

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 January 18, 2018, is named 36431_PCT_CRF_sequencelisting.txt.

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, wherein the said peptide 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.
8. A pharmaceutical composition comprising the mimetic peptide of any one of claims 1 to 7 and a pharmaceutically acceptable carrier.
9. The pharmaceutical composition of claim 8, wherein the pharmaceutical composition is suitable for subcutaneous injection.
10. A method of making the mimetic peptide of any one of claims 0 to 7, comprising producing the mimetic peptide recombinantly.

11. A method of making the mimetic peptide of any one of claims 0 to 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.