

APOC-II MIMETIC PEPTIDES

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0001] This invention was created in the performance of Cooperative Research and Development Agreement No. HL-CR-16-005 with the National Institutes of Health, an Agency of the Department of Health and Human Services. The Government of the United States has certain rights in this invention.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted via EFS-Web and is hereby incorporated herein by reference in its entirety. Said ASCII copy, created on ~~Month XX~~, January 18, 2018, is named ~~XXXXXXUS~~
36431 PCT_CRF sequencelisting.txt, and is ~~X,XXX,XXX~~ bytes in size.

BACKGROUND

[0003] Hypertriglyceridemia is typically defined as serum triglyceride levels over 150 mg/dL (Berglund et al., *J. Clin. Endocrinol. Metab.* 97:2969-2989, 2012). Patients with moderate increases in triglycerides are at risk for cardiovascular disease (Budoff, *Am J Cardiol* 118:138-45, 2016). Patients with severe hypertriglyceridemia are additionally at risk for acute pancreatitis (Viljoen and Wierzbicki, *Expert Rev Cardiovasc Ther* 10:505-514, 2012).

[0004] Hypertriglyceridemia is most commonly secondary to obesity, diabetes mellitus, pregnancy, alcohol and a wide variety of drugs (Anderson et al., *Pancreatology* 9:252-257, 2009; Dominguez-Munoz et al., *Int. J. Pancreatol.* 10:261-267, 1991). Triglycerides are enriched in chylomicrons and very low density lipoprotein (VLDL), and lipolysis by lipoprotein lipase (LPL) is a critical step in the catabolism of these triglyceride-rich lipoprotein particles. Rarely, hypertriglyceridemia is the result of genetic defects in LPL or apoC-II, an obligate activator of LPL (Fojo et al., *J. Intern. Med.* 231:669-677, 1992) or in other genes.

[0005] Fibrates and supplements rich in omega-3 polyunsaturated fatty acids, such as fish oils, are the main treatment for hypertriglyceridemia (Berglund et al., *J. Clin. Endocrinol. Metab.* 97:2969-2989, 2012). However, it has not been clearly demonstrated that these agents are efficacious in lowering the risks associated with elevated triglycerides, such as cardiovascular disease (Budoff, *Am J Cardiol* 118:138-45, 2016).

CLAIMS

1. An isolated apoC-II mimetic peptide of no more than 50 amino acids, ~~comprising from N-terminus to C-terminus a first helical domain, a hinge region, and a second helical domain,~~

~~wherein the first helical domain is amphipathic, and wherein the apoC-II mimetic said peptide is not a peptide of SEQ ID NO: 56~~ has at least 90% sequence identity to the full length of SEQ ID NO:9.

2. The isolated apoC-II mimetic peptide of claim 1, wherein said peptide comprises a proline at a position corresponding to position 19 of SEQ ID NO:9.

3. The isolated apoC-II mimetic peptide of claim 1, wherein said peptide comprises an alanine at a position corresponding to position 20 of SEQ ID NO:9.

4. The isolated apoC-II mimetic peptide of claim 1, wherein said peptide comprises a valine at a position corresponding to position 21 of SEQ ID NO:9.

5. The isolated apoC-II mimetic peptide of any one of claims 1 to 4, wherein said peptide has at least 95% sequence identity to the full length of SEQ ID NO:9.

6. The isolated apoC-II mimetic peptide of any one of claims 1 to 5, comprising the sequence set forth in SEQ ID NO: 9.

7. The isolated apoC-II mimetic peptide of claim 1, consisting of the sequence set forth in SEQ ID NO: 9.

~~2. The peptide of claim 1, wherein the first domain is native helix 1 of apoC II.~~

~~3. The peptide of claim 1, wherein the first domain is a variant of helix 1 of apoC II.~~

~~4. The peptide of claim 1, wherein the first domain is native helix 2 of apoC II.~~

~~5. The peptide of claim 1, wherein the first domain is a variant of helix 2 of apoC II.~~

