide wherein X is SEQ ID NO: 205 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala or a variant thereof and
30

Z is SEQ ID NO: 204 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe or a variant thereof, and Y is proline (P), is

SEQ ID NO: 265 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
35

1) Removal of residues from the C terminal of Z with X intact:

SEQ ID NO: 266 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala;

SEQ ID NO: 267 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu;

SEQ ID NO: 268 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys;

5 SEQ ID NO: 269 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu;

SEQ ID NO: 270 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys;

10 SEQ ID NO: 271 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu;

2) Removal of residues from the C terminal of X with Z intact:

SEQ ID NO: 272 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Pro
Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

15 SEQ ID NO: 273 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Pro Asp
Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 274 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Pro Asp Trp
Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

20 SEQ ID NO: 275 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Pro Asp Trp Leu
Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 276 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Pro Asp Trp Leu Lys
Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 277 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Pro Asp Trp Leu Lys Ala
Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

25 SEQ ID NO: 288 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Pro Asp Trp Leu Lys Ala Phe
Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

3) Removal of residues from the N terminal of Z with X intact:

30 SEQ ID NO: 289 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 290 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 291 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

35 SEQ ID NO: 292 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 293 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
Pro Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 294 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

4) Removal of residues from the N terminal of X with Z intact:

- 5 SEQ ID NO: 295 Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 SEQ ID NO: 296 Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 SEQ ID NO: 297 Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 10 SEQ ID NO: 298 Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 SEQ ID NO: 299 Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 15 SEQ ID NO: 300 Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

5) Removal of residues from the N terminal of X and the N terminal of Z:

- SEQ ID NO: 301 Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 20 SEQ ID NO: 302 Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 SEQ ID NO: 303 Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 25 SEQ ID NO: 304 Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 SEQ ID NO: 305 Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 SEQ ID NO: 306 Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;
 30

6) Removal of residues from the C terminal of X and the C terminal of Z:

- SEQ ID NO: 239 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala;
 35 SEQ ID NO: 240 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu;
 SEQ ID NO: 241 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys;

SEQ ID NO: 242 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala;

SEQ ID NO: 243 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys;

5 SEQ ID NO: 244 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu;

SEQ ID NO: 245 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala;

10 7) Removal of residues from the C terminal of Z and the N terminal of X:

SEQ ID NO: 307 Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala;

SEQ ID NO: 308 Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu;

15 SEQ ID NO: 309 Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys;

SEQ ID NO: 310 Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu;

SEQ ID NO: 311 Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys

20 Ala Phe Tyr Asp Lys Val Ala Glu Lys;

SEQ ID NO: 312 Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu;

8) Removal of residues from the C terminal of X and the N terminal of Z:

25 SEQ ID NO: 313 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Pro Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 314 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Pro Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 315 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Pro Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

30 SEQ ID NO: 316 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Pro Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 317 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Pro Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

35 SEQ ID NO: 318 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Pro Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

Multiple Repeats of these orientations of X and Z.

$(X_n-Y_z-Z_m)_s$

wherein: n is an integer from 1 to 3, m is an integer from 1 to 3, z is an integer from 1 to 13, and s is an integer from 1 to 5, wherein in some embodiments when s is more than 1, Y is optionally present between repeating units of X-Y-Z, and in some embodiments when n or m is greater than 1, Y is optionally present between repeats of X and/or between repeats of Z.

SEQ ID NO: 319 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 320 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 321 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 322 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 323 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

d) reversal of the N to C orientation of the X in $X_n-Y_z-Z_m$

when X is SEQ ID NO: 204 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 324 Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

e) reversal of the N to C orientation of the Z in $X_n-Y_z-Z_m$ when Z is

SEQ ID NO: 205 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala:
 SEQ ID NO: 325 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Ala Ala Glu Lys Ala Lys Glu Ala Ala Lys Asp Tyr Ala Ala Lys Ala Trp Asp

- 5 f) reversal of the N terminal to C terminal orientation of Z and
 reversal of the N terminal to C terminal orientation of X in $X_n-Y_z-Z_m$:

SEQ ID NO: 326 Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp
 Pro Ala Ala Glu Lys Ala Lys Glu Ala Ala Lys Asp Tyr Ala Ala Lys Ala Trp Asp

- 10 g) reversal of the N terminal to C terminal orientation of Z and reversal of the N terminal to C
 terminal orientation of X in $X_n-Y_z-Z_m$ and change in the order, Z-Y-X:

SEQ ID NO: 327 Ala Ala Glu Lys Ala Lys Glu Ala Ala Lys Asp Tyr Ala Ala Lys Ala Trp Asp
 Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp

- 15 h) reversal of the N terminal to C terminal orientation of Z when Z is SEQ ID NO: 204 Asp Trp
 Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe and X is SEQ ID NO: 205
 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala:

SEQ ID NO: 328 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala
 Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp

- 20 i) insertion of D amino acids in the one or more C-terminal six amino acids of Z, specifically SEQ
 ID NO: 207 Lys Ala Lys Glu Ala Ala.

Exemplary embodiments include but are not limited to the following:

- SEQ ID NO: 329 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 25 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA
 SEQ ID NO: 330 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala
 SEQ ID NO: 331 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala
 30 SEQ ID NO: 332 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala
 SEQ ID NO: 333 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala
 SEQ ID NO: 334 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 35 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala
 SEQ ID NO: 335 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu ALA ALA
 SEQ ID NO: 336 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu ALA Ala

SEQ ID NO: 337 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala ALA

SEQ ID NO: 338 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS ALA Lys Glu Ala ALA

5 SEQ ID NO: 339 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala LYS Glu Ala ALA

SEQ ID NO: 340 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala ALA

10 SEQ ID NO: 341 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys GLU Ala Ala

SEQ ID NO: 342 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala LYS Glu ALA Ala

SEQ ID NO: 343 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys GLU Ala ALA

15 It is to be understood that any of the peptides described above in the X_n - Y_z - Z_m component may be combined with the D and/or D' components described below and with the W and/or W' components described below, or with other components of formulae VII-XVIII.

Substitutions for D or D'

20 D or D' is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro. It is to be understood that one or more of the first six N-terminal amino acids of D or D', namely SEQ ID NO: 17 Pro Arg Gly Gly Ser Val or SEQ ID NO: 18 Thr Val Leu Val Ser
25 Gly may occur as D-amino acids.

Conservative amino acid substitutions for amino acids have been described within this application. A few exemplary, non-limiting examples of such substitutions for SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr follow:

P - proline, leucine, valine, isoleucine or methionine;

30 R - arginine, lysine, valine, leucine, N-nitroarginine, β -cycloarginine, γ -hydroxy-arginine; N-amidinocitruline or 2-amino-4-guanidino-butanoic acid;

G - glycine, serine, alanine, cysteine or threonine;

G - glycine, serine, alanine, cysteine or threonine;

V - valine, leucine, isoleucine or methionine;

35 L - leucine, isoleucine, methionine or valine;

V - valine, leucine, isoleucine or methionine;

T - threonine, serine, glycine, alanine or cysteine.

Exemplary embodiments for D or D' include but are not limited to the following:

SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr; SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro; SEQ ID NO: 344 PRO Arg Gly Gly Ser Val Leu Val Thr; SEQ ID NO: 345 Pro ARG Gly Gly Ser Val Leu Val Thr; SEQ ID NO: 346 Pro Arg GLY Gly Ser Val Leu Val Thr; SEQ ID NO: 347 Pro Arg Gly GLY Ser Val Leu Val Thr; SEQ ID NO: 348 Pro Arg Gly Gly SER Val Leu Val Thr; SEQ ID NO: 349 Pro Arg Gly Gly Ser VAL Leu Val Thr; SEQ ID NO: 350 THR Val Leu Val Ser Gly Gly Arg Pro; SEQ ID NO: 351 Thr VAL Leu Val Ser Gly Gly Arg Pro; SEQ ID NO: 352 Thr Val LEU Val Ser Gly Gly Arg Pro; SEQ ID NO: 353 Thr Val Leu VAL Ser Gly Gly Arg Pro; SEQ ID NO: 354 Thr Val Leu Val SER Gly Gly Arg Pro; SEQ ID NO: 355 Thr Val Leu Val Ser GLY Gly Arg Pro

Substitutions for W or W'

This section discloses an expansion of the peptides in the W and or W' domains of Formula VII

D-R-S-W-T-N-O-(X_n-Y_z-Z_m)_s-O'-N'-T'-W'-S'-R'-D')_r and other formulae containing W or W', wherein W or W' is individually absent or present and is a peptide as defined in the present specification. In one embodiment, W or W' is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, or multiples, variations or conservative substitutions thereof. These amino acids may also appear in reverse orientation, namely SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp. It is to be understood that one or more of the amino acids in the W or W' peptide may be D amino acids. While not wanting to be bound by the following statement, it is believed that W and/or W' provide an anti-inflammatory component to the peptides of the present invention.

W or W' may be any one of the following peptides: SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp; SEQ ID NO: 356 Trp Trp Arg Trp Trp Trp; SEQ ID NO: 357 Trp Trp Trp Arg Trp Trp; SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp; SEQ ID NO: 358 Trp Trp Trp Trp Trp Arg; SEQ ID NO: 359 Arg Trp Trp Trp Trp Trp, or multiples, variations or combinations thereof, including but not limited to the following,

SEQ ID NO: 360 Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp

SEQ ID NO: 361 Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Arg Trp Trp Trp

SEQ ID NO: 362 Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp

SEQ ID NO: 363 Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Arg Trp Trp

SEQ ID NO: 364 Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp

SEQ ID NO: 365 Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Arg Trp Trp

SEQ ID NO: 366 Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp

SEQ ID NO: 367 Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Arg Trp

SEQ ID NO: 368 Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg

SEQ ID NO: 369 Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Arg

SEQ ID NO: 370 Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp

SEQ ID NO: 371 Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp

SEQ ID NO: 372 Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp

SEQ ID NO: 373 Trp Arg Trp Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg Trp Trp

SEQ ID NO: 374 Trp Arg Trp Trp Trp Trp Trp Trp Trp Arg Trp

SEQ ID NO: 375 Trp Arg Trp Trp Trp Trp Trp Trp Trp Arg Trp Trp Trp Trp Trp Arg.

- 5 The present invention includes substitution of amino acids in the peptides listed above. It is to be understood that tryptophan (W) may be conservatively substituted with alanine, phenylalanine, tyrosine or glycine in W or W'. It is also to be understood that arginine (R) may be substituted with lysine, valine or leucine in W or W'.

10 *Insertion of D amino acids in W or W'*

Exemplary embodiments include but are not limited to the following:

- SEQ ID NO: 376 TRP Arg Trp Trp Trp Trp; SEQ ID NO: 377 Trp ARG Trp Trp Trp Trp; SEQ ID NO: 378 Trp Arg TRP Trp Trp Trp; SEQ ID NO: 379 Trp Arg Trp TRP Trp Trp; SEQ ID NO: 380 Trp Arg Trp Trp TRP Trp; SEQ ID NO: 381 Trp Arg Trp Trp Trp TRP; SEQ ID NO: 382 TRP Trp Arg Trp Trp Trp; SEQ ID NO: 383 Trp TRP Arg Trp Trp Trp; SEQ ID NO: 384 Trp Trp ARG Trp Trp Trp; SEQ ID NO: 385 Trp Trp Arg TRP Trp Trp; SEQ ID NO: 386 Trp Trp Arg Trp TRP Trp; SEQ ID NO: 387 Trp Trp Arg Trp Trp TRP; SEQ ID NO: 388 TRP Trp Trp Arg Trp Trp; SEQ ID NO: 389 Trp TRP Trp Arg Trp Trp; SEQ ID NO: 390 Trp Trp TRP Arg Trp Trp; SEQ ID NO: 391 Trp Trp Trp ARG Trp Trp; SEQ ID NO: 392 Trp Trp Trp Arg TRP Trp; SEQ ID NO: 393 Trp Trp Trp Arg Trp TRP
- 15
- 20

Exemplary embodiments for D-W (Formula XVI) and W-D (Formula XVII)

- 25 The following are non-limiting examples of D-W which is reversed in orientation for W-D (Formula XVII) and would apply to W'-D' and D'-W' as W' may be equivalent to W and D' may be equivalent to D.

- SEQ ID NO: 394 Pro Arg Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 395 PRO Arg Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 396 Pro ARG Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 397 Pro Arg GLY Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 398 Pro Arg Gly GLY Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 399 Pro Arg Gly Gly SER Val Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 400 Pro Arg Gly Gly Ser VAL Leu Val Thr Trp Arg Trp Trp Trp Trp; SEQ ID NO: 401 Trp Arg Trp Trp Trp Trp Pro Arg Gly Gly Ser Val Leu Val Thr; SEQ ID NO: 402 Trp Arg Trp Trp Trp Trp PRO Arg Gly Gly Ser Val Leu Val Thr; SEQ ID NO: 403 Trp Arg Trp Trp Trp Trp Pro ARG Gly Gly Ser Val Leu Val Thr; SEQ ID NO: 404 Trp Arg Trp Trp Trp Trp Pro Arg GLY Gly Ser Val Leu Val Thr; SEQ ID NO: 405 Trp Arg Trp Trp Trp Trp Pro Arg Gly GLY Ser Val Leu Val Thr; SEQ ID NO: 406 Trp Arg Trp Trp Trp Trp Pro Arg Gly Gly SER Val Leu Val Thr; SEQ ID NO: 407 Arg Trp Trp Trp Trp Pro Arg Gly Gly Ser VAL Leu Val Thr; SEQ ID NO: 408 Pro Arg Gly Gly Ser Val Leu Val Thr TRP Arg Trp Trp Trp Trp; SEQ ID NO: 409 Pro Arg Gly Gly Ser Val Leu Val Thr Trp ARG Trp Trp Trp Trp; SEQ ID NO: 410
- 30
- 35

Pro Arg Gly Gly Ser Val Leu Val Thr Trp Arg TRP Trp Trp Trp SEQ ID NO: 411 Pro Arg Gly Gly Ser Val Leu Val Thr Trp Arg Trp TRP Trp Trp; SEQ ID NO: 412 Pro Arg Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp TRP Trp; SEQ ID NO: 413 Pro Arg Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp TRP

5 *Exemplary embodiments of the invention*

The following peptides are exemplary embodiments of the present invention:

SEQ ID NO: 414 Trp Arg Trp Trp Trp Trp -(GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

10 SEQ ID NO: 415 Trp Arg Trp Trp Trp Trp (GABA-GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

SEQ ID NO: 416 Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp

15 Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

SEQ ID NO: 417 Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

20 SEQ ID NO: 418 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

SEQ ID NO: 419 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala

25 SEQ ID NO: 420 Trp Arg Trp Trp Trp Trp (GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 421 Trp Arg Trp Trp Trp Trp -(GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala

30 Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA)- Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 422 Trp Arg Trp Trp Trp Trp -(GABA-GABA-GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA)- Trp Arg Trp Trp Trp Trp;

35 SEQ ID NO: 423 Trp Arg Trp Trp Trp Trp -(GABA-GABA-GABA-GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA-GABA)-Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 424 Trp Arg Trp Trp Trp Trp -(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)-Trp Trp Trp Trp Arg Trp

5 SEQ ID NO: 425 Trp Arg Trp Trp Trp Trp -(GABA-GABA)- Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA) Trp Trp Trp Trp Arg Trp

SEQ ID NO: 426 Trp Arg Trp Trp Trp Trp -(GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA)- Trp Trp Trp Trp Arg

10 Trp

SEQ ID NO: 427 Trp Arg Trp Trp Trp Trp -(GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA-GABA)-Trp Trp Trp Trp Arg Trp

15 SEQ ID NO: 428 Trp Arg Trp Trp Trp Trp -(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA)-Pro Pro Arg Gly Gly Ser Val Leu Val Thr

SEQ ID NO: 429 TRP Arg Trp Trp Trp Trp -(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA) Pro Pro Arg Gly Gly Ser Val Leu Val THR

20

SEQ ID NO: 430 Trp Arg Trp Trp Trp Trp -(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA) Thr Val Leu Val Ser Gly Gly Arg Pro

SEQ ID NO: 431 TRP Arg Trp Trp Trp Trp -(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA)- Thr Val Leu Val Ser Gly Gly Arg PRO

25

Series including SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr

SEQ ID NO: 432 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

30

SEQ ID NO: 433 PRO ARG GLY GLY SER VAL LEU VAL THR (gaba)PRO TRP ARG TRP TRP TRP TRP (gaba) ASP TRP LEU LYS ALA PHE TYR ASP LYS VAL ALA GLU LYS LEU LYS GLU ALA PHE PRO ASP TRP ALA LYS ALA ALA TYR ASP LYS ALA ALA GLU LYS ALA LYS GLU ALA ALA;