- ~~6. The peptide of claim 5, wherein the variant of helix 2 of apoC II comprises elongation of helix 2 of ApoC II.~~
- ~~7. The peptide of claim 6, wherein the helix 2 of apoC II is elongated by 1-10 amino acids at the N terminus.~~
- ~~8. The peptide of claim 7, wherein the helix 2 of apoC II is elongated by 1 amino acid at the N terminus.~~
- ~~9. The peptide of claim 8, wherein the amino acid is aspartic acid.~~
- ~~10. The peptide of claim 7, wherein the helix 2 of apoC II is elongated by 2 amino acids at the N terminus.~~
- ~~11. The peptide of claim 10, wherein the amino acids are lysine and alanine from N terminus to C terminus.~~
- ~~12. The peptide of claim 7, wherein the helix 2 of apoC II is elongated by 5 amino acids at the N terminus.~~
- ~~13. The peptide of claim 12, wherein the helix 2 of apoC II is elongated by the native upstream amino acid sequence of human apoC II, or a mutant of native upstream amino acid sequence of human apoC II.~~
- ~~14. The peptide of claim 12 or claim 13, wherein the variant of helix 2 of apoC II comprises an aspartic acid at position 40.~~
- ~~15. The peptide of any one of claims 12 to 14, wherein the variant of helix 2 of apoC II comprises a tyrosine or a tryptophan at position 41.~~
- ~~16. The peptide of any one of claims 12 to 15, wherein the variant of helix 2 of apoC II comprises a leucine at position 42.~~
- ~~17. The peptide of any one of claims 12 to 16, wherein the variant of helix 2 of apoC II comprises a lysine or an arginine at position 43.~~
- ~~18. The peptide of any one of claims 12 to 17, wherein the variant of helix 2 of apoC II comprises an alanine or a glutamic acid at position 44.~~
- ~~19. The peptide any one of claims 12 to 18, wherein the variant of helix 2 of apoC II comprises an aspartic acid at position 40, a tyrosine at position 41, a leucine at position 42, a lysine at position 43, and a glutamic acid at position 44.~~

- ~~20. The peptide of claim 5, wherein the variant of helix 2 of apoC II comprises truncation of helix 2 of apoC II.~~
- ~~21. The peptide of claim 20, wherein the amino acid residues 45-46 of native helix 2 of apoC II are deleted.~~
- ~~22. The peptide of claim 20, wherein the amino acid residues 45-48 of native helix 2 of apoC II are deleted.~~
- ~~23. The peptide of claim 20, wherein the amino acid residues 45-49 of native helix 2 of apoC II are deleted.~~
- ~~24. The peptide of claim 20, wherein the amino acid residues 45-50 of native helix 2 of apoC II are deleted.~~
- ~~25. The peptide of claim 20, wherein the amino acid residues 45-53 of native helix 2 of apoC II are deleted.~~
- ~~26. The peptide of any one of claims 5 to 25, wherein the variant of helix 2 of apoC II comprises at least one mutation of helix 2 of apoC II.~~
- ~~27. The peptide of claim 26, wherein the mutation is an amino acid substitution.~~
- ~~28. The peptide of claim 27, wherein an original amino acid of helix 2 of apoC II is substituted by a natural amino acid.~~
- ~~29. The peptide of claim 27, wherein an original amino acid of helix 2 of apoC II is substituted by an unnatural amino acid.~~
- ~~30. The peptide of claim 27, wherein an original amino acid of helix 2 of apoC II is substituted by an amino acid analog.~~
- ~~31. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 45.~~
- ~~32. The peptide of claim 31, wherein the valine at position 45 is substituted by phenylalanine.~~
- ~~33. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 46.~~
- ~~34. The peptide of claim 33, wherein the aspartic acid at position 46 is substituted by a phenylalanine.~~
- ~~35. The peptide of claim 33, wherein the aspartic acid at position 46 is substituted by a lysine.~~

- ~~36. The peptide of claim 33, wherein the aspartic acid at position 46 is substituted by an aminoisobutyric acid.~~
- ~~37. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 48.~~
- ~~38. The peptide of claim 37, wherein the lysine at position 48 is substituted by an arginine.~~
- ~~39. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 49.~~
- ~~40. The peptide of claim 39, wherein the leucine at position 49 is substituted by a lysine.~~
- ~~41. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 50.~~
- ~~42. The peptide of claim 41, wherein the arginine at position 50 is substituted by a lysine.~~
- ~~43. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 53.~~
- ~~44. The peptide of claim 43, wherein the tyrosine at position 53 is substituted by a leucine.~~
- ~~45. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 54.~~
- ~~46. The peptide of claim 45, wherein the serine at position 54 is substituted by a glutamic acid.~~
- ~~47. The peptide of claim 45, wherein the serine at position 54 is substituted by a lysine.~~
- ~~48. The peptide of claim 45, wherein the serine at position 54 is substituted by an aspartic acid.~~
- ~~49. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 55.~~
- ~~50. The peptide of claim 49, wherein the lysine at position 55 is substituted by an arginine.~~
- ~~51. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 56.~~
- ~~52. The peptide of claim 51, wherein the serine at position 56 is substituted by a phenylalanine.~~
- ~~53. The peptide of claim 51, wherein the serine at position 56 is substituted by a lysine.~~

- ~~54. The peptide of claim 51, wherein the serine at position 56 is substituted by an alanine.~~
- ~~55. The peptide of claim 51, wherein the serine at position 56 is substituted by an aminoisobutyric acid.~~
- ~~56. The peptide of any one of claims 27 to 30, wherein the amino acid substitution is at position 57.~~
- ~~57. The peptide of claim 56, wherein the threonine at position 57 is substituted by a phenylalanine.~~
- ~~58. The peptide of any one of claims 27 to 30, wherein the variant of helix 2 of apoC II comprises three amino acid substitutions, wherein the amino acid substitutions are at position 46, position 54, and position 56.~~
- ~~59. The peptide of claim 58, wherein the aspartic acid at position 46 is substituted by a phenylalanine, the serine at position 54 is substituted by a glutamic acid, and the serine at position 56 is substituted by a phenylalanine.~~
- ~~60. The peptide of any one of claims 5 to 59, wherein the variant of helix 2 of apoC II comprises at least one chemical modification.~~
- ~~61. The peptide of claim 60, wherein the chemical modification is a covalent linkage of a fatty acid.~~
- ~~62. The peptide of claim 61, wherein the fatty acid comprises 4 to 26 carbons.~~
- ~~63. The peptide of claim 62, wherein the fatty acid comprises 10 carbons.~~
- ~~64. The peptide of claim 62, wherein the fatty acid comprises 12 carbons.~~
- ~~65. The peptide of claim 62, wherein the fatty acid comprises 14 carbons.~~
- ~~66. The peptide of claim 62, wherein the fatty acid comprises 16 carbons.~~
- ~~67. The peptide of claim 62, wherein the fatty acid comprises 18 carbons.~~
- ~~68. The peptide of claim 62, wherein the fatty acid comprises 20 carbons.~~
- ~~69. The peptide of any one of claims 61 to 68, wherein the fatty acid is saturated.~~
- ~~70. The peptide of any one of claims 61 to 68, wherein the fatty acid is unsaturated.~~
- ~~71. The peptide of any one of claims 61 to 70, wherein the fatty acid is linked to the N-terminal amino acid.~~

- ~~72. The peptide of any one of claims 61 to 71, wherein the fatty acid is linked to an amino acid side group.~~
- ~~73. The peptide of claim 72, wherein the fatty acid is linked to the ϵ amine of a lysine residue.~~
- ~~74. The peptide of any of the preceding claims, wherein the hinge region comprises 5-10 amino acids.~~
- ~~75. The peptide of claim 74, wherein the hinge region comprises 7 amino acids.~~
- ~~76. The peptide of claim 74, wherein the hinge region comprises a proline.~~
- ~~77. The peptide of claim 76, wherein the hinge region comprises a proline at position 58.~~
- ~~78. The peptide of claim 74, wherein the hinge region comprises an alanine.~~
- ~~79. The peptide of claim 78, wherein the hinge region comprises an alanine at position 58.~~
- ~~80. The peptide of claim 74, wherein the hinge region comprises a norleucine.~~
- ~~81. The peptide of claim 80, wherein the hinge region comprises a norleucine at position 60.~~
- ~~82. The peptide of claim 74, wherein the hinge region comprises a lysine.~~
- ~~83. The peptide of claim 82, wherein the hinge region comprises a lysine at position 60.~~
- ~~84. The peptide of claim 74, wherein the hinge region comprises a valine.~~
- ~~85. The peptide of claim 84, wherein the hinge region comprises a valine at position 60.~~
- ~~86. The peptide of claim 74, wherein the hinge region comprises a leucine.~~
- ~~87. The peptide of claim 86, wherein the hinge region comprises a leucine at position 60.~~
- ~~88. The peptide of claim 74, wherein the hinge region comprises a methionine.~~
- ~~89. The peptide of claim 88, wherein the hinge region comprises a methionine at position 60.~~
- ~~90. The peptide of any one of claims 74 to 89, wherein the hinge region comprises at least one chemical modification.~~
- ~~91. The peptide claim 90, wherein the chemical modification is a covalent linkage of a fatty acid.~~
- ~~92. The peptide claim 91, wherein the fatty acid comprises 4 to 26 carbons.~~
- ~~93. The peptide claim 92, wherein the fatty acid comprises 10 carbons.~~