35

SEQ ID NO: 434 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA;

- SEQ ID NO: 435 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 5 SEQ ID NO: 436 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 10 SEQ ID NO: 437 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 15 SEQ ID NO: 438 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp Arg Trp Trp Trp Trp;
- 20 SEQ ID NO: 439 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA) Trp Arg Trp Trp Trp Trp;
- 25 SEQ ID NO: 440 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp;
- 30 SEQ ID NO: 441 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp;
- 35 SEQ ID NO: 442 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 443 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA) Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 444 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA) Trp Trp Trp Trp Arg Trp;

- SEQ ID NO: 445 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA-GABA) Trp Trp Trp Trp Arg Trp;
- 5 SEQ ID NO: 446 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 447 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
- 10 Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 448 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 449 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 15 SEQ ID NO: 450 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA)-Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp Arg Trp
- 20 Trp Trp Trp;
- SEQ ID NO: 451 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA) Trp Arg Trp Trp Trp Trp;
- 25 SEQ ID NO: 452 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 453 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp;
- 30 SEQ ID NO: 454 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 35 SEQ ID NO: 455 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

- SEQ ID NO: 456 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 5 SEQ ID NO: 457 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 458 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 10 SEQ ID NO: 459 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 460 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)- Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- 15 SEQ ID NO: 461 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- 20 SEQ ID NO: 462 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- 25 SEQ ID NO: 463 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA-GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- 30 SEQ ID NO: 464 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 465 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA) Trp Arg Trp Trp Trp Trp;
- 35 SEQ ID NO: 466 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp;

- SEQ ID NO: 467 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)
Trp Trp Trp Trp Arg Trp;
- 5 SEQ ID NO: 468 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 469 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Trp Trp Trp Trp Arg Trp;
- 10 SEQ ID NO: 470 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA-GABA) Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 471 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Trp Trp Trp
15 Trp Arg Trp;
- SEQ ID NO: 472 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Trp Trp
Trp Trp Arg Trp;
- SEQ ID NO: 473 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
20 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)
Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- SEQ ID NO: 474 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- 25 SEQ ID NO: 475 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;
- SEQ ID NO: 476 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
30 GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Pro Arg Gly Gly Ser Val Leu Val
Thr;
- SEQ ID NO: 477 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)
Trp Arg Trp Trp Trp Trp Pro Pro Arg Gly Gly Ser Val Leu Val Thr;
- 35 SEQ ID NO: 478 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Trp Arg Trp Trp Trp Trp Pro Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 479 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Trp Arg Trp Trp Trp Trp Pro Pro Arg Gly Gly Ser Val Leu Val Thr;

5 SEQ ID NO: 480 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp Pro Pro Arg Gly Gly Ser Val Leu Val Thr;

*Inversion of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr to be SEQ ID NO: 16 Thr Val
Leu Val Ser Gly Gly Arg Pro*

10 SEQ ID NO: 481 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)
Trp Arg Trp Trp Trp Trp Pro (GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;

15 SEQ ID NO: 482 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;

SEQ ID NO: 483 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;

20 SEQ ID NO: 484 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp Pro (GABA) Thr Val Leu Val Ser Gly Gly Arg
Pro;

25 SEQ ID NO: 485 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp
Arg Trp Trp Trp Trp Pro Thr Val Leu Val Ser Gly Gly Arg Pro;

SEQ ID NO: 486 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Trp Arg Trp Trp Trp Trp Pro Thr Val Leu Val Ser Gly Gly Arg Pro;

30 SEQ ID NO: 487 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Trp Arg Trp Trp Trp Trp Pro Thr Val Leu Val Ser Gly Gly Arg Pro;

SEQ ID NO: 488 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA-GABA) Trp Arg Trp Trp Trp Trp Pro Thr Val Leu Val Ser Gly Gly Arg Pro;

35 SEQ ID NO: 489 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)
Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 490 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;

5 SEQ ID NO: 491 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 492 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA-GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;

10 SEQ ID NO: 493 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala -(GABA) Pro
Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 494 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA-
15 GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 495 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA-
GABA-GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;

20 SEQ ID NO: 496 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA-
GABA-GABA-GABA) Pro Arg Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 497 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Arg Gly
Gly Ser Val Leu Val Thr;

25 SEQ ID NO: 498 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Pro Arg
Gly Gly Ser Val Leu Val Thr;

SEQ ID NO: 499 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA)
30 Thr Val Leu Val Ser Gly Gly Arg Pro

SEQ ID NO: 500 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;

35 SEQ ID NO: 501 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;

SEQ ID NO: 502 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA-GABA-GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;

- SEQ ID NO: 503 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA) Thr
Val Leu Val Ser Gly Gly Arg Pro
- 5 SEQ ID NO: 504 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA-
GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;
- 10 SEQ ID NO: 505 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA-
GABA-GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;
- 15 SEQ ID NO: 506 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala (GABA-
GABA-GABA-GABA) Thr Val Leu Val Ser Gly Gly Arg Pro;
- SEQ ID NO: 507 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Thr Val Leu
Val Ser Gly Gly Arg Pro;
- 20 SEQ ID NO: 508 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Thr Val
Leu Val Ser Gly Gly Arg Pro;
- 20 *Insertion of D amino acids in SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr*
- SEQ ID NO: 509 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA); Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 25 SEQ ID NO: 510 Pro ARG Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 511 Pro Arg GLY Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 30 SEQ ID NO: 512 Pro Arg Gly GLY Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- SEQ ID NO: 513 Pro Arg Gly Gly SER Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;
- 35 SEQ ID NO: 514 Pro Arg Gly Gly Ser VAL Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 515 PRO Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp (GABA)
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA) Trp Trp Trp
Trp Arg Trp;

5 SEQ ID NO: 516 Pro ARG Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-
GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro (GABA-
GABA) Trp Trp Trp Trp Arg Trp;

10 SEQ ID NO: 517 Pro Arg GLY Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-
GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala
Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro
(GABA-GABA-GABA) Trp Trp Trp Trp Arg Trp;

15 SEQ ID NO: 518 Pro Arg Gly GLY Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA-
GABA-GABA-GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu
Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro
(GABA-GABA-GABA-GABA) Trp Trp Trp Trp Arg Trp;

SEQ ID NO: 519 Pro Arg Gly Gly SER Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA);
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

20 SEQ ID NO: 520 Pro Arg Gly Gly Ser VAL Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA)
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala;

SEQ ID NO: 521 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 522 Pro ARG Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp;

25 SEQ ID NO: 523 Pro Arg GLY Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 524 Pro Arg Gly GLY Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 525 Pro Arg Gly Gly SER Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 526 Pro Arg Gly Gly Ser VAL Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 527 Pro Arg Gly Gly Ser VAL Leu Val Thr Pro Trp Arg Trp Trp Trp Trp

30 SEQ ID NO: 528 PRO Arg Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp

SEQ ID NO: 529 Pro ARG Gly Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp

SEQ ID NO: 530 Pro Arg GLY Gly Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp

SEQ ID NO: 531 Pro Arg Gly GLY Ser Val Leu Val Thr Trp Arg Trp Trp Trp Trp

SEQ ID NO: 532 Pro Arg Gly Gly SER Val Leu Val Thr Trp Arg Trp Trp Trp Trp

35 SEQ ID NO: 533 Pro Arg Gly Gly Ser VAL Leu Val Thr Trp Arg Trp Trp Trp Trp

Insertion of D amino acids in Z

SEQ ID NO: 534 Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA;

5 SEQ ID NO: 535 Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala;

10 SEQ ID NO: 536 Trp Arg Trp Trp Trp Trp (GABA) Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala;

SEQ ID NO: 537 Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala;

15 SEQ ID NO: 538 Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala;

SEQ ID NO: 539 Trp Arg Trp Trp Trp Trp (GABA) Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala;

20 SEQ ID NO: 540 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA;

25 SEQ ID NO: 541 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala;

SEQ ID NO: 542 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala;

30 SEQ ID NO: 543 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala;

SEQ ID NO: 544 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala

35 SEQ ID NO: 545 Trp Arg Trp Trp Trp Trp Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala

SEQ ID NO: 546 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys
Glu Ala ALA

SEQ ID NO: 547 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
5 Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys
Glu ALA Ala

SEQ ID NO: 548 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys
GLU Ala Ala

10 SEQ ID NO: 549 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS
Glu Ala Ala

SEQ ID NO: 560 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys
15 Glu Ala Ala

SEQ ID NO: 561 Trp Arg Trp Trp Trp Trp Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys
Glu Ala Ala

SEQ ID NO: 562 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
20 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA Pro (GABA)
Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 563 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala Pro (GABA) Trp
Arg Trp Trp Trp Trp;

25 SEQ ID NO: 564 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala Pro (GABA)
Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 565 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala Pro (GABA)
30 Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 566 Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala Pro (GABA) Trp
Arg Trp Trp Trp Trp;

SEQ ID NO: 567 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
35 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala Pro (GABA)
Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 568 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA Pro Trp Arg
Trp Trp Trp Trp;

- SEQ ID NO: 569 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala Pro Trp Arg
Trp Trp Trp Trp;
- 5 SEQ ID NO: 570 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala Pro Trp Arg
Trp Trp Trp Trp;
- SEQ ID NO: 571 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala Pro Trp Arg
Trp Trp Trp Trp;
- 10 SEQ ID NO: 572 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala Pro Trp Arg
Trp Trp Trp Trp;
- SEQ ID NO: 573 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala Pro Trp Arg
15 Trp Trp Trp Trp;
- SEQ ID NO: 574 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA Trp Arg Trp
Trp Trp Trp;
- SEQ ID NO: 575 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
20 Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala Trp Arg Trp
Trp Trp Trp;
- SEQ ID NO: 576 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala Trp Arg Trp
Trp Trp Trp;
- 25 SEQ ID NO: 577 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala Trp Arg Trp
Trp Trp Trp;
- SEQ ID NO: 578 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala Trp Arg Trp
30 Trp Trp Trp;
- SEQ ID NO: 579 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe
Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala Trp Arg Trp
Trp Trp Trp;
- SEQ ID NO: 580 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)- Pro Trp Arg Trp Trp Trp Trp
35 (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA;
- SEQ ID NO: 581 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala;

SEQ ID NO: 582 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala;

5 SEQ ID NO: 583 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala;

SEQ ID NO: 584 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala;

10 SEQ ID NO: 585 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala;

Insertion of D amino acids in SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr and Insertion of D amino acids in Z

15 SEQ ID NO: 586 Pro ARG Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala;

20 SEQ ID NO: 587 Pro Arg GLY Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala;

SEQ ID NO: 588 Pro Arg Gly GLY Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala;

25 SEQ ID NO: 589 Pro Arg Gly Gly SER Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala;

SEQ ID NO: 590 Pro Arg Gly Gly Ser VAL Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala;

30 SEQ ID NO: 591 PRO Arg Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala ALA;

35 SEQ ID NO: 592 Pro ARG Gly Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu ALA Ala;

SEQ ID NO: 593 Pro Arg GLY Gly Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA) Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys GLU Ala Ala;

SEQ ID NO: 594 Pro Arg Gly GLY Ser Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA)
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala LYS Glu Ala Ala;

SEQ ID NO: 595 Pro Arg Gly Gly SER Val Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA)
5 Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys ALA Lys Glu Ala Ala;

SEQ ID NO: 596 Pro Arg Gly Gly Ser VAL Leu Val Thr Pro Trp Arg Trp Trp Trp Trp (GABA)
Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Asp Trp
Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu LYS Ala Lys Glu Ala Ala;

10

Other exemplary embodiments of the Present Invention

SEQ ID NO: 597 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Asp Trp Ala Lys Ala Ala Tyr
Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val
Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Arg Trp Trp Trp Trp;

15 SEQ ID NO: 598 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA) Asp Trp Ala Lys Ala
Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp
Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 599 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA) Asp Trp Ala
Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe
20 Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 600 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA)-(GABA)
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu
Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Arg Trp Trp Trp Trp;

25 SEQ ID NO: 601 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys
Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 602 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Ala Lys Ala Ala Tyr Asp
Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala
Glu Lys Leu Lys Glu Ala Phe Pro Trp Arg Trp Trp Trp Trp;

30 SEQ ID NO: 603 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Asp Trp Ala Lys Ala Ala Tyr
Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val
Ala Glu Lys Leu Lys Glu Ala Phe (GABA) Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 604 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro
35 Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe;

SEQ ID NO: 605 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Trp Arg Trp Trp Trp Trp
(GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro
Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala PHE;

SEQ ID NO: 606 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA) Pro Trp Arg Trp Trp Trp Trp;

5 SEQ ID NO: 607 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA) Pro Trp Arg Trp Trp Trp TRP;

SEQ ID NO: 608 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA)-(GABA) Trp Arg Trp Trp Trp Trp;

10 SEQ ID NO: 609 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA)-(GABA)-(GABA) Trp Arg Trp Trp Trp Trp;

15 SEQ ID NO: 610 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA)-(GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA)-(GABA)-(GABA)-(GABA) Trp Arg Trp Trp Trp Trp;

20 SEQ ID NO: 611 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Trp Arg Trp Trp Trp Trp;

SEQ ID NO: 612 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Trp Trp Trp Arg Trp;

25 SEQ ID NO: 613 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Trp Trp Trp Arg Trp;

SEQ ID NO: 614 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Trp Trp Trp Arg Trp;

30 SEQ ID NO: 615 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA)-(GABA) Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Trp Trp Trp Arg Trp;

35 SEQ ID NO: 616 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Trp Trp Trp Trp Arg Trp;

SEQ ID NO: 617 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe Pro Trp Trp Trp Trp Arg Trp;

- SEQ ID NO: 618 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Asp Trp Ala Lys Ala Ala Tyr
Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val
Ala Glu Lys Leu Lys Glu Ala Phe (GABA)- Trp Trp Trp Trp Arg Trp;
- 5 SEQ ID NO: 619 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala
Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys
Val Ala Glu Lys Leu Lys Glu Ala Phe-(GABA) Pro Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 620 PRO Arg Gly Gly Ser Val Leu Val Thr Pro (GABA) Asp Trp Ala Lys Ala Ala
Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys
Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA) Pro Trp Trp Trp Trp Arg TRP;
- 10 SEQ ID NO: 621 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA) Asp Trp Ala Lys Ala
Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp
Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA)-(GABA) Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 622 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA) Asp Trp Ala
Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe
15 Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA)-(GABA)-(GABA)- Trp Trp Trp Trp
Arg Trp;
- SEQ ID NO: 623 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA)-(GABA)-(GABA)-(GABA)-
Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu
Lys Ala Phe Tyr Asp Lys Val Ala Glu Lys Leu Lys Glu Ala Phe (GABA)-(GABA)-(GABA)-
20 (GABA) Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 624 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys
Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Asp Trp Leu Lys Ala Phe Tyr Asp Lys Val Ala Glu
Lys Leu Lys Glu Ala Phe Trp Trp Trp Trp Arg Trp;
- SEQ ID NO: 625 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys
25 Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr
Phe Ala Lys Leu Trp Asp Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 626 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Ala Lys Ala Ala Tyr Asp
Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp
Tyr Phe Ala Lys Leu Trp Asp Pro Trp Arg Trp Trp Trp Trp;
- 30 SEQ ID NO: 627 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala
Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val
Lys Asp Tyr Phe Ala Lys Leu Trp Asp (GABA) Pro Trp Arg Trp Trp Trp Trp;
- SEQ ID NO: 628 PRO Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys
Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr
35 Phe Ala Lys Leu Trp Asp Trp Arg Trp Trp Trp TRP;
- SEQ ID NO: 629 PRO Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Ala Lys Ala Ala Tyr Asp
Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp
Tyr Phe Ala Lys Leu Trp Asp Pro Trp Arg Trp Trp Trp TRP;

SEQ ID NO: 630 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp (GABA) Pro Trp Arg Trp Trp Trp TRP;

SEQ ID NO: 631 Pro Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp Trp Trp Trp Trp Arg Trp;

SEQ ID NO: 632 Pro Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp Pro Trp Trp Trp Trp Arg Trp;

SEQ ID NO: 633 Pro Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp (GABA) Pro Trp Trp Trp Trp Arg Trp;

SEQ ID NO: 634 PRO Arg Gly Gly Ser Val Leu Val Thr Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp Trp Trp Trp Trp Arg TRP;

SEQ ID NO: 635 PRO Arg Gly Gly Ser Val Leu Val Thr Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp Pro Trp Trp Trp Trp Arg TRP;

SEQ ID NO: 636 PRO Arg Gly Gly Ser Val Leu Val Thr (GABA) Pro Asp Trp Ala Lys Ala Ala Tyr Asp Lys Ala Ala Glu Lys Ala Lys Glu Ala Ala Pro Phe Ala Glu Lys Leu Lys Glu Ala Val Lys Asp Tyr Phe Ala Lys Leu Trp Asp (GABA) Pro Trp Trp Trp Trp Arg TRP.