- ~~94.~~ The peptide claim 92, wherein the fatty acid comprises 12 carbons.
- ~~95.~~ The peptide claim 92, wherein the fatty acid comprises 14 carbons.
- ~~96.~~ The peptide claim 92, wherein the fatty acid comprises 16 carbons.
- ~~97.~~ The peptide claim 92, wherein the fatty acid comprises 18 carbons.
- ~~98.~~ The peptide claim 92, wherein the fatty acid comprises 20 carbons.
- ~~99.~~ The peptide of any one of claims 91 to 98, wherein the fatty acid is saturated.
- ~~100.~~ The peptide of any one of claims 91 to 98, wherein the fatty acid is unsaturated.
- ~~101.~~ The peptide of any one of claims 91 to 100, wherein the fatty acid is linked to an amino acid side group.
- ~~102.~~ The peptide of claim 101, wherein the fatty acid is linked to the ϵ amine of a lysine residue.
- ~~103.~~ The peptide of any of the preceding claims, wherein the hinge region allows the first helical domain and the second helical domain to retain a nearly straight conformation, wherein the second domain bends away from the first domain over an angle of no more than about 20°.
- ~~104.~~ The peptide of any of the preceding claims, wherein the second domain is native helix 3 of apoC II.
- ~~105.~~ The peptide of any one of claims 1 to 103, wherein the second domain is a variant of helix 3 of apoC II.
- ~~106.~~ The peptide of claim 105, wherein the variant of helix 3 of apoC II comprises elongation of helix 3 of apoC II.
- ~~107.~~ The peptide of claim 106, wherein the helix 3 of apoC II is elongated by 1-10 amino acids at the C terminus.
- ~~108.~~ The peptide of claim 107, wherein the helix 3 of apoC II is elongated by 4 amino acids at the C terminus.
- ~~109.~~ The peptide of claim 108, wherein the helix 3 of apoC II is elongated by amino acids lysine, glycine, glutamic acid, and glutamic acid from N terminus to C terminus.
- ~~110.~~ The peptide of any one of claims 105 to 109, wherein the variant of helix 3 of apoC II comprises at least one mutation of helix 3 of apoC II.

- ~~111.~~—The peptide of claim 110, wherein the mutation is an amino acid substitution.
- ~~112.~~—The peptide of claim 111, wherein an original amino acid of helix 3 of apoC II is substituted by a natural amino acid.
- ~~113.~~—The peptide of claim 111, wherein an original amino acid of helix 3 of apoC II is substituted by an unnatural amino acid.
- ~~114.~~—The peptide of claim 111, wherein an original amino acid of helix 3 of apoC II is substituted by an amino acid analog.
- ~~115.~~—The peptide of any one of claims 111 to 114, wherein the amino acid substitution is at position 70.
- ~~116.~~—The peptide of claim 115, wherein the glutamine at position 70 is substituted by an arginine.
- ~~117.~~—The peptide of claim 115, wherein the glutamine at position 70 is substituted by a lysine.
- ~~118.~~—The peptide of any one of claims 105 to 117, wherein the variant of helix 3 of apoC II comprises at least one chemical modification.
- ~~119.~~—The peptide of claim 118, wherein the chemical modification is a covalent linkage of a fatty acid.
- ~~120.~~—The peptide of claim 119, wherein the fatty acid comprises 4 to 26 carbons.
- ~~121.~~—The peptide of claim 120, wherein the fatty acid comprises 10 carbons.
- ~~122.~~—The peptide of claim 120, wherein the fatty acid comprises 12 carbons.
- ~~123.~~—The peptide of claim 120, wherein the fatty acid comprises 14 carbons.
- ~~124.~~—The peptide of claim 120, wherein the fatty acid comprises 16 carbons.
- ~~125.~~—The peptide of claim 120, wherein the fatty acid comprises 18 carbons.
- ~~126.~~—The peptide of claim 120, wherein the fatty acid comprises 20 carbons.
- ~~127.~~—The peptide of any one of claims 119 to 126, wherein the fatty acid is saturated.
- ~~128.~~—The peptide of any one of claims 119 to 126, wherein the fatty acid is unsaturated.
- ~~129.~~—The peptide of any one of claims 119 to 128, wherein the fatty acid is linked to the C-terminal amino acid.

- ~~130.~~—The peptide of any one of claims 119 to 129, wherein the fatty acid is linked to an amino acid side group.
- ~~131.~~—The peptide of claim 130, wherein the fatty acid is linked to the ϵ -amine of a lysine residue.
- ~~132.~~—The peptide of any one of claims 119 to 131, wherein the C-terminal amino acid is modified by a C-terminal amide.
- ~~133.~~—The peptide of any of the preceding claims, wherein the isolated apoC-II mimetic peptide further comprises a purification tag.
- ~~134.~~—The peptide of claim 133, wherein the purification tag is a polyhistidine tag, a myc-tag, or an HA tag.
- ~~135.~~—The peptide of any of the preceding claims, wherein the first domain has an affinity for binding to lipoproteins.
- ~~136.~~—The peptide of any of the preceding claims, wherein the second domain is capable of activating lipoprotein lipase (LPL).
- ~~137.~~—The peptide of claim 135 or claim 136, wherein the peptide is capable of activating lipolysis by LPL.
- ~~138.~~—The peptide of claim 135 or claim 136, wherein the peptide is capable of displacing apoC-III in lipoproteins.
- ~~139.~~—The peptide of any of the preceding claims, wherein the peptide is capable of reducing triglyceride (TG) level *in vivo*.
- ~~140.~~—The peptide of claim 139, wherein the peptide is capable of reducing elevated TG level caused by LPL deficiency.
- ~~141.~~—The peptide of claim 139, wherein the peptide is capable of reducing elevated TG level caused by elevated apoC-III.
- ~~142.~~—The peptide of claim 139, wherein the peptide is capable of reducing elevated TG level caused by apoC-II deficiency.
- ~~143.~~—The peptide of claim 139, wherein the peptide is capable of reducing post-prandial elevated TG level.

- ~~144.~~—The isolated apoC II mimetic peptide of claim 1, wherein the peptide has the sequence set forth in SEQ ID NO: 6.
- ~~145.~~—The isolated apoC II mimetic peptide of claim 1, wherein the peptide has the sequence set forth in SEQ ID NO: 9.
- ~~146.~~—An isolated apoC II mimetic peptide of no more than 30 amino acids, consisting of a variant of helix 3 of apoC II.
- ~~147.~~—The peptide of claim 146, wherein the variant of helix 3 of apoC II comprises elongation of helix 3 of apoC II.
- ~~148.~~—The peptide of claim 147, wherein the helix 3 of apoC II is elongated by 1–10 amino acids at the N terminus.
- ~~149.~~—The peptide of claim 148, wherein the helix 3 of apoC II is elongated by 6 amino acids at the N terminus.
- ~~150.~~—The peptide of claim 149, wherein the variant of helix 3 of apoC II comprises a lysine or methionine at position 60.
- ~~151.~~—The peptide of anyone of claims 147 to 150, wherein the helix 3 of apoC II is elongated by 1–10 amino acids at the C terminus.
- ~~152.~~—The peptide of claim 151, wherein the helix 3 of apoC II is elongated by 4 amino acids at the C terminus.
- ~~153.~~—The peptide of claim 152, wherein the helix 3 of apoC II is elongated by amino acids lysine, glycine, glutamic acid, and glutamic acid from N terminus to C terminus.
- ~~154.~~—The peptide of any one of claims 146 to 153, wherein the variant of helix 3 of apoC II comprises at least one mutation of helix 3 of apoC II.
- ~~155.~~—The peptide of claim 154, wherein the mutation is an amino acid substitution.
- ~~156.~~—The peptide of claim 155, wherein an original amino acid of helix 3 of apoC II is substituted by a natural amino acid.
- ~~157.~~—The peptide of claim 155, wherein an original amino acid of helix 3 of apoC II is substituted by an unnatural amino acid.
- ~~158.~~—The peptide of claim 155, wherein an original amino acid of helix 3 of apoC II is substituted by an amino acid analog.