It is to be understood that the letters in the generic formulae I through XVIII or in components thereof are defined by the text that follows each letter and do not designate an individual amino acid.

It is to be understood that in some embodiments, one or more of the amino acids of the peptides of the present invention are D amino acids. In one embodiment, the N-terminal amino acid, the C-terminal amino acid or both are D amino acids. The presence of these D amino acids can help protect against peptide degradation. In another embodiment, all the amino acids of the peptides of the present invention are D amino acids. This embodiment is useful for protection against degradation following oral administration of a pharmaceutical composition comprising the peptides of the present invention.

N-Terminal Modification and/or C-terminal Modification of the Peptides of the Present Invention

The peptides of the present invention may optionally be acetylated at the N-terminus. The peptides of the present invention may optionally have a carboxy terminal amide. In some embodiments, the peptides of the present invention may have both an acetylated N-terminus and a carboxy terminal amide. Methods of acetylating the N-terminus or adding a carboxy terminal amide are well known to one of ordinary skill in the art. While it is to be understood that any of the

peptides disclosed in this application may be modified at the N-terminus, at the C-terminus, or both at the N-terminus and at the C-terminus, the following sequences are presented as exemplary embodiments.

- SEQ ID NO: 637 Ac-Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu
 5 Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr
 Thr Lys Lys Leu Asn Thr Gln-NH₂;
 SEQ ID NO: 638 Ac-Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu
 Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr
 Thr Lys Lys Leu Asn Thr Gln-NH₂;
 10 SEQ ID NO: 639 Ac-Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn
 Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys-NH₂;
 SEQ ID NO: 640 Ac-Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met
 Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe
 Ac-Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp
 15 Trp Trp Trp-NH₂;
 SEQ ID NO: 641 Ac-Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Gly Glu Glu Met
 Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe
 Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln-NH₂;
 SEQ ID NO: 642 Ac-Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala
 20 Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe
 Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp
 Trp Trp-NH₂;
 SEQ ID NO: 643 Ac-Ser Pro Leu Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu
 Arg Thr His Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr
 25 Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp-NH₂;
 SEQ ID NO: 644 Ac-Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala
 Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr
 Thr Lys Lys Leu Asn Thr Gln-NH₂;
 SEQ ID NO: 645 Ac-Pro Arg Gly Gly Ser Val Leu Val Thr Leu Pro Ser Leu Lys Leu Glu Ser Ala
 30 Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe
 Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln-NH₂;
 SEQ ID NO: 646 Ac-Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala
 Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr
 Thr Lys Lys Ala Leu Ser Pro Leu Trp Arg Trp Trp Trp Trp-NH₂;
 35 SEQ ID NO: 647 Ac-Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys
 Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys-
 NH₂;
 SEQ ID NO: 649 Ac-Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys
 Pro Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys-NH₂

Modified Peptides of the Present Invention

The present invention may be used for the production of the peptides or peptide analogs of the present invention. "Proteins", "peptides," "polypeptides" and "oligopeptides" are chains of amino acids (typically L-amino acids) whose alpha carbons are linked through peptide bonds formed by a condensation reaction between the carboxyl group of the alpha carbon of one amino acid and the amino group of the alpha carbon of another amino acid. The terminal amino acid at one end of the chain (i.e., the amino terminal) has a free amino group, while the terminal amino acid at the other end of the chain (i.e., the carboxy terminal) has a free carboxyl group. As such, the term "amino terminus" (abbreviated N-terminus) refers to the free alpha-amino group on the amino acid at the amino terminal of the protein, or to the alpha-amino group (imino group when participating in a peptide bond) of an amino acid at any other location within the protein. Similarly, the term "carboxy terminus" (abbreviated C-terminus) refers to the free carboxyl group on the amino acid at the carboxy terminus of a protein, or to the carboxyl group of an amino acid at any other location within the protein.

Typically, the amino acids making up a protein are numbered in order, starting at the amino terminal and increasing in the direction toward the carboxy terminal of the protein. Thus, when one amino acid is said to "follow" another, that amino acid is positioned closer to the carboxy terminal of the protein than the preceding amino acid.

The term "residue" is used herein to refer to an amino acid (D or L) or an amino acid mimetic that is incorporated into a protein by an amide bond. When a D amino acid is present in the peptides of the present invention, the three letter designation for the amino acid appears in upper case instead of a capital letter. For example the amino acid serine, represented as Ser indicates an L amino acid. The D amino acid form is represented as the upper case letters SER. This is not to be confused with letters appearing as subscripts used in generic formula and defined as variables herein. As such, the amino acid may be a naturally occurring amino acid or, unless otherwise limited, may encompass known analogs of natural amino acids that function in a manner similar to the naturally occurring amino acids (i.e., amino acid mimetics). Moreover, an amide bond mimetic includes peptide backbone modifications well known to those skilled in the art.

Furthermore, one of skill will recognize that, as mentioned above, individual substitutions, deletions or additions which alter, add or delete a single amino acid or a small percentage of amino acids (typically less than about 5%, or typically less than about 1%) in a sequence are conservatively modified variations where the alterations result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. The following six groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Serine (S), Threonine (T);
- 2) Aspartic acid (D), Glutamic acid (E);

- 3) Asparagine (N), Glutamine (Q), Histidine (H);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

5 A conservative substitution is a substitution in which the substituting amino acid (naturally occurring or modified) is structurally related to the amino acid being substituted, i.e., has about the same size and electronic properties as the amino acid being substituted. Thus, the substituting amino acid would have the same or a similar functional group in the side chain as the original amino acid. A "conservative substitution" also refers to utilizing a substituting amino acid which is identical to
10 the amino acid being substituted except that a functional group in the side chain is protected with a suitable protecting group. Peptides of the present invention include conservatively substituted peptides, wherein these conservative substitutions occur at 1%, 3%, 5%, 7%, 10%, 15%, 20%, 25%, 30%, 40%, or 50% of the amino acid residues. Peptides of the present invention include peptides that are homologous at 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% of the entire sequence of
15 the peptide.

Suitable protecting groups are described in Green and Wuts, "Protecting Groups in Organic Synthesis", John Wiley and Sons, Chapters 5 and 7, 1991, the teachings of which are incorporated herein by reference. Preferred protecting groups are those which facilitate transport of the peptide through membranes, for example, by reducing the hydrophilicity and increasing the lipophilicity of
20 the peptide, and which can be cleaved, either by hydrolysis or enzymatically (Ditter et al., 1968. J. Pharm. Sci. 57:783; Ditter et al., 1968. J. Pharm. Sci. 57:828; Ditter et al., 1969. J. Pharm. Sci. 58:557; King et al., 1987. Biochemistry 26:2294; Lindberg et al., 1989. Drug Metabolism and Disposition 17:311; Tunek et al., 1988. Biochem. Pharm. 37:3867; Anderson et al., 1985 Arch. Biochem. Biophys. 239:538; and Singhal et al., 1987. FASEB J. 1:220). Suitable hydroxyl
25 protecting groups include ester, carbonate and carbamate protecting groups. Suitable amine protecting groups include acyl groups and alkoxy or aryloxy carbonyl groups, as described above for N-terminal protecting groups. Suitable carboxylic acid protecting groups include aliphatic, benzyl and aryl esters, as described below for C-terminal protecting groups. In one embodiment, the carboxylic acid group in the side chain of one or more glutamic acid or aspartic acid residues in a
30 peptide of the present invention is protected, preferably as a methyl, ethyl, benzyl or substituted benzyl ester, more preferably as a benzyl ester.

Provided below are groups of naturally occurring and modified amino acids in which each amino acid in a group has similar electronic and steric properties. Thus, a conservative substitution can be made by substituting an amino acid with another amino acid from the same group. It is to be
35 understood that these groups are non-limiting, i.e. that there are additional modified amino acids which could be included in each group.

Group I includes leucine, isoleucine, valine, methionine and modified amino acids having the following side chains: ethyl, n-propyl n-butyl. Preferably, Group I includes leucine, isoleucine, valine and methionine.

Group II includes glycine, alanine, valine and a modified amino acid having an ethyl side chain. Preferably, Group II includes glycine and alanine.

Group III includes phenylalanine, phenylglycine, tyrosine, tryptophan, cyclohexylmethyl glycine, and modified amino residues having substituted benzyl or phenyl side chains. Preferred substituents include one or more of the following: halogen, methyl, ethyl, nitro, —NH_2 , methoxy, ethoxy and —CN . Preferably, Group III includes phenylalanine, tyrosine and tryptophan.

Group IV includes glutamic acid, aspartic acid, a substituted or unsubstituted aliphatic, aromatic or benzylic ester of glutamic or aspartic acid (e.g., methyl, ethyl, n-propyl iso-propyl, cyclohexyl, benzyl or substituted benzyl), glutamine, asparagine, —CO—NH— alkylated glutamine or asparagines (e.g., methyl, ethyl, n-propyl and iso-propyl) and modified amino acids having the side chain $\text{—(CH}_2)_3\text{—COOH}$, an ester thereof (substituted or unsubstituted aliphatic, aromatic or benzylic ester), an amide thereof and a substituted or unsubstituted N-alkylated amide thereof. Preferably, Group IV includes glutamic acid, aspartic acid, methyl aspartate, ethyl aspartate, benzyl aspartate and methyl glutamate, ethyl glutamate and benzyl glutamate, glutamine and asparagine.

Group V includes histidine, lysine, ornithine, arginine, N-nitroarginine, β -cycloarginine, γ -hydroxyarginine, N-amidinocitruline and 2-amino-4-guanidinobutanoic acid, homologs of lysine, homologs of arginine and homologs of ornithine. Preferably, Group V includes histidine, lysine, arginine and ornithine. A homolog of an amino acid includes from 1 to about 3 additional or subtracted methylene units in the side chain.

Group VI includes serine, threonine, and modified amino acids having C1-C5 straight or branched alkyl side chains substituted with —OH or —SH , for example, $\text{—CH}_2\text{CH}_2\text{OH}$, $\text{—CH}_2\text{CH}_2\text{CH}_2\text{OH}$ or $\text{—CH}_2\text{CH}_2\text{OHCH}_3$. Preferably, Group VI includes serine, or threonine.

In another aspect, suitable substitutions for amino acid residues include “severe” substitutions. A “severe substitution” is a substitution in which the substituting amino acid (naturally occurring or modified) has significantly different size and/or electronic properties compared with the amino acid being substituted. Thus, the side chain of the substituting amino acid can be significantly larger (or smaller) than the side chain of the amino acid being substituted and/or can have functional groups with significantly different electronic properties than the amino acid being substituted. Examples of severe substitutions of this type include the substitution of phenylalanine or cyclohexylmethyl glycine for alanine, isoleucine for glycine, a D amino acid for the corresponding L amino acid, or $\text{—NH—CH[(—CH}_2)_5\text{—COOH]—CO—}$ for aspartic acid. Alternatively, a functional group may be added to the side chain, deleted from the side chain or exchanged with another functional group. Examples of severe substitutions of this type include adding of valine, leucine or isoleucine, exchanging the carboxylic acid in the side chain of aspartic acid or glutamic acid with an amine, or deleting the amine group in the side chain of lysine or ornithine. In yet another alternative, the side chain of the substituting amino acid can have

significantly different steric and electronic properties that the functional group of the amino acid being substituted. Examples of such modifications include tryptophan for glycine, lysine for aspartic acid and $-(CH_2)_4COOH$ for the side chain of serine. These examples are not meant to be limiting.

5 In addition to the naturally occurring genetically encoded amino acids, amino acid residues in the peptides may be substituted with naturally occurring non-encoded amino acids and synthetic amino acids. Certain commonly encountered amino acids which provide useful substitutions include, but are not limited to, β -alanine and other omega-amino acids, such as 3-aminopropionic acid, 2,3-diaminopropionic acid, 4-aminobutyric acid and the like; α -aminoisobutyric acid; ϵ -aminohexanoic acid; δ -aminovaleric acid; N-methylglycine or sarcosine; 10 ornithine; citrulline; t-butylalanine; t-butylglycine; N-methylisoleucine; phenylglycine; cyclohexylalanine; norleucine; naphthylalanine; 4-chlorophenylalanine; 2-fluorophenylalanine; 3-fluorophenylalanine; 4-fluorophenylalanine; penicillamine; 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; β 2-thienylalanine; methionine sulfoxide; homoarginine; N-acetyl lysine; 2,4-15 diaminobutyric acid; 2,3-diaminobutyric acid; p-aminophenylalanine; N-methyl valine; homocysteine; homophenylalanine; homoserine; hydroxyproline; homoproline; N-methylated amino acids; and peptoids (N-substituted glycines).

While in certain embodiments, the amino acids of the peptides will be substituted with L-amino acids, the substitutions are not limited to L-amino acids. Thus, also encompassed by the 20 present disclosure are modified forms of the peptides, wherein an L-amino acid is replaced with an identical D-amino acid (*e.g.*, L-Arg $\rightarrow$ D-Arg) or with a conservatively-substituted D-amino acid (*e.g.*, LArg $\rightarrow$ D-Lys), and vice versa.

Additional aspects of the disclosure include analogs, variants, derivatives, and mimetics based on the amino acid sequence of the peptides disclosed herein. Typically, mimetic 25 compounds are synthetic compounds having a three-dimensional structure (of at least part of the mimetic compound) that mimics, for example, the primary, secondary, and/or tertiary structural, and/or electrochemical characteristics of a selected peptide, structural domain, active site, or binding region (*e.g.*, a homotypic or heterotypic binding site, a catalytic active site or domain, a receptor or ligand binding interface or domain, or a structural motif) thereof. The mimetic 30 compound will often share a desired biological activity with a native peptide, as discussed herein (*e.g.*, the ability to interact with lipids). Typically, at least one subject biological activity of the mimetic compound is not substantially reduced in comparison to, and is often the same as or greater than, the activity of the native peptide on which the mimetic was modeled.

A variety of techniques well known to one of skill in the art are available for constructing 35 synthetic peptide mimetics with the same, similar, increased, or reduced biological activity as the corresponding native peptide. Often these analogs, variants, derivatives and mimetics will exhibit one or more desired activities that are distinct or improved from the corresponding native peptide, for example, improved characteristics of solubility, stability, lipid interaction, and/or susceptibility to hydrolysis or proteolysis (see, *e.g.*, Morgan and Gainor, *Ann. Rep. Med. Chem.*

24:243-252, 1989). In addition, mimetic compounds of the disclosure can have other desired characteristics that enhance their therapeutic application, such as increased cell permeability, greater affinity and/or avidity for a binding partner, and/or prolonged biological half-life. The mimetic compounds of the disclosure can have a backbone that is partially or completely non-peptide, but with side groups identical to the side groups of the amino acid residues that occur in the peptide on which the mimetic compound is modeled. Several types of chemical bonds, for example, ester, thioester, thioamide, retroamide, reduced carbonyl, dimethylene and ketomethylene bonds, are known in the art to be generally useful substitutes for peptide bonds in the construction of protease-resistant mimetic compounds.

In one embodiment, peptides useful within the disclosure are modified to produce synthetic peptide mimetics by replacement of one or more naturally occurring side chains of the 20 genetically encoded amino acids (or D-amino acids) with other side chains, for example with groups such as alkyl, lower alkyl, cyclic 4-, 5-, 6-, to 7-membered alkyl, amide, amide lower alkyl, amide di(lower alkyl), lower alkoxy, hydroxy, carboxy and the lower ester derivatives thereof, and with 4-, 5-, 6-, to 7-membered heterocyclics. For example, proline analogs can be made in which the ring size of the proline residue is changed from a 5-membered ring to a 4-, 6-, or 7-membered ring. Cyclic groups can be saturated or unsaturated, and if unsaturated, can be aromatic or non-aromatic. Heterocyclic groups can contain one or more nitrogen, oxygen, and/or sulphur heteroatoms. Examples of such groups include furazanyl, furyl, imidazolidinyl, imidazolyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl (*e.g.*, morpholino), oxazolyl, piperazinyl (*e.g.*, 1-piperazinyl), piperidyl (*e.g.*, 1-piperidyl, piperidino), pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl (*e.g.*, 1-pyrrolidinyl), pyrrolinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, thiomorpholinyl (*e.g.*, thiomorpholino), and thiazolyl groups. These heterocyclic groups can be substituted or unsubstituted. Where a group is substituted, the substituent can be alkyl, alkoxy, halogen, oxygen, or substituted or unsubstituted phenyl. Peptides, as well as peptide analogs and mimetics, can also be covalently bound to one or more of a variety of nonproteinaceous polymers, for example, polyethylene glycol, polypropylene glycol, or polyoxyalkenes, as described in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; and 4,179,337.