~~159.~~—The peptide of any one of claims 146 to 158, wherein the variant of helix 3 of apoC-II comprises at least one chemical modification.

~~160.~~—The peptide of claim 159, wherein the chemical modification is a covalent linkage of a fatty acid.

~~161.~~—The peptide of claim 160, wherein the fatty acid comprises 4 to 26 carbons.

~~162.~~—The peptide of claim 161, wherein the fatty acid comprises 10 carbons.

~~163.~~—The peptide of claim 161, wherein the fatty acid comprises 12 carbons.

~~164.~~—The peptide of claim 161, wherein the fatty acid comprises 14 carbons.

~~165.~~—The peptide of claim 161, wherein the fatty acid comprises 16 carbons.

~~166.~~—The peptide of claim 161, wherein the fatty acid comprises 18 carbons.

~~167.~~—The peptide of claim 161, wherein the fatty acid comprises 20 carbons.

~~168.~~—The peptide of any one of claims 160 to 167, wherein the fatty acid is saturated.

~~169.~~—The peptide of any one of claims 160 to 167, wherein the fatty acid is unsaturated.

~~170.~~—The peptide of any one of claims 160 to 169, wherein the fatty acid is linked to the N-terminal amino acid.

~~171.~~—The peptide of any one of claims 160 to 169, wherein the fatty acid is linked to the C-terminal amino acid.

~~172.~~—The peptide of any one of claims 160 to 171, wherein the fatty acid is linked to an amino acid side group.

~~173.~~—The peptide of claim 172, wherein the fatty acid is linked to the ϵ amine of a lysine residue.

~~174.~~—The peptide of any one of claims 146 to 173, wherein the isolated apoC-II mimetic peptide further comprises a purification tag.

~~175.~~—The peptide of claim 174, wherein the purification tag is a polyhistidine tag, a myc-tag, or an HA tag.

~~176.~~—The peptide of any one of claims 146 to 175, wherein the variant of helix 3 of apoC-II has an affinity for binding to lipoproteins.

~~177.~~—The peptide of any one of claims 146 to 176, wherein the variant of helix 3 of apoC II is capable of activating lipoprotein lipase (LPL).

~~178.~~—The peptide of claim 176 or claim 177, wherein the peptide is capable of activating lipolysis by LPL.

~~179.~~—The peptide of claim 176 or claim 177, wherein the peptide is capable of displacing apoC III in lipoproteins.

~~180.~~—The peptide of any one of claims 146 to 179, wherein the peptide is capable of reducing triglyceride (TG) level *in vivo*.

~~181.~~—The peptide of claim 180, wherein the peptide is capable of reducing elevated TG level caused by LPL deficiency.

~~182.~~—The peptide of claim 180, wherein the peptide is capable of reducing elevated TG level caused by elevated apoC III.

~~183.~~—The peptide of claim 180, wherein the peptide is capable of reducing elevated TG level caused by apoC II deficiency.

~~184.~~—The peptide of claim 180, wherein the peptide is capable of reducing post prandial elevated TG level.

~~185.~~ 8.—A pharmaceutical composition comprising the mimetic peptide of any one of the preceding claims 1 to 7 and a pharmaceutically acceptable carrier.

~~186.~~ 9.—The pharmaceutical composition of claim ~~185~~ 8, wherein the pharmaceutical composition is suitable for subcutaneous injection.