Other peptide analogs and mimetics within the scope of the disclosure include glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in amino acid side chains or at the N- or C-termini, by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues (*e.g.*, lysine or arginine). Acyl groups are selected from the group of alkyl-moieties including C3 to C18 alkyl, thereby forming alkanoyl aroyl species. Also embraced are

versions of a native primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, for example, phosphotyrosine, phosphoserine, or phosphothreonine, or other moieties, including ribosyl groups or cross-linking reagents.

5 In the peptides disclosed herein, the linkage between amino acid residues can be a peptide bond or amide linkage (*e.g.*, -C-C(O)NH-). Alternatively, one or more amide linkages is optionally replaced with a linkage other than amide, for example, a substituted amide. Substituted amides generally include, but are not limited to, groups of the formula -C(O)NR-, where R is (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl, (C₅-C₂₀) aryl, substituted (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, substituted (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl, substituted 5-20 membered heteroaryl, 6-26 membered alkheteroaryl, and substituted 6-26 membered alkheteroaryl. Additionally, one or more amide linkages can be replaced with peptidomimetic or amide mimetic moieties which do not significantly interfere with the structure or activity of the peptides. Suitable amide mimetic moieties are described, for example, in Olson *et al.*, *J. Med. Chem.* 15 36:3039-3049, 1993.

The peptides of the present invention may optionally be acetylated at the N-terminus. The peptides of the present invention may optionally have a carboxy terminal amide. In some embodiments, the peptides of the present invention may have both an acetylated N-terminus and a carboxy terminal amide. Methods of acetylating the N-terminus or adding a carboxy terminal amide are well known to one of ordinary skill in the art. 20

IV. Overview of Several Embodiments

Isolated peptides and peptide analogs with domains that promote lipid efflux from cells are disclosed herein. The isolated peptides and peptide analogs are believed to stimulate LCAT activity. In some embodiments, the isolated peptides and peptide analogs of the present invention contain domains that promote lipid efflux and also possess anti-inflammatory activity, for example the A and C domains in the ABC peptides or the X and Z domains in the XYZ peptides. Isolated peptides and peptide analogs that also include an additional functional domain or peptide are also disclosed herein. This additional functional domain provides anti-inflammatory biological activity, especially with regard to the domains indicated by W and/or D. This additional anti-inflammatory domain, or the domains that possess both lipid efflux and anti-inflammatory activity, provide additional benefit as many vascular conditions are considered by one of ordinary skill in the art to have inflammation as a component of the disease etiology. 25 30

For administration to an animal or a human, the peptides and peptide analogs of the present invention are combined with an acceptable carrier to form a pharmaceutical composition and are administered to the animal or the human. 35

In another embodiment, a method is provided for treating or inhibiting dyslipidemic and vascular disorders in an animal or a human. This method includes administering to the animal or the human a therapeutically effective amount of a pharmaceutical composition that includes one

or more isolated peptides or peptide analogs and one or more anti-inflammatory domains. In specific, non-limiting examples, the dyslipidemic and vascular disorders include hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, HDL deficiency, apoA-I deficiency, coronary artery disease, atherosclerosis, myocardial infarction, stroke, thrombotic stroke, peripheral vascular disease, restenosis, acute coronary syndrome, and reperfusion myocardial injury. In yet another specific example of the provided method, the isolated peptide includes two domains, one or more anti-inflammatory domains (D and W) and has an amino acid sequence as set forth herein. In yet another specific example of the provided method, the isolated peptide includes a domain or domains (A and C, X and Z) that possess both anti-inflammatory and lipid efflux activity and has an amino acid sequence as set forth herein.

Additionally, in representative peptides disclosed herein, the amino- and carboxy-terminal ends can be modified by conjugation with various functional groups. Neutralization of the terminal charge of synthetic peptide mimetics of apolipoproteins has been shown to increase their lipid affinity (Yancey *et al.*, *Biochem.* 34:7955-7965, 1995; Venkatachalapathi *et al.*, *Protein: Structure, Function and Genetics* 15:349-359, 1993). For example, acetylation of the amino terminal end of amphipathic peptides increases the lipid affinity of the peptide (Mishra *et al.*, *J. Biol. Chem.* 269:7185-7191, 1994). Other possible end modifications are described, for example, in Brouillette *et al.*, *Biochem. Biophys. Acta* 1256:103-129, 1995; Mishra *et al.*, *J. Biol. Chem.* 269:7185-7191, 1994; and Mishra *et al.*, *J. Biol. Chem.* 270:1602-1611, 1995.

In another embodiment, a detectable moiety can be linked to any of the peptides disclosed herein, creating a peptide-detectable moiety conjugate. The peptides or peptide analogs disclosed herein may be labeled using labels and techniques known to one of ordinary skill in the art. Some of these labels are described in the "Handbook of Fluorescent Probes and Research Products", ninth edition, Richard P. Haugland (ed) Molecular Probes, Inc. Eugene, OR), which is incorporated herein in its entirety. Detectable moieties suitable for such use include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical, magnetic or chemical means. The detectable moieties contemplated for the present disclosure can include, but are not limited to, an immunofluorescent moiety (*e.g.*, fluorescein, rhodamine, Texas red, and the like), a radioactive moiety (*e.g.*, ^3H , ^{32}P , ^{125}I , ^{131}I , ^{35}S), an enzyme moiety (*e.g.*, horseradish peroxidase, alkaline phosphatase), a colorimetric moiety (*e.g.*, colloidal gold, biotin, colored glass or plastic, and the like). The detectable moiety can be linked to the peptide or peptide analog at either the N- and/or C-terminus. Optionally, a linker can be included between the peptide or peptide analog and the detectable moiety.

The detectable peptides of the present invention may be employed in imaging techniques to identify sites of atherosclerotic plaque and sites of cholesterol efflux. Such imaging techniques may occur in vivo using IVUS, NMR, CAT, PET or other techniques commonly known to one of ordinary skill in the art.

Means of detecting such moieties are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film, gamma counters or scintillation

counters. Fluorescent markers may be detected using a photodetector to detect emitted illumination. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

5 The linkers contemplated by the present disclosure can be any bifunctional molecule capable of covalently linking two peptides to one another. Thus, suitable linkers are bifunctional molecules in which the functional groups are capable of being covalently attached to the N- and/or C-terminus of a peptide. Functional groups suitable for attachment to the N- or C-terminus of peptides are well known in the art, as are suitable chemistries for effecting such
10 covalent bond formation.

The linker may be flexible, rigid or semi-rigid. Suitable linkers include, for example, amino acid residues such as Pro or Gly or peptide segments containing from about 2 to about 5, 10, 15, 20, or even more amino acids, bifunctional organic compounds such as $H_2N(CH_2)_nCOOH$ where n is an integer from 1 to 12, and the like. Examples of such linkers, as well as methods of
15 making such linkers and peptides incorporating such linkers, are well-known in the art (see, e.g., Hunig *et al.*, *Chem. Ber.* 100:3039-3044, 1974 and Basak *et al.*, *Bioconjug. Chem.* 5:301-305, 1994).

Conjugation methods applicable to the present disclosure include, by way of non-limiting example, reductive amination, diazo coupling, thioether bond, disulfide-bond, amidation and
20 thiocarbamoyl chemistries. In one embodiment, the amphipathic α -helical domains are "activated" prior to conjugation. Activation provides the necessary chemical groups for the conjugation reaction to occur. In one specific, non-limiting example, the activation step includes derivatization with adipic acid dihydrazide. In another specific, non-limiting example, the activation step includes derivatization with the *N*-hydroxysuccinimide ester of 3-(2-pyridyl
25 dithio)-propionic acid. In yet another specific, non-limiting example, the activation step includes derivatization with succinimidyl 3-(bromoacetamido) propionate. Further, non-limiting examples of derivatizing agents include succinimidylformylbenzoate and succinimidyllevulinate.

V. *Synthesis and Purification of the Peptides*

30 The peptides or peptide analogs of the disclosure can be prepared using virtually any technique known to one of ordinary skill in the art for the preparation of peptides. For example, the peptides can be prepared using step-wise solution or solid phase peptide syntheses, or recombinant DNA techniques, or the equivalents thereof

A. *Chemical Synthesis*

35 Peptides of the disclosure containing amino acids having either the D- or L-configuration can be readily synthesized by automated solid phase procedures well known in the art. Suitable syntheses can be performed by utilizing "T-boc" or "F-moc" procedures. Techniques and procedures for solid phase synthesis are described in *Solid Phase Peptide Synthesis: A Practical Approach*, by E. Atherton and R. C. Sheppard, published by IRL, Oxford University Press, 1989.

Alternatively, the peptides may be prepared by way of segment condensation, as described, for example, in Liu *et al.*, *Tetrahedron Lett.* 37:933-936, 1996; Baca *et al.*, *J. Am. Chem. Soc.* 117:1881-1887, 1995; Tam *et al.*, *Int. J. Peptide Protein Res.* 45:209-216, 1995; Schnolzer and Kent, *Science* 256:221-225, 1992; Liu and Tam, *J. Am. Chem. Soc.* 116:4149-4153, 1994; Liu and Tam, *Proc. Natl. Acad. Sci. USA* 91:6584-6588, 1994; and Yamashiro and Li, *Int. J. Peptide Protein Res.* 31:322-334, 1988). This is particularly the case with glycine containing peptides. Other methods useful for synthesizing the peptides of the disclosure are described in Nakagawa *et al.*, *J. Am. Chem. Soc.* 107:7087-7092, 1985.

Additional exemplary techniques known to those of ordinary skill in the art of peptide and peptide analog synthesis are taught by Bodanszky, M. and Bodanszky, A., *The Practice of Peptide Synthesis*, Springer Verlag, New York, 1994; and by Jones, J., *Amino Acid and Peptide Synthesis*, 2nd ed., Oxford University Press, 2002. The Bodanszky and Jones references detail the parameters and techniques for activating and coupling amino acids and amino acid derivatives. Moreover, the references teach how to select, use and remove various useful functional and protecting groups.

Peptides of the disclosure having either the D- or L-configuration can also be readily purchased from commercial suppliers of synthetic peptides. Such suppliers include, for example, Advanced ChemTech (Louisville, KY), Applied Biosystems (Foster City, CA), Anaspec (San Jose, CA), and Cell Essentials (Boston, MA).

B. Recombinant Synthesis

If the peptide is composed entirely of gene-encoded amino acids, or a portion of it is so composed, the peptide or the relevant portion can also be synthesized using conventional recombinant genetic engineering techniques. For recombinant production, a polynucleotide sequence encoding the peptide is inserted into an appropriate expression vehicle, that is, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence, or in the case of an RNA viral vector, the necessary elements for replication and translation. The expression vehicle is then transfected into a suitable target cell which will express the peptide. Depending on the expression system used, the expressed peptide is then isolated by procedures well-established in the art. Methods for recombinant protein and peptide production are well known in the art (see, *e.g.*, Sambrook *et al.* (ed.), *Molecular Cloning: A Laboratory Manual*, 2nd ed., vol. 1-3, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, Ch. 17 and Ausubel *et al.* *Short Protocols in Molecular Biology*, 4th ed., John Wiley & Sons, Inc., 1999).

To increase efficiency of production, the polynucleotide can be designed to encode multiple units of the peptide separated by enzymatic cleavage sites. The resulting polypeptide can be cleaved (*e.g.*, by treatment with the appropriate enzyme) in order to recover the peptide units. This can increase the yield of peptides driven by a single promoter. In one embodiment, a polycistronic polynucleotide can be designed so that a single mRNA is transcribed which encodes multiple peptides, each coding region operatively linked to a cap-independent translation control

sequence, for example, an internal ribosome entry site (IRES). When used in appropriate viral expression systems, the translation of each peptide encoded by the mRNA is directed internally in the transcript, for example, by the IRES. Thus, the polycistronic construct directs the transcription of a single, large polycistronic mRNA which, in turn, directs the translation of multiple, individual peptides. This approach eliminates the production and enzymatic processing of polyproteins and can significantly increase yield of peptide driven by a single promoter.

A variety of host-expression vector systems may be utilized to express the peptides described herein. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage DNA or plasmid DNA expression vectors containing an appropriate coding sequence; yeast or filamentous fungi transformed with recombinant yeast or fungi expression vectors containing an appropriate coding sequence; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing an appropriate coding sequence; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus (CaMV) or tobacco mosaic virus (TMV)) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing an appropriate coding sequence; or animal cell systems.

The expression elements of the expression systems vary in their strength and specificities. Depending on the host/vector system utilized, any of a number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used in the expression vector. For example, when cloning in bacterial systems, inducible promoters such as pL of bacteriophage λ , plac, ptrp, ptac (ptrp-lac hybrid promoter) and the like can be used. When cloning in insect cell systems, promoters such as the baculovirus polyhedron promoter can be used. When cloning in plant cell systems, promoters derived from the genome of plant cells (*e.g.*, heat shock promoters, the promoter for the small subunit of RUBISCO, the promoter for the chlorophyll a/b binding protein) or from plant viruses (*e.g.*, the 35S RNA promoter of CaMV, the coat protein promoter of TMV) can be used. When cloning in mammalian cell systems, promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter, the vaccinia virus 7.5 K promoter) can be used.

C. Purification

The peptides or peptide analogs of the disclosure can be purified by many techniques well known in the art, such as reverse phase chromatography, high performance liquid chromatography, ion exchange chromatography, size exclusion chromatography, affinity chromatography, gel electrophoresis, and the like. The actual conditions used to purify a particular peptide or peptide analog will depend, in part, on synthesis strategy and on factors such as net charge, hydrophobicity, hydrophilicity, and the like, and will be apparent to those of ordinary skill in the art.

For affinity chromatography purification, any antibody which specifically binds the peptide or peptide analog may be used.

The peptides of the present invention may optionally be acetylated at the N-terminus. The peptides of the present invention may optionally have a carboxy terminal amide. In some embodiments, the peptides of the present invention may have both an acetylated N-terminus and a carboxy terminal amide. Methods of acetylating the N-terminus or adding a carboxy terminal amide are well known to one of ordinary skill in the art.

D. Antibody Production

For the production of antibodies, various host animals, including but not limited to, rabbits, mice, rats, and the like, may be immunized by injection with a peptide or peptide analog. The peptide or peptide analog can be attached to a suitable carrier (e.g., bovine serum albumin (BSA)) by means of a side chain functional group or linker attached to a side chain functional group. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, and oil emulsions), keyhole limpet hemocyanin, dinitrophenol, and potentially useful human adjuvants such as BCG (bacilli Calmette-Guerin) and *Corynebacterium parvum*.

Booster injections can be given at regular intervals, and antiserum harvested when the antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, e.g., Ouchterlony *et al.*, *Handbook of Experimental Immunology*, Wier, D. (ed.), Chapter 19, Blackwell, 1973. A plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 μ M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher (*Manual of Clinical Immunology*, Ch. 42, 1980).

Monoclonal antibodies to a peptide or peptide analog may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture, for example the classic method of Kohler & Milstein (*Nature* 256:495-97, 1975), or a derivative method thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein immunogen (e.g., a peptide or peptide analog) over a period of a few weeks. The mouse is then sacrificed, and the antibody-producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as enzyme-linked immunosorbent assay (ELISA), as originally described by Engvall (*Meth. Enzymol.*, 70:419-39, 1980), or a derivative method thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Harlow and Lane, *Using Antibodies: A Laboratory Manual*, CSHL, New York, 1999. Polyclonal antiserum containing

antibodies can be prepared by immunizing suitable animals with a polypeptide comprising at least one peptide or peptide analog, which can be unmodified or modified, to enhance immunogenicity.

Antibody fragments may be used in place of whole antibodies and may be readily expressed in prokaryotic host cells. Methods of making and using immunologically effective portions of monoclonal antibodies, also referred to as "antibody fragments," are well known and include those described in Better & Horowitz, *Methods Enzymol.* 178:476-96, 1989; Glockshuber *et al.*, *Biochemistry* 29:1362-67, 1990; and U.S. Patent Nos. 5,648,237 (Expression of Functional Antibody Fragments); 4,946,778 (Single Polypeptide Chain Binding Molecules); and 5,455,030 (Immunotherapy Using Single Chain Polypeptide Binding Molecules), and references cited therein. Conditions whereby a polypeptide/binding agent complex can form, as well as assays for the detection of the formation of a polypeptide/binding agent complex and quantitation of binding affinities of the binding agent and polypeptide, are standard in the art. Such assays can include, but are not limited to, Western blotting, immunoprecipitation, immunofluorescence, immunocytochemistry, immunohistochemistry, fluorescence activated cell sorting (FACS), fluorescence *in situ* hybridization (FISH), immunomagnetic assays, ELISA, ELISPOT (Coligan *et al.*, *Current Protocols in Immunology*, Wiley, NY, 1995), agglutination assays, flocculation assays, cell panning, etc., as are well known to one of skill in the art.

E. Peptide Reconstitution

The peptides of the present invention may be reconstituted in any pharmaceutically acceptable carrier before use or administration. In one embodiment, the peptides may be reconstituted with saline, a lipid or a phospholipid, or a combination thereof. Some phospholipids that may be employed include but are not limited to the following: dipalmitoylphosphatidylcholine (DPPC); dioleoylphosphatidylcholine (DOPC); 1-palmitoyl-2-oleoylphosphatidylcholine (POPC); 1-palmitoyl-2-linoleoylphosphatidylcholine (PLPC); 1-palmitoyl-2-arachidonylphosphatidylcholine (PAPC); 1-palmitoyl-2-docosahexanoylphosphatidylcholine (PDPC); and, PMLC. DPPC, DOPC have been used to reconstitute peptides (Shah *et al.*, *Circulation*. 2001 Jun 26;103(25):3047-50.)

The peptides of the present invention may be complexed with lipids or phospholipids in weight ratios ranging from 1:0.5 to 1:10, or 1:1 to 1: 5. Any ratio within these ranges may be employed.

The phospholipids may also be complexed with other agents, such as sphingomyelin before complexing with the peptides of the present invention. Ratios of phospholipids to sphingomyelin include ratios occurring in the ranges of 1:9 to 9:1, 1:5 to 5:1, 1.2 to 2.1 (all weight %).

The peptides of the present invention may be complexed with the combination of phospholipid:sphingomyelin in weight ratios ranging from 1:0.5 to 1:10, or 1:1 to 1: 5. Any ratio within these ranges may be employed.

VI. *Pharmaceutical Compositions and Uses Thereof*

The peptides or peptide analogs of the disclosure can be used, alone or in combination, together with a pharmaceutically acceptable carrier, to treat any disorder in animals, especially mammals (*e.g.*, humans), for which promoting lipid efflux and/or decreasing inflammation is beneficial. Such conditions include, but are not limited to, hyperlipidemia (*e.g.*, hypercholesterolemia), cardiovascular disease (*e.g.*, atherosclerosis), cerebrovascular disease, restenosis (*e.g.*, atherosclerotic plaques), peripheral vascular disease, acute coronary syndrome, reperfusion myocardial injury, and the like. The peptides or peptide analogs of the disclosure can also be used alone or in combination during the treatment of thrombotic stroke, infarcts secondary to occlusion of a vessel and during thrombolytic treatment of occluded coronary artery disease. The peptides or peptide analogs of the disclosure can be used to treat tissue following hypoxia, ischemia and infarction due to impairment of blood supply, and also following hemorrhage following rupture or trauma of a blood vessel. Such tissue includes, without limitation, neural tissue in the central or peripheral nervous system, peripheral vascular tissue, and cardiac muscle.

It is to be understood that a mixture of peptides may include different amounts of the individual peptides. For example, in one embodiment, each peptide component of the combination may be present in a different relative percentage than each other peptide component due to differences in relative efficacy to promote lipid efflux or to provide one or more types of anti-inflammatory activity. In one exemplary embodiment, one or more of the peptides shown in SEQ ID NOs: 121, 130, 155, 638, 644, may be combined in a mixture for administration.

The peptides or peptide analogs can be used alone or in combination therapy with other lipid lowering compositions or drugs and/or other anti-inflammatory compositions or drugs used to treat the foregoing conditions. Such therapies include, but are not limited to simultaneous or sequential administration of the drugs involved. For example, in the treatment of hypercholesterolemia or atherosclerosis, the peptide or peptide analog formulations can be administered with any one or more of the cholesterol lowering therapies currently in use, for example, bile-acid resins, niacin, statins, fat uptake inhibitors, and HDL raising drugs.

In another embodiment, the peptides or peptide analogs can be used in conjunction with statins or fibrates to treat hyperlipidemia, hypercholesterolemia and/or cardiovascular disease, such as atherosclerosis. In yet another embodiment, the peptides or peptide analogs of the disclosure can be used in combination with an anti-microbial agent and/or an anti-inflammatory agent, such as aspirin. In another embodiment peptides or peptide analogs of the disclosure can be used in combination with anti-hypertensive medicines known to one of ordinary skill in the art. It is to be understood that more than one additional therapy may be combined with administration of the peptides or peptide analogs of the disclosure.

In a further embodiment, the peptides can also be expressed *in vivo*, by using any of the available gene therapy approaches.

In yet another embodiment, the peptides or peptide analogs can be used in conjunction with medicines used to treat patients with cerebrovascular and cardiovascular disease resulting in

hypoxia, ischemia and infarction due to impairment of blood supply, and also following hemorrhage following rupture or trauma of a blood vessel. Such medicines are commonly known to one of ordinary skill in the art and include without limitation, modulators of excitatory amino acids and modulators of platelet aggregation.

5 A. Administration of Peptides or Peptide Analogs

In some embodiments, peptides or peptide analogs can be isolated from various sources and administered directly to the animal or human. For example, a peptide or peptide analog can be expressed *in vitro*, such as in an *E. coli* expression system, as is well known in the art, and isolated in amounts useful for therapeutic compositions. The peptide or peptide analogs of the
10 present invention may also be made through peptide synthetic methods known to one of ordinary skill in the art, such as solid phase synthesis.

In exemplary applications, therapeutic compositions comprising the peptide or peptide analogs in an acceptable carrier are administered to an animal or a human suffering from a dyslipidemic or vascular disorder, such as hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia, HDL deficiency, apoA-I deficiency, coronary artery disease, atherosclerosis, stroke, ischemia, infarction, myocardial infarction, hemorrhage, peripheral vascular disease, restenosis, acute coronary syndrome, or reperfusion myocardial injury, in an amount sufficient to inhibit or treat the dyslipidemic or vascular disorder. Amounts effective for this use will depend upon the severity of the disorder and the general state of the
15 subject's health. A therapeutically effective amount of the compound is that which provides either subjective relief of a symptom(s) or an objectively identifiable improvement as noted by the clinician or other qualified observer.

A peptide or peptide analog can be administered by any means known to one of skill in the art (see, *e.g.*, Banga, "Parenteral Controlled Delivery of Therapeutic Peptides and Proteins,"
25 in *Therapeutic Peptides and Proteins*, Technomic Publishing Co., Inc., Lancaster, PA, 1995), such as by intramuscular, subcutaneous, or intravenous injection, but even oral, nasal, or anal administration is contemplated. In one embodiment, administration is by subcutaneous or intramuscular injection. To extend the time during which the peptide or peptide analog is available to inhibit or treat a dyslipidemic or vascular disorder, the peptide or peptide analog can be provided as an implant, an oily injection, or as a particulate system. The particulate system can be a microparticle, a microcapsule, a microsphere, a nanoparticle, or similar particle (Banga, "Parenteral Controlled Delivery of Therapeutic Peptides and Proteins," in *Therapeutic Peptides and Proteins*, Technomic Publishing Co., Inc., Lancaster, PA, 1995). The peptide or peptide analog may also be applied to a medical device for delivery to a specific location. For example, a
30 surgical tool, catheter, stent, balloon, electrode, suture, or an artificial vessel or transplanted vessel may contain or be coated with the peptide or peptide analog.

It is to be understood that in some embodiments, one or more of the amino acids of the peptides of the present invention are D amino acids. In one embodiment, the N-terminal amino acid, the C-terminal amino acid or both are D amino acids. The presence of these D amino acids

can help protect against peptide degradation. In another embodiment, all the amino acids of the peptides of the present invention are D amino acids. This embodiment is useful for protection against degradation following oral administration of a pharmaceutical composition comprising the peptides of the present invention.

5 In one specific, non-limiting example, a peptide is administered that includes one or more of the amino acid sequences disclosed herein.

B. Representative Methods of Administration, Formulations and Dosage

The provided peptides or peptide analogs, constructs, or vectors encoding such peptides, can be combined with a pharmaceutically acceptable carrier (*e.g.*, a phospholipid or other type of
10 lipid) or vehicle for administration to human or animal subjects. As described previously in the application, the peptides may be reconstituted with acceptable carriers such as saline, lipid, phospholipid, lipid:sphingomyelin complexes and phospholipid: sphingomyelin complexes. In some embodiments, more than one peptide or peptide analog can be combined to form a single preparation. The peptides or peptide analogs can be conveniently presented in unit dosage form
15 and prepared using conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants,
20 buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid carrier, for example, water
25 for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets commonly used by one of ordinary skill in the art.

In certain embodiments, unit dosage formulations are those containing a dose or unit, or an appropriate fraction thereof, of the administered ingredient. It should be understood that in
30 addition to the ingredients particularly mentioned above, formulations encompassed herein may include other agents commonly used by one of ordinary skill in the art.

The pharmaceutical compositions provided herein, including those for use in treating dyslipidemic and vascular disorders, may be administered through different routes, such as oral, including buccal and sublingual, rectal, parenteral, aerosol, nasal, intramuscular, intraperitoneal,
35 intravascular, subcutaneous, intradermal, and topical. They may be administered in different forms, including but not limited to solutions, emulsions and suspensions, microspheres, particles, microparticles, nanoparticles, and liposomes. In one embodiment, peptides or peptide analogs with suitable features of lipid efflux and low cytotoxicity can be precomplexed with

phospholipids or other lipids into either discoidal or spherical shape particles prior to administration to subjects.

In another embodiment, it may be desirable to administer the pharmaceutical compositions locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local or regional infusion or perfusion during surgery, direct perfusion into a vessel, such as an atherosclerotic vessel, topical application (e.g., wound dressing, peptide coated stent), injection, catheter, suppository, or implant (e.g., implants formed from porous, non-porous, or gelatinous materials, including membranes, such as silastic membranes or fibers), and the like. In one embodiment, administration can be by direct injection at the site (or former site) of a tissue that is to be treated, such as the heart or the peripheral vasculature. In another embodiment, the pharmaceutical compositions are delivered in a vesicle, in particular liposomes (see, e.g., Langer, *Science* 249:1527-1533, 1990; Treat *et al.*, in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, N.Y., pp. 353-365, 1989). Combinations of administration methods may also be employed such as a systemic or local infusion of a peptide of the present invention, before, after or during placement of a stent coated with a peptide of the present invention.

In yet another embodiment, the pharmaceutical compositions can be delivered in a controlled release system. In one embodiment, a pump can be used (see, e.g., Langer *Science* 249:1527-1533, 1990; Sefton *Crit. Rev. Biomed. Eng.* 14:201-240, 1987; Buchwald *et al.*, *Surgery* 88:507-516, 1980; Saudek *et al.*, *N. Engl. J. Med.* 321:574-579, 1989). In another embodiment, polymeric materials can be used (see, e.g., Ranger *et al.*, *Macromol. Sci. Rev. Macromol. Chem.* 23:61-64, 1983; Levy *et al.*, *Science* 228:190-192, 1985; During *et al.*, *Ann. Neurol.* 25:351-356, 1989; and Howard *et al.*, *J. Neurosurg.* 71:105-112, 1989). Other controlled release systems, such as those discussed in the review by Langer (*Science* 249:1527-1533, 1990), can also be used.

The amount of the pharmaceutical compositions that will be effective depends on the nature of the disorder or condition to be treated, as well as the stage of the disorder or condition. Effective amounts can be determined by standard clinical techniques. The precise dose to be employed in the formulation will also depend on the route of administration, and should be decided according to the judgment of the health care practitioner and each subject's circumstances. An example of such a dosage range is 0.1 to 200 mg/kg body weight in single or divided doses. Another example of a dosage range is 1.0 to 100 mg/kg body weight in single or divided doses.

The specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, and severity of the condition of the subject undergoing therapy.

The pharmaceutical compositions of the present disclosure can be administered at about the same dose throughout a treatment period, in an escalating dose regimen, or in a loading-dose regime (e.g., in which the loading dose is about two to five times the maintenance dose). In some embodiments, the dose is varied during the course of a treatment based on the condition of the subject being treated, the severity of the disease or condition, the apparent response to the therapy, and/or other factors as judged by one of ordinary skill in the art. The volume of administration will vary depending on the route of administration. By way of example, intramuscular injections may range from about 0.1 ml to about 1.0 ml. Those of ordinary skill in the art will know appropriate volumes for different routes of administration.

The following examples will serve to further illustrate the present invention without, at the same time, however, constituting any limitation thereof. On the contrary, it is to be clearly understood that resort may be had to various embodiments, modifications and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the invention.

The subject matter of the present disclosure is further illustrated by the following non-limiting Examples.

Example 1

Lipid efflux from cells mediated by peptides of the present invention

This example demonstrates a method to test the ability of peptides of the present invention to efflux lipid from ABCA1-expressing cells.

HeLa cells stably transfected with human ABCA1 cDNA (ABCA1 cells) and HeLa cells transfected with only a hygromycin-resistant control plasmid (control cells) are produced and grown in α -modified Eagle's medium (aMEM) plus 10% fetal calf serum, as described by Remaley *et al.* (*Biochem. Biophys. Res. Commun.* 280:818-823, 2001). Cholesterol and phospholipid efflux is performed for 18 hours on noncholesterol-loaded cells radiolabeled with either cholesterol or choline (Remaley *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 17:1813-1821, 1997). Percentage efflux is calculated after subtracting the radioactive counts in the blank media (aMEM plus 1 mg/ml of BSA), and expressed as the percent of total radioactive counts removed from the cells during the efflux period.

Cell fixation is performed by a 10 minute treatment with 3% paraformaldehyde in phosphate buffered saline (PBS), followed by three washes with blank media. Lactate dehydrogenase (LDH) release from cells into the media is measured enzymatically (Roche Diagnostics, Indianapolis, IN) and expressed, after subtraction of LDH released into blank media, as the percentage of total cell LDH. Total cell LDH is determined after cell solubilization with 1% Triton X-100.

The peptides of the present invention are synthesized by a solid-phase procedure, using a Fmoc/DIC/HOBt protocol on a Biosearch 9600 peptide synthesizer (Applied Biosystems, Foster City, CA), or an equivalent instrument. Both L-amino acid and D-amino acid enantiomers are

synthesized. All peptides are purified to greater than 98% homogeneity by reverse-phase HPLC on an Aquapore RP-300 column, or similar chromatographic procedure.

ABCA1 cells are used to assess the ability of apoA-I and synthetic peptides to efflux lipid from cells. As previously described (Hamon *et al.*, *Nat. Cell Biol.* 2:399-406, 2000 and Remaley *et al.*, *Biochem. Biophys. Res. Commun.* 280:818-823, 2001), control cells do not efflux significant amounts of cholesterol and phospholipid to apoA-I, but do so after transfection with ABCA1. The peptides of the present invention efflux approximately 2- to 4-fold more cholesterol and phospholipid from ABCA1 cells than from control cells. Both the peptides of the present invention and apoA-I began to show saturation for lipid efflux at approximately the same protein concentration of 10 µg/ml. The peptides of the present invention remove more cholesterol and phospholipids from control cells than apoA-I.

Example 2

Lipid efflux time course

This example demonstrates the cholesterol efflux time course from ABCA1-expressing cells to apoA-I and peptides of the present invention.

Cholesterol efflux from ABCA1 cells to apoA-I is first detectable after 2 hours and increases throughout the 30 hour efflux period. In contrast, there is no significant increase above background in cholesterol efflux to apoA-I from control cells. Overall, the kinetics for cholesterol efflux to peptides of the present invention from ABCA1 cells is similar to that of apoA-I, except that cholesterol efflux is first detectable after 30 minutes. The peptides of the present invention, unlike apoA-I, also promote cholesterol efflux from control cells but at a lower rate.

Example 3

Identification of non-cytotoxic peptides that promote ABCA1-dependent lipid efflux

This example illustrates a method for identifying non-cytotoxic peptides that promote ABCA1-dependent lipid efflux from cells.

Peptide Design: Based on the principles and procedures described in the present application, an amino acid sequence can be designed for a peptide that promotes lipid efflux.

Peptide production: Peptides to be tested can be produced synthetically or by recombinant DNA methods, as described in the present application, and purified by reverse phase HPLC or other suitable techniques well known to one of skill in the art.

Peptide Cytotoxicity Testing: Peptides can be tested for cytotoxicity by any number of methods well known to one of skill in the art, such as the release of intracellular LDH.