~~187.~~ A method of treating hypertriglyceridemia in a patient, comprising administering to the patient an effective amount of the peptide or the pharmaceutical composition of any of the preceding claims.

~~188.~~—The method of claim 187, wherein the hypertriglyceridemia is associated with obesity.

~~189.~~—The method of claim 187, wherein the hypertriglyceridemia is associated with diabetes mellitus.

~~190.~~—The method of claim 187, wherein the hypertriglyceridemia is associated with alcohol consumption.

- ~~191.~~—The method of claim 187, wherein the hypertriglyceridemia is associated with medication.
- ~~192.~~—The method of claim 187, wherein the hypertriglyceridemia is caused by LPL deficiency.
- ~~193.~~—The method of claim 192, wherein the hypertriglyceridemia is familial lipoprotein lipase deficiency.
- ~~194.~~—The method of claim 192 or 193, wherein the LPL deficiency is caused by a mutation in the LPL gene.
- ~~195.~~—The method of claim 194, wherein the mutation leads to reduced LPL enzyme activity.
- ~~196.~~—The method of claim 194, wherein the mutation leads to absent LPL enzyme activity.
- ~~197.~~—The method of any one of claims 192 to 196, wherein the LPL deficiency is diagnosed by the absence of LPL activity in serum of the patient.
- ~~198.~~—The method of any one of claims 194 to 196, wherein the mutation is detected by DNA sequence analysis.
- ~~199.~~—The method of claim 187, wherein the hypertriglyceridemia is caused by apoC II deficiency.
- ~~200.~~—The method of claim 187, wherein the hypertriglyceridemia is caused by elevated apoC III.
- ~~201.~~—The method of any one of claims 187 to 200, wherein the pre-treatment serum triglyceride (TG) concentration of the patient is between 150 mg/dL and 199 mg/dL.
- ~~202.~~—The method of any one of claims 187 to 200, wherein the pre-treatment serum triglyceride (TG) concentration of the patient is between 200 mg/dL to 499 mg/dL.
- ~~203.~~—The method of any one of claims 187 to 200, wherein the pre-treatment serum triglyceride (TG) concentration of the patient is between 500 mg/dL to 999 mg/dL.
- ~~204.~~—The method of any one of claims 187 to 200, wherein the pre-treatment serum triglyceride (TG) concentration of the patient is between 1000 mg/dL and 1999 mg/dL.
- ~~205.~~—The method of any one of claims 187 to 200, wherein the pre-treatment serum triglyceride (TG) concentration of the patient is equal to or higher than 2000 mg/dL.

~~206.~~ The method of any one of claims ~~187 to 205~~, wherein the patient has developed or is at risk for acute pancreatitis.

~~207.~~ The method of any one of claims ~~187 to 206~~, wherein the patient has developed or is at risk for acute cardiovascular disease.

~~208.~~10. A method of making the mimetic peptide of any one of claims 1 to ~~184~~ 7, comprising producing the mimetic peptide recombinantly.

~~209.~~11. A method of making the mimetic peptide of any one of claims 1 to ~~184~~ 7, comprising producing the mimetic peptide by chemical synthesis.

12. The mimetic peptide produced by the method of claim 10 or claim 11.

13. Use of a mimetic peptide of any one of claims 1 to 7 and 12 in the manufacture of a medicament for treating hypertriglyceridemia in a patient.

14. The use of claim 13, wherein the hypertriglyceridemia is associated with obesity, diabetes mellitus, alcohol consumption or medication.

15. The use of claim 13, wherein

(a) the hypertriglyceridemia is caused by LPL deficiency; or

(b) the hypertriglyceridemia is caused by LPL deficiency and the LPL deficiency is familial LPL deficiency.

16. The use of claim 15, wherein the LPL deficiency is caused by a mutation in the LPL gene.

17. The use of claim 16, wherein the mutation leads to reduced or absent LPL enzyme activity.

18. The use of claim 13, wherein the hypertriglyceridemia is caused by apoC-II deficiency or by elevated apoC-III.

19. The use of any one of claims 13 to 18, wherein the patient has developed or is at risk for acute pancreatitis or acute cardiovascular disease.