Peptide ABCA1-specificity for Lipid Efflux: Peptides to be tested can be added to serum-free cell culture media in the approximate concentration range of 1-20 micrograms and incubated with a control cell line that does not express the ABCA1 transporter and the same cell line after transfection with human cDNA for the ABCA1 transporter, as described herein. Alternatively,

cells, such as macrophages, that either express or do not express the ABCA1 transporter depending on their cholesterol content and/or exposure to agents that induce the ABCA1 transporter (e.g., cAMP and LXR agonists) can also be used. After a suitable period of approximately 4 to 24 hours, the conditioned media can be removed from the cells and the amount of cholesterol and or phospholipid effluxed can be quantified, as described herein. ABCA1-specific lipid efflux is calculated by subtracting the total lipid efflux of the cell line that does not express the ABCA1 transporter from the lipid efflux from the ABCA1 expressing cell line.

Example 4

Peptides of the present invention reduce atherosclerosis in animal models

The ability of the peptides of the present invention and associated fragments are tested in apoE knockout mice on a chow diet and LDL receptor knockout mice on a western high fat diet to determine the effect of these peptides to reduce atherosclerosis in a mouse model system. One or more of the peptides of the present invention, in a range of concentration of 2 mg/kg to 50 mg/kg, is injected intravenously (iv) or intraperitoneally (ip) 2 to 3 times per week over a period of approximately 6 weeks. Aortic atherosclerosis is quantitated in the aortic arch before administration of the peptides and after the 6 week period of administration. (Wu et al., J. Biol. Chem.; 2004: 279, 22913-22925). The results demonstrate reduced atherosclerosis in the aortic arch in mice in both treatment groups.

Example 5

Administration of the peptides of the present invention to treat atherosclerosis in humans

Individuals with acute coronary syndrome and documented atherosclerosis have a cardiac catheterization with intravascular ultrasound (IVUS) to document coronary atherosclerosis of 20 to 50% obstruction in the target artery. Each individual is on stable hypolipidemic drug therapy and receives an acceptable dose of a peptide of the present invention and /or an associated fragment iv weekly for a period of 5 to 8 weeks. A repeat IVUS measurement is made at the end of the treatment period to assess the effect of the peptide infusion on coronary atherosclerosis in the target vessel. Plaque is reduced in the atherosclerotic coronary artery following the peptide treatment demonstrating efficacy of the peptides of the present invention to treat atherosclerosis.

Example 6

Administration of the peptides of the present invention to prevent or delay the onset of atherosclerosis in humans

Individuals with documented risk factors for atherosclerosis and having high plasma cholesterol levels have a ultrasound analysis of the coronary (IVUS), carotid (IMT) or popliteal arteries to establish a baseline measurement. A portion of these individuals are daily administered individual peptides of the present invention at a dose of 2 mg/kg to 50 mg/kg

intravenously (iv) or intramuscular (im) 1 to 3 times per week over a period of approximately one to six months. The other individuals receive a control peptide. A new ultrasound analysis at the end of the treatment period indicates higher levels of plaque in the vessels of individuals receiving the control peptide. This example indicates that the individual peptides of the present invention are effective in preventing or reducing atherosclerosis in individuals at risk for developing atherosclerosis and in reducing plaque accumulation in coronary, carotid or popliteal arteries.

Example 7

Administration of the peptides of the present invention on stents to reduce inflammation and restenosis

Individuals with acute coronary syndrome and having plaque in coronary vessels which require a stent to reduce the obstruction receive an IVUS procedure to document the coronary anatomy. A representative protocol divides these individuals into three groups. One group receives a stent coated with a peptide of the present invention. A second group receives an iv infusion of a peptide of the present invention at a dose of 2 mg/kg to 50 mg/kg, 1 to 3 times per week over a period of approximately 5 to 10 weeks. A third group receives a stent coated with a peptide of the present invention and an iv infusion of a peptide of the present invention at a dose of 2 mg/kg to 50 mg/kg, 1 to 3 times per week over a period of approximately 5 to 10 weeks.

All individuals receive a second IVUS procedure at the end of 5 or 10 weeks. The results demonstrate that individuals receiving either a peptide coated stent, a peptide coated stent plus iv peptide infusion, or iv peptide infusion alone, all display reduced inflammation and restenosis when compared to their condition at the time of the first IVUS procedure.

Example 8

Blockade of ICAM-1/LFA-1 mediated T-cell adhesion to Caco-2 cell monolayers by the peptides of the present invention

The ability of the peptides of the present invention and associated fragments are tested to decrease inflammation by their ability to block the binding of ICAM-1 to LFA-1 using a model cell adhesion assay of T cells (Mott-3) and Caco-2 cells (Anderson et al., Bioorganic & Medicinal Chemistry Letters; 2004:14, 1399-1402). Peptide concentrations of from 0 μ M to 500 μ M are tested. The results demonstrate dose dependent inhibition of ICAM-1/LFA-1 mediated T-cell adhesion to Caco-2 cell monolayers by the peptides of the present invention. While not wanting to be bound by the following statement, it is believed that the D or D' domains of the peptides of the present invention are involved in this inhibitory effect. While not wanting to be bound by the following statement, it is believed in other embodiments that the A or C, or the X and Z, domains of some of the peptides of the present invention are involved in this inhibitory effect.

These results indicate that the interaction of ICAM-1 and LFA-1 in the vessel wall can be blocked by the D domain of the peptides of the present invention, and result in decreased

movement of inflammatory cells, particularly T cells, from the plasma into the vessel wall. A decrease in the influx of inflammatory cells into the vessel wall decreases this inflammatory component of the atherosclerotic process and decreases the frequency of clinical vascular events (Yusuf-Makagiansar, *Inflammation*: 2001; 25,203-213).

5

Example 9

Blockade of neutrophils through inhibition of the formyl peptide receptor-like-1 (FPRL1) by the peptides of the present invention

The anti-inflammatory properties of the peptides of the present invention and associated
10 fragments are tested by evaluating the peptides, and particularly the W and W' domains, and peptides containing these domains, to block the binding of neutrophils to the formyl peptide-like 1 receptor using techniques as described by Bae et al., (Bae et al *Journal of Immunology*; 2004: 173,607-614; Bae et al., *Journal of Immunology*; 2003: 171,6807-6813). The peptides of the present invention are tested in a range of 1 pM to 10 µM for their ability to inhibit the binding of
15 radiolabelled SEQ ID NO: 650 Trp Lys Tyr Met Val MET peptide to FPRL1 expressing RBL-2H3 cells, and for their ability to block SEQ ID NO: 650 Trp Lys Tyr Met Val MET induced cellular chemotaxis in FPRL1 expressing RBL-2H3 cells. The peptides of the present invention are also tested in other assays described in these two references by Bae et al.

The results demonstrate that the anti-inflammatory properties of the peptides of the
20 present invention and associated fragments, including peptides containing the W domain, inhibit the binding of radiolabelled SEQ ID NO: 650 Trp Lys Tyr Met Val MET peptide to FPRL1 expressing RBL-2H3 cells, inhibit SEQ ID NO: 650 Trp Lys Tyr Met Val MET induced cellular chemotaxis in FPRL1 expressing RBL-2H3 cells and decrease superoxide generation.

While not wanting to be bound by the following statement, it is believed that
25 administration of the peptides of the present invention to individuals decreases the early neutrophil influx into the vessel wall mediated by the formyl peptide-like 1 receptor in acute myocardial infarction or acute coronary syndrome resulting in a decrease in the inflammatory component of atherosclerosis, thereby reducing subsequent clinical events and post-perfusion injury.

30

Example 10

*Use of Labelled Peptides of the Present Invention to Visualize and Locate Plaque in
35 Atherosclerotic Vessels*

The peptides of the present invention are complexed with phospholipids as well as gadolinium or other suitable reagent and the recombined particle is targeted to cholesterol filled cells which have increased expression of the ABCA1 transporter in the vulnerable plaque of the coronary artery. It is believed that the peptides of the present invention have a high affinity for

the ABCA1 transporter and are anticipated to bind to only those cells with an increased intracellular level of cholesterol which induced upregulation of the ABCA1 transporter.

These studies on the peptides of the present invention and associated fragments are compared to results from studies employing ApoA-I protein/phospholipid complex to determine the specificity and selectivity of the peptides of the present invention versus ApoA-I in the localization of the label to vulnerable plaque. The use of the labeled peptides of the present invention to visualize vulnerable plaque provides a valuable tool for diagnosis and treatment of patients at risk for developing cardiovascular disease. (Frias et al., J Am Chem Soc; 2004:126, 16316-7).

Example 11

Synthesis of SEQ ID NO: 121 Ser Pro Leu Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala Leu Lys Glu Asn Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln

The peptide was synthesized manually on Fmoc-Gln(Trt) PEG resin via Fmoc chemistry. Protecting groups used for amino acids were: t-Butyl group for Ser, Thr, Asp, Glu and Tyr, Trt group for Asn and Gln, Boc group for Lys, Pbf for Arg. Fmoc protected amino acids were purchased from EMD Biosciences. Reagents for coupling and cleavage were purchased from Aldrich. Solvents were purchased from Fisher Scientific. The peptide chain was assembled on resin by repetitive removal of the Fmoc protecting group and coupling of protected amino acid. DIC and HOBt were used as coupling reagent and NMM was used as base. 20% piperidine in DMF was used as de-Fmoc-reagent. After removal of last Fmoc protecting group, resin was treated with cocktail K for cleavage and removal of the side chain protecting groups.

Crude peptide was precipitated from cold ether and collected by filtration. Purification of crude peptide was achieved via RP-HPLC by using polymer column from Polymer Laboratories. Peptide was purified using TFA Buffer. Pooled fractions were lyophilized. The peptide was verified by MS analysis and amino acid analysis. The peptide purity was determined by analytical HPLC column (Phenomenex, JupiterC18, 4.6 x 250 mm, 5 micron).

Example 12

Synthesis of SEQ ID NO: 644 Ac-Ser Pro Leu Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys Lys Leu Ser Pro Leu Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu Asn Thr Gln-NH₂

The peptide was synthesized manually on Fmoc-Rink Amide PEG resin via Fmoc chemistry. Protecting groups used for amino acids were: t-Butyl group for Ser, Thr, Glu and Tyr, Trt group for Asn and Gln, Boc group for Lys. Fmoc protected amino acids were purchased

from EMD Biosciences. Reagents for coupling and cleavage were purchased from Aldrich. Solvents were purchased from Fisher Scientific. The peptide chain was assembled on resin by repetitive removal of the Fmoc protecting group and coupling of protected amino acid. HBTU and HOBt were used as coupling reagent and NMM was used as base. 20% piperidine in DMF was used as de-Fmoc-reagent. After removal of last Fmoc protecting group, resin was treated with TFA/TIS/H₂O (95:3:2) for cleavage and removal of the side chain protecting groups.

Crude peptide was precipitated from cold ether and collected by filtration. Purification of crude peptide was achieved via RP-HPLC using 47mm x 300mm column from Waters. Peptide was purified using TFA Buffer. Pooled fractions were lyophilized. The peptide has been verified by MS analysis and amino acid analysis. The peptide purity was determined by analytical HPLC column (Supelco C18, 4.6 x 250mm).

Example 13

Analysis of SR-B1 Mediated Efflux and ABCA1 Mediated Efflux

The methods employed in this study have been described in U.S. Patents Nos: 7,029,863, 7,060,452, U.S. Patent Application Publication No. 2005/0191715, and in Moya et al., *Arteriosclerosis & Thrombosis* 1994;14:1056-1065 and Liu et al., *J. Biol. Chem.*, 2003:278(44), 42976-42984. SR-B1 mediated cholesterol efflux was examined in FU5AH rat hepatoma cells and ABCA1 mediated cholesterol efflux was examined in J774 mouse macrophage cells as described in these references.

TABLE 1
A. Efflux Assay with Peptides minus blank

Peptides *	SR-BI Mediated Efflux % Per 4h	ABCA1 Mediated Efflux % Per 4h	+ ABCA1 Cells	-ABCA1 Cells
1	0.15	18.71	20.338 ± 0.136	1.624 ± 0.126
2	0.16	13.08	14.283 ± 0.545	1.205 ± 0.211
3	0.16	12.14	13.447 ± 0.549	1.306 ± 0.261
4	0.10	11.20	12.420 ± 1.019	1.224 ± 0.121
5	0.25	14.50	15.718 ± 0.123	1.215 ± 0.288

5 Legend: 1=SEQ ID NO: 644, 2=SEQ ID NO: 121, 3=SEQ ID NO: 121, 4=SEQ ID NO: 130,
5=SEQ ID NO: 644

TABLE 2 B. Controls for Efflux Assay with Samples minus blank

Controls	SR-BI Mediated Efflux % Per 4h	ABCA1 Mediated Efflux % Per 4h	+ ABCA1 Cells	-ABCA1 Cells
2% Human Serum Pool	8.47	12.56	24.658 ± 0.130	12.100 ± 0.485
Apo A-I @ 20 µg /ml	0.26	18.97	20.682 ± 0.724	1.713 ± 0.409

* Efflux for all peptide samples was run at 30 µg/ml.

15 The results demonstrate that peptides SEQ ID NO: 121, SEQ ID NO: 130, and the N-terminally acetylated and C-terminally amidated form of LSI 130 which is SEQ ID NO:644, each stimulated efflux of cholesterol from J774 macrophage cells (ABCA1 pathway) while having negligible or no effect on cholesterol efflux from the Fu5AH cells (SRBI pathway), similar to the effect of Apo AI. These selective effects of these peptides demonstrates their efficacy to act as

20 ApoA-I mimetics and selectively efflux cholesterol from cells.

These effects were also dose dependent as shown in Figure 4 with increasing efflux activity demonstrated through the range of 5 ug/ml to 30 ug/ml. Based on these in vitro efflux studies, the

elevation of the Apo AI mimetic peptides of the present invention, in plasma, is expected to decrease coronary and other forms of atherosclerosis in high risk patients.

Example 14

5 *Effect of the Peptides of the Present Invention on CD11b Expression in Monocytes Methods*

Monocyte Isolation Peripheral whole blood (PWB) was drawn from healthy consenting individuals into syringes containing sodium citrate (final concentration – 19.2 mM). Resting human monocytes were isolated from PWB by density centrifugation with Lymphoprep (Axis Shield). Mononuclear cells (MNCs) were collected and monocytes were further separated to purity using the Dynal
10 negative isolation kit (Invitrogen). Monocytes were resuspended in phosphate buffered saline (PBS) and cell number was determined counting cell suspension on an automated hematology analyzer (Sysmex, KX-21N, USA).

Purification of HDL and apoA-1 Human plasma apoA-1 was isolated as previously described and the purity determined using total mass spectrometry.

15 *Flow Cytometry* 100 μ L of monocytes were stimulated with either 1 μ mol/L phorbol-myristate-acetate (PMA) or 1 μ g/ml lipopolysaccharide (LPS) (Sigma, Australia) in the presence or absence of apoA-1 (20 μ g/ml), or 20 μ g/ml of the test peptides SEQ ID NOs: 155, 644, each tested separately. The cells were incubated with the FITC conjugated antibody to either the active epitope of CD11b (eBiosciences, USA, Clone CBRM1/5) or total CD11b (Serotec, USA, Clone ICRF44) for 15 min at
20 37 °C. Cells were then fixed with 4% para-formaldehyde. Samples were controlled for by using the appropriately matched isotype matched negative control (FITC-anti-mouse IgG) (Serotec, USA, Clone W3/25). CD11b expression was measured by flow cytometry using FACS Calibur (Becton Dickinson). Analysis was conducted using the Cell Quest Pro software.

Statistical Analysis Values are presented as the mean $\pm$ SD or percentage of control $\pm$ SD. FACS
25 results were analyzed for statistical significance using one-way ANOVA followed by Bonferroni post-hoc test. Significance was accepted at $P < 0.05$.

Results As expected, ApoA1 (SEQ ID NO: 36) significantly reduced PMA induces CD11b expression. SEQ ID NO: 644 significantly reduced PMA induced CD11b expression (Figure 2).
30 SEQ ID NO: 155 significantly reduced the inflammatory response measured as a reduction in CD11b expression (Figure 3). These results demonstrate that SEQ ID NO: 644 and SEQ ID NO: 155, significantly inhibited PMA induced CD11b expression. Taken together, the results demonstrate the anti-inflammatory properties of these peptides of the present invention. The combined effects of increasing cholesterol efflux and decreasing inflammation indicate that the
35 peptides of the present invention effectively mimic the function of Apo AI and will decrease atherosclerosis.

Example 15

Evaluation of Peptide Utility in ApoE knockout and LDL receptor knockout mice

ApoE knockout and LDL receptor knockout mice, two well established animal models for the study of atherosclerosis, are injected with either saline as control or the synthetic peptides of the present invention to ascertain if these peptides can be used to increase HDL and decrease atherosclerosis.

The mice receive 3 injections per week for either 4-6 or 8-10 weeks. After the completion of the injection, the amount of hardening of the arteries or atherosclerosis is determined in the control injected animals and peptide injected animals to determine if the injections of the synthetic peptide decreased development of atherosclerosis.

The proposed studies test if intraperitoneal infusions of the apoA-I mimetic peptides of the present invention result in decreased aortic atherosclerosis in apoE and LDL receptor knockout mice, two well established mouse models of atherosclerosis.

The mouse is ideal animal specie for the proposed study since well characterized and established mouse models of atherosclerosis are readily available. In particular, apoE and LDL receptor knockout mouse models have been universally employed as animal models for atherosclerosis. Because they are available with a homogenous genetic background, these knockout mice are ideal models for analysis of atherosclerotic lesion formation which is readily impacted by genetic background variability. Additionally, lesion development in apoE and LDL-receptor knockout mice is readily modified by changes in plasma lipoproteins, including HDL, the levels of which are altered by the peptide infusion in this study.

The knockout mouse model is a well established and widely employed animal model for the study of atherosclerosis. Mice are used because of their homogenous genetic background and are ideal models for analysis of atherosclerotic lesion formation which is readily impacted by genetic background variability. Importantly, lesion development in apoE and LDL- receptor knockout mice is highly affected by changes in LDL, HDL and other plasma lipoproteins.

The peptides of the present invention are synthesized according to standard synthetic techniques using tBOC amino acids. The peptides are purified for study by high pressure liquid chromatography. Some peptides are N-acetylated and/or C-terminally amidated.

Mouse Models of Atherosclerosis

Four to six week old C57Bl/6 mice, apoE knockout (JAX 2052) and LDL-receptor knockout (JAX'2207) mice, all in the C57Bl/6 background, are obtained from Jackson Laboratories. During the entire study, C57Bl/6 and apoE knockout mice are maintained on a regular chow diet (0.02% cholesterol, 3% fat) and LDL-receptor mice are maintained on a Western diet (TD88137; Harlan Teklad; Madison, WI- containing 0.20% cholesterol and 21% fat).

Infusion of Synthetic ApoA-I Mimetic Peptides

Three different infusion studies are conducted.

Aim A (Infusion Study A) to determine the functional half-life of the injection of the synthetic peptide on plasma HDL levels.

In the first study (Infusion Study A), C57Bl/6 mice as well as apoE knockout and LDL receptor knockout mice are injected by the intraperitoneal (ip) route or intravenous (iv) route with synthetic peptides of the present invention mimetic (30 mg/kg) on up to four different occasions two weeks apart. To evaluate changes in the plasma lipid and lipoprotein profile associated with injection of the synthetic peptide, blood for lipid analyses is obtained before and at 2, 4, 6, 24 and 48 hours after peptide injection. At the end of the study the animals are sacrificed.

Aim B (Infusion Study B) To determine whether ip injection of the synthetic peptide 3x/wk decreases development of atherosclerosis when assayed 4-5 weeks after initiation of treatment.

Aim C (Infusion Study C) To determine whether ip injection of the synthetic peptide 3x/wk decreases development of atherosclerosis when assayed 8-10 weeks after initiation of treatment.

For infusion studies B and C, mice are injected ip with either placebo or a synthetic peptide of the present invention (30 mg/kg) three times per week for either 4 to 5 weeks (Infusion Study B) or 8 to 10 weeks (Infusion Study C). Blood for lipid and lipoprotein analyses is obtained at the beginning of the study (day 0) and every two weeks after placebo/peptide injection and at the completion of the study. At the completion of the study (4 to 5 weeks for Infusion Study B and 8 to 10 weeks for Infusion Study C), the animals are sacrificed, organs harvested for analyses of cholesterol content and for aortic atherosclerosis.

Statistical methods used to analyze data.

All statistical analyses are conducted in SAS8.2 (SAS Institute, NC). After completion of the atherosclerosis study the mean with standard deviation between the control (C57Bl/6) and treated group (apoE knockout or LDL-receptor knockout) is calculated. The differences are tested by t test (PROC TTEST) and p-values less than 0.05 are considered significant. Non-parametric analysis of aortic atherosclerosis are performed by the Mann-Whitney test.

In the first infusion study (Infusion Study A), 5 C57Bl/6, 5 apoE knockout and 5 LDL receptor knockout mice are injected (IP) with a synthetic peptide of the present invention and blood is obtained for lipid and lipoprotein analyses. A total of 15 mice are used for Infusion Study A.

A total of 40 mice (20 control-placebo injected and 20 study-peptide injected mice) are utilized in each of the two other infusion studies (Infusion Study B- 4 to 5 weeks duration as well as Infusion Study C- 8 to 10 weeks duration). Since each infusion study is conducted in two different mouse lines (i.e.: apoE-KO and LDL receptor KO), the total number of mice used for both Infusion Studies B and C is 160.

Total number of mice used for the entire protocol is 175 (five- C57Bl/6, eighty five-apoE KO mice and eighty five-LDL receptor KO mice) (These animal numbers take into account an estimated 10% morbidity rate during the course of the study as well as the number of animals previously required to achieve statistical significance during analysis of the non-random distribution aortic lesion pattern that develops in mice).

For Infusion Study A, 5 four to six week old C57Bl/6, apoE knockout (JAX 2052) and LDL receptor knockout (JAX 2207) control mice receive ip or iv injections of the synthetic peptide of the

present invention for up to four times two weeks apart. The sequence of procedures for this study is as follows:

- 1) Mice are first anaesthetized by using 1-3% isoflurane by inhalation prior to each ip injection to insure appropriate and complete delivery of placebo/peptide.
- 2) Mice are injected with either placebo (0.2 ml saline) or apoA-I synthetic peptide (30mg/kg in 0.2 ml saline) via either the intraperitoneal or intravenous route.
- 3) In order to evaluate changes in the plasma lipids and lipoproteins in the time-frame between injections, each mouse in this study group is bled from the retro-orbital sinus following administration of a topical anesthesia. before and at 2, 4, 6, 24 and 48 hours after the peptide injection. No more than 300 ul blood is drawn during this 48 hour period.
- 4) At the end of infusion study A all mice are sacrificed by using Avertin (2.5%, 0.011 ml/gm, ip) or ketamine (80ug/gm, ip).

For Infusion Studies B and C, 20 control and 20 study four to six weeks old apoE knockout (JAX 2052) and LDL-receptor knockout (JAX 2207) mice receive ip injections of either placebo or the synthetic peptide of the present invention three times per week for a total of either 4-5 weeks (Infusion Study B) or 8-10 weeks (Infusion Study C).

- 1) Mice are first anaesthetized by using 1-3% isoflurane by inhalation prior to each IP injection to insure appropriate and complete delivery of placebo/peptide.
- 2) Mice are injected ip with either placebo (0.2 ml saline) or apoA-I synthetic peptide (30 mg/kg in 0.2 ml saline) on Monday, Wednesday and Friday of each study week.
- 3) To measure plasma lipids and lipoproteins, each mouse in the two study groups is fasted for 4 hours in the morning (7AM to 11 AM) and then bled from the retro-orbital sinus at the start and end of the infusion study as well as every two weeks after the initial infusion for a total of either 4 weeks (Infusion Study B) or 8 weeks (Infusion Study C). No more than 300 ul blood every two weeks is obtained from each mouse.
- 4) At the end of Infusion Study B and C all mice are sacrificed by cervical dislocation following isoflurane anesthesia and organs are harvested for analyses of cholesterol as well as aortic atherosclerosis.

Before intraperitoneal injections, brief inhaled analgesia will be obtained by isoflurane utilizing the E-Z Rodent Anesthesia System in the procedure room. A topical anesthetic (proparacaine) will be applied prior to obtaining blood from the retro-orbital sinus.

The results indicate that the synthetic peptides of the present invention decrease aortic atherosclerosis compared to controls. In one test, peptides SEQ ID NOs; 121 and 644 are tested and are found to decrease aortic atherosclerosis compared to controls.

Example 16

Evaluation of Peptide Utility in Rabbits

The isolated peptides of the present invention are examined for anti-inflammatory activity using an *in vivo* rabbit model of acute proinflammatory changes in the carotid artery.

This method is explained in detail by Nicholls et al., (Circulation 2005:111, 1543-1550). Normocholesterolemic rabbits are administered the isolated peptides of the present invention iv in a dose of from 1 to 50 mg per day for 3 days, optionally contained in unilamellar vesicles of phosphatidylcholine, with only unilamellar vesicles of phosphatidylcholine with no peptide, or saline as a control. In one test, SEQ ID NOs; 121 and 644 are administered. On the second day, after administration of the peptides, a periarterial collar is introduced around the carotid artery and filled with saline. Two days later, the rabbits are humanely sacrificed and the carotid arteries are processed and analyzed for the presence of reactive oxygen species, the infiltration of neutrophils, and the expression of adhesion proteins and chemokines. The administration of the peptides of the present invention decrease the presence of reactive oxygen species, the infiltration of neutrophils, and the expression of adhesion proteins and chemokines compared to controls, thereby demonstrating anti-inflammatory activity *in vivo*, which can help retard the atherogenic process.

Example 17

Evaluation of Peptide Utility to Promote Reverse Cholesterol Transport In Vivo

The isolated peptides of the present invention are examined for the ability to release cholesterol in mice using the method described by Zhang et al., (Circulation. 2003; 108: 661-663). Macrophages (J774 cells) are loaded with tritiated cholesterol *in vitro* and injected ip into mice. These mice are administered isolated peptides of the present invention, iv, at a dose of from 1 ug to 1 mg, or saline as a control. In one test, SEQ ID NOs; 121 and 644 are administered. The peptides are administered either in saline as a vehicle or in lipid vesicles, such as vesicles of phosphatidylcholine. The mice receiving the peptides of the present invention demonstrate increased levels of tritiated cholesterol in the liver, plasma and feces, than mice receiving saline. The results demonstrate that the peptides of the present invention stimulate reverse cholesterol transport from macrophages to the liver and feces.

All patents, publications and abstracts cited above are incorporated herein by reference in their entirety. It should be understood that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the present invention as defined in the following claims. It will be apparent that the precise details of the constructs, compositions, and methods described herein may be varied or modified without departing from the spirit of the described invention. We claim all such modifications and variations that fall within the scope and spirit of the claims below.

CLAIMS

1. An isolated peptide of formula I comprising:
 - I. (A-B-C)_n, wherein
 - 5 A comprises helix 5 of ApoA-I, helix 6 of ApoA-I, or a modified form of helix 8 of ApoA-I;
 - C comprises helix 8 of ApoA-I;
 - B comprises a linking group between A and C; and,
 - n is an integer from 1 to 10.
- 10 2. The isolated peptide of Claim 1, wherein,
 - A is SEQ ID NO: 1 Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His, SEQ ID NO: 2 His Thr Arg Leu Ala Asp Val His Ala Arg Ala Arg Asp Arg Met Glu Glu Gly, SEQ ID NO: 3 Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu
 - 15 Glu Ala Leu Lys Glu Asn, SEQ ID NO: 4 Asn Glu Lys Leu Ala Glu Leu Arg Ala Ala Leu Arg Gln Arg Leu Glu Asp Ser, SEQ ID NO: 5 Leu Glu Ser Ala Lys Val Ser Ala Leu Ser Ala Leu Glu Glu Ala Thr Lys Lys, or SEQ ID NO: 6 Lys Lys Thr Ala Glu Glu Leu Ala Ser Leu Ala Ser Val Lys Ala Ser Glu Leu, or a conservative substitution thereof,
 - B is Pro, SEQ ID NO: 7 Lys Leu Ser Pro Leu, SEQ ID NO: 8 Leu Ser Pro Leu, or
 - 20 SEQ ID NO: 9 Ser Pro Leu, SEQ ID NO: 12 Leu Pro Ser, SEQ ID NO: 11 Leu Pro Ser Leu, SEQ ID NO: 10 Leu Pro Ser Leu Lys, or a conservative substitution thereof,
 - C is SEQ ID NO: 13 Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys, SEQ ID NO: 14 Lys Lys Thr Tyr Glu Glu Leu Ala Ser Leu Phe Ser Val Lys Phe Ser Glu Leu, or a conservative substitution thereof, and
 - 25 n is 1.
 3. The isolated peptide of Claim 1, wherein a N-terminal amino acid is acetylated and and a C-terminal amino acid is amidated.
 - 30 4. The isolated peptide of Claim 1, further comprising one or more of D, E, F, and W, to form subgeneric formula II,

II. D-E-(A-B-C)_n-F-W, wherein

D is absent or present and is selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro, or multiples, variations or conservative substitutions thereof;

5 E is absent or present and is Pro, SEQ ID NO: 10 Leu Pro Ser Leu Lys, SEQ ID NO: 7 Lys Leu Ser Pro Leu, or a conservative substitution thereof, provided E is present if D is present;

10 F is absent or present and is Pro, SEQ ID NO: 19 Ala Leu Ser Pro Leu, SEQ ID NO: 20 Leu Pro Ser Leu Ala or a conservative substitution thereof, provided F is present if W is present; and,

W is absent or present and is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp, or multiples, variations or conservative substitutions thereof.

15 5. The isolated peptide of Claim 1, further comprising one or more of G and H, to form subgeneric formula IV

IV. G-(A-B-C)_n-H, wherein

G is absent or present and is SEQ ID NO: 9 Ser Pro Leu, SEQ ID NO: 12 Leu Pro Ser or a variation or a conservative substitution thereof; and,

20 H is absent or present and is SEQ ID NO: Leu Asn Thr Gln, Gln Thr, SEQ ID NO: Gln Thr Asn or a variation or a conservative substitution thereof.

6. The isolated peptide of Claim 1, further comprising one or more of D, E, F, W, G and H to form subgeneric formula V

25 V. D-E-G-(A-B-C)_n-H-F-W, wherein

D is absent or present and is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro, or multiples, variations or conservative substitutions thereof;

30 E is absent or present and is Pro, SEQ ID NO: 10 Leu Pro Ser Leu Lys, SEQ ID NO: 7 Lys Leu Ser Pro Leu, or a conservative substitution thereof, provided E is present if D is present;

F is absent or present and is Pro, SEQ ID NO: 19 Ala Leu Ser Pro Leu, SEQ ID NO: 20 Leu Pro Ser Leu Ala or a conservative substitution thereof, provided that F is present when W is present;

W is absent or present and is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp, or multiples, variations or conservative substitutions thereof;

G is absent or present and is SEQ ID NO: 9 Ser Pro Leu, SEQ ID NO: 12 Leu Pro Ser or a variation or a conservative substitution thereof, provided G is present when D is absent;

H is absent or present and is SEQ ID NO: 23 Leu Asn Thr Gln, SEQ ID NO: 24 Gln Thr Asn Leu or a variation or a conservative substitution thereof, provided H is present when W is absent.

7. An isolated peptide of formula VI

VI. D-I-W, wherein

D is absent or present and is a peptide selected from the group consisting of SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro, or multiples, variations or conservative substitutions thereof;

I is a group linking D and W and is GABA, Pro, SEQ ID NO: 7 Lys Leu Ser Pro Leu, SEQ ID NO: 25 Leu Lys Leu Ser Pro Leu, SEQ ID NO: 26 Leu Pro Ser Leu Lys Leu or multiples, variations, combinations thereof or conservative substitutions thereof;

W is absent or present and is a peptide selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp, or multiples, variations or conservative substitutions thereof.

8. An isolated peptide of formula VII comprising:

VII. $(D-R-S-W-T-N-O-(X_n-Y_z-Z_m)_s-O'-N'-T'-W'-S'-R'-D')_r$ wherein:

n is an integer from 1 to 3, m is an integer from 1 to 3, r is an integer from 1 to 10, and s is an integer from 1 to 5;

z is an integer from 1 to 13 and is number of times Y may be present in $X_n-Y_z-Z_m$ when n or m in $X_n-Y_z-Z_m$ are more than 1 or when s is more than 1,

D or D' is individually absent or present and is SEQ ID NO: 15 Pro Arg Gly Gly Ser Val Leu Val Thr, SEQ ID NO: 16 Thr Val Leu Val Ser Gly Gly Arg Pro, or multiples, variations or conservative substitutions thereof;

R or R' is individually absent or present and is comprised of at least one GABA, or one or more neutral amino acids;

S or S' is individually absent or present and is comprised of from 1 to 10 amino acid residues, wherein the amino acid residues are proline, alanine, leucine, lysine, serine,

glycine, polymers thereof or combinations thereof, or is an alkyl group $(CH_2)_n$, wherein n is an integer from 1-20;

W or W' is individually absent or present and is selected from the group consisting of SEQ ID NO: 21 Trp Arg Trp Trp Trp Trp, SEQ ID NO: 22 Trp Trp Trp Trp Arg Trp, or multiples, variations or conservative substitutions thereof;

T or T' is individually absent or present and is comprised of at least one GABA, or one or more neutral amino acids or polymers thereof and combinations thereof;

N or N' is individually absent or present and is comprised of from 1 to 10 amino acid residues, wherein the amino acid residues are proline, alanine, leucine, serine, glycine, polymers thereof or combinations (co-polymers) thereof, or is an alkyl group $(CH_2)_n$, wherein n is an integer from 1-20;

O or O' is individually absent or present and is comprised of at least one GABA, or one or more neutral amino acids, or combinations thereof;

X is comprised of from 5 to 25 amino acid residues, provided an amphipathic alpha helix is obtained;

Y is absent or present and is comprised of amino acids of from 1 to 10 amino acid residues, wherein the amino acid residues are proline, alanine, leucine, serine, glycine, lysine, polymers thereof or combinations thereof, or is an alkyl group $(CH_2)_n$, wherein n is an integer from 1-20; and,

Z is comprised of from 5 to 25 amino acids residues, provided an amphipathic alpha helix is obtained.

9. The isolated peptide of any one of claims 1-8, wherein an N-terminus is acetylated and a C-terminus is amidated.

10. The isolated peptide of any one of claims 1-9, further comprising a label.

11. A pharmaceutical composition comprising any of the isolated peptides of claims 1-9, and a pharmaceutically acceptable carrier.

12. Use of the isolated peptide of any one of claims 1-9, in the preparation of a medicament.

13. Use of the isolated peptide of any one of claims 1-9, in the preparation of a medicament useful for treating a dyslipidemic disorder or a vascular disorder.

14. Use of the isolated peptide of any one of claims 1-9, in the preparation of a medicament useful for treating a disease.
- 5 15. A method of treating disease in an animal or a human comprising administering to the animal or the human the pharmaceutical composition of claim 11.
16. A method of visualizing plaque comprising:
administering the labeled peptide of Claim 10 in an acceptable carrier to a
10 vascular system of an animal or a human; and,
detecting the labeled peptide bound to the plaque within the vascular system of the animal or the human.
17. A method of treating or inhibiting a dyslipidemic disorder or a vascular disorder
15 in an animal or a human, comprising administering to the animal or the human a therapeutically effective amount of the pharmaceutical composition of claim 11.
18. The method of claim 17, wherein the dyslipidemic disorder or the vascular disorder comprises hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia,
20 hypertriglyceridemia, HDL deficiency, apoA-I deficiency, coronary artery disease, atherosclerosis, thrombotic stroke, peripheral vascular disease, restenosis, acute coronary syndrome, post-perfusion myocardial injury, stroke, ischemia, myocardial infarction, or a combinations thereof.
- 25 19. The method of claim 17, further comprising administering an additional lipid lowering composition, an HDL raising composition, or an inhibitor of fat uptake.
20. The method of claim 17, further comprising administering an additional anti-inflammatory composition.

1/4

Amino Acid Sequence of ApoA-I

Asp Glu Pro Pro Gln Ser Pro Trp Asp Arg Val Lys Asp Leu Ala Thr Val Tyr Val Asp Val Leu Lys Asp Ser Gly Arg Asp Tyr Val	1	10	20	30
Ser Gln Phe Glu Gly Ser Ala Leu Gly Lys Gln Leu Asn Leu Lys Leu Leu Asp Asn Trp Asp Ser Val Thr Ser Thr Phe Ser Lys Leu	31	40	50	60
Arg Glu Gln Leu Gly Pro Val Thr Gln Glu Phe Trp Asp Asn Leu Glu Lys Glu Thr Glu Gly Leu Arg Gln Glu Met Ser Lys Asp Leu	61	70	80	90
Glu Glu Val Lys Ala Lys Val Gln Pro Tyr Leu Asp Asp Phe Gln Lys Lys Trp Gln Glu Glu Met Glu Leu Tyr Arg Gln Lys Val Glu	91	100	110	120
Pro Leu Arg Ala Glu Leu Gln Glu Gly Ala Arg Gln Lys Leu His Glu Leu Gln Glu Lys Leu Ser Pro Leu Gly Glu Glu Met Arg Asp	121	130	140	150
Arg Ala Arg Ala His Val Asp Ala Leu Arg Thr His Leu Ala Pro Tyr Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala Arg Leu Glu Ala	151	160	170	180
Leu Lys Glu Asn Gly Gly Ala Arg Leu Ala Glu Tyr His Ala Lys Ala Thr Glu His Leu Ser Thr Leu Ser Glu Lys Ala Lys Pro Ala	181	190	200	210
Leu Glu Asp Leu Arg Gln Gly Leu Leu Pro Val Leu Glu Ser Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu	211	220	230	240
Asn Thr Gln	241	243		

FIG. 1

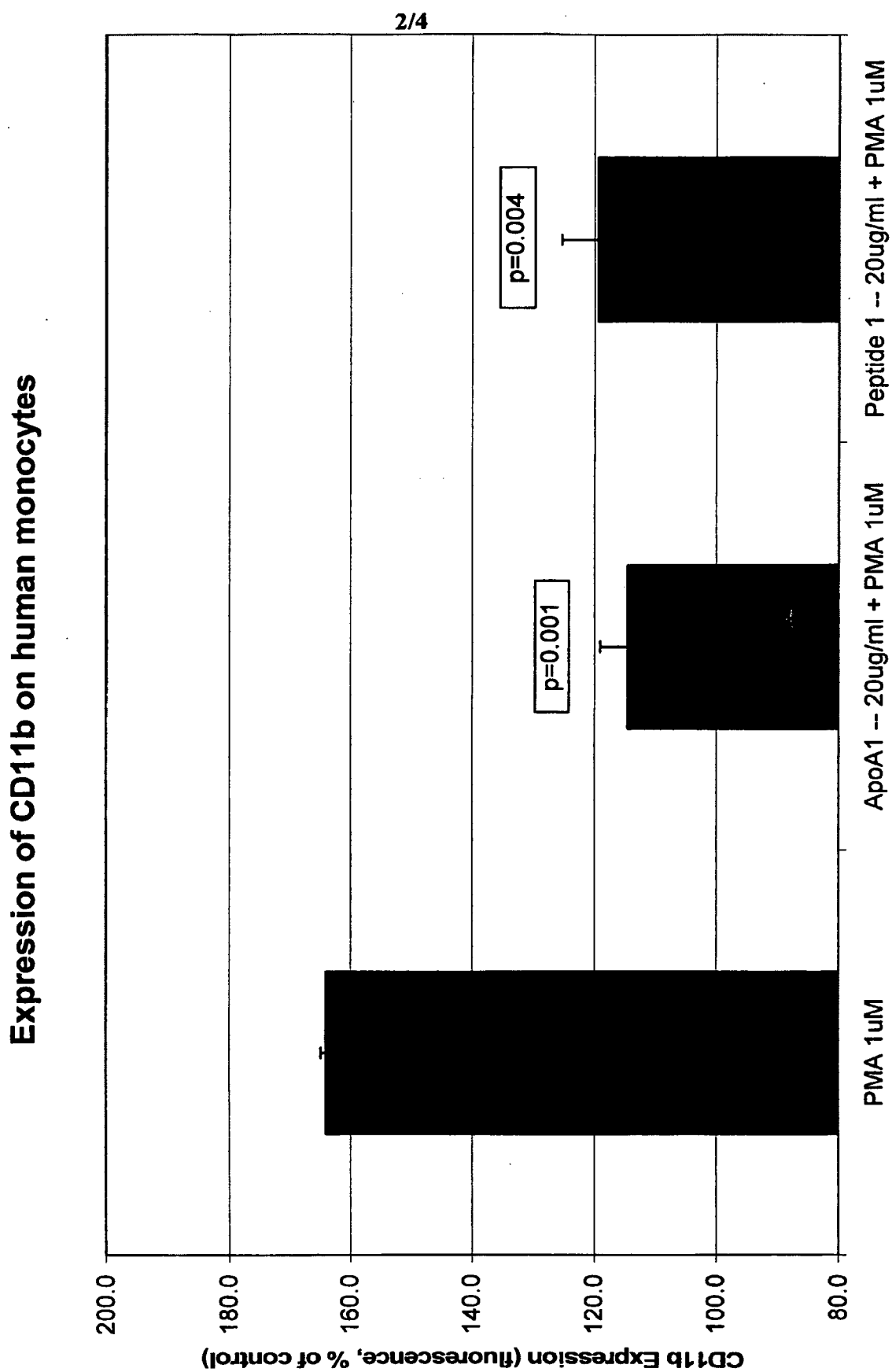
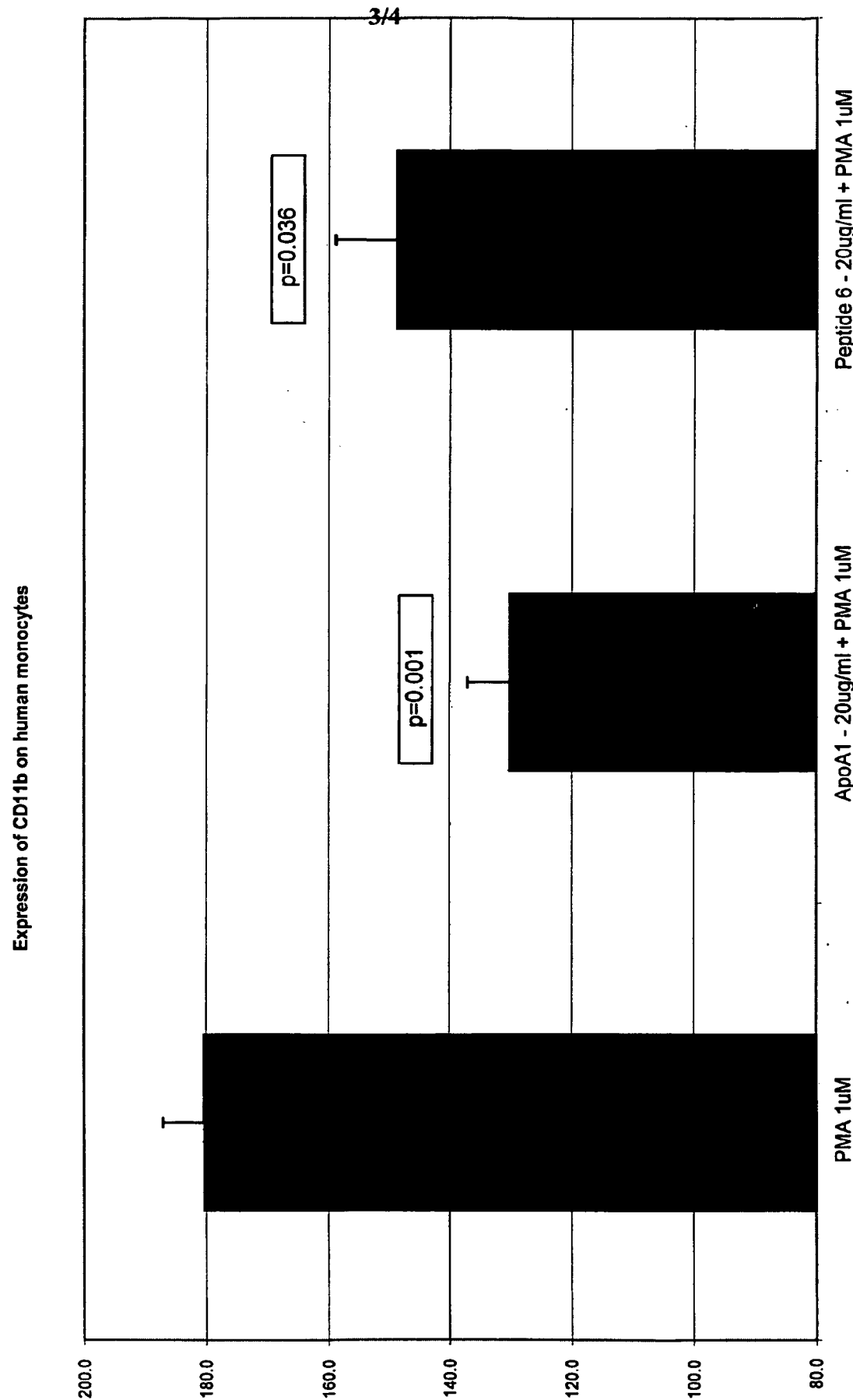


FIG. 2

FIG. 3



ABCA1-dependent Cholesterol Efflux

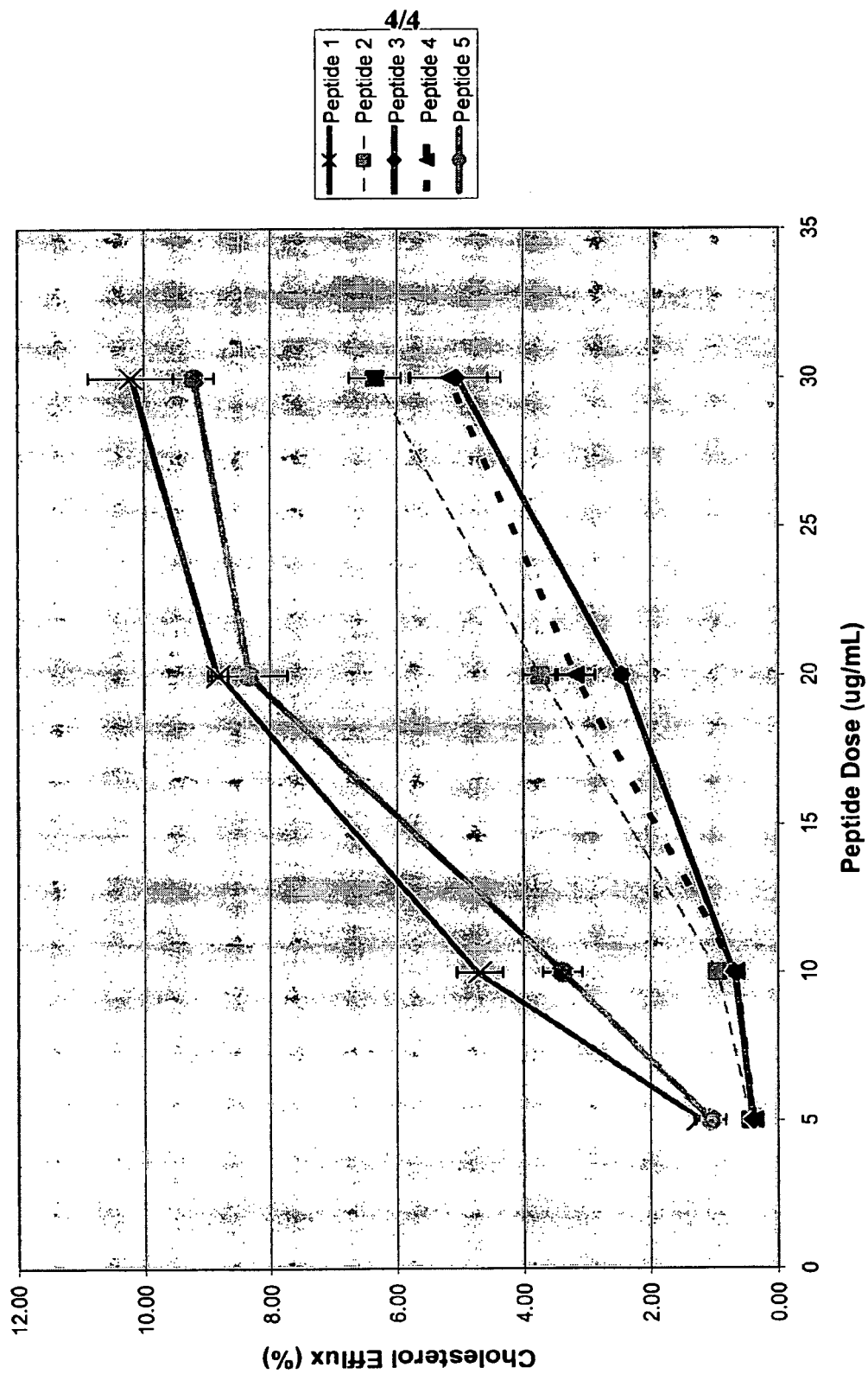


FIG. 4