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ApoM-Fc Fusion Protein in Complex with S1P for the Treatment of Vascular Diseases

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It can be used for the treatment of hypertension, ischemia, and vascular diseases with increased in vivo stability

Background

Endothelial cell function is critical for normal cardiovascular homeostasis. Endothelial dysfunction hence leads to the development of cardiovascular diseases such as hypertension and Ischemia. Recently, endogenous factors – such as plasma Apolipoprotein M-containing high density lipoproteins (ApoM-HDLs) –have been shown to promote the well-being of the endothelium. Thus, ApoM-based therapeutics have a great potential in reducing the burden of cardiovascular disease, which is the leading cause of death globally.

ApoM-HDL is the physiological carrier of the bioactive lipid sphingosine-1-phosphate (S1P) and engages S1P receptors to promote endothelial survival.

Technology Overview

The researchers devised a strategy to develop a soluble ApoM therapeutic that carries S1P to activate vascular S1P receptors during pathological conditions.

The following summarizes the proof of concept for this invention:

- Fusion of ApoM with the constant domain (Fc) of immunoglobulins stabilizes it
- The ApoM-Fc fusion bound tightly to S1P with an EC50 of ~0.22 μM
- ApoM-Fc-S1P complex activated S1P receptors in reporter assays
- In vitro: ApoM-Fc-S1P induces sustained enhancement of endothelial cell barrier function of endothelial HUVEC cells
- In vivo: ApoM-Fc bound S1P was stabilized and potently reduced blood pressure in a mouse model of hypertension
- In vivo: ApoM-Fc administration attenuated ischemia/reperfusion (MI/R) injury in the brain and heart in mouse models.

Further Detail

- Swendeman, Steven L et al. “An engineered S1P chaperone attenuates hypertension and ischemic injury.” Science signaling vol. 10,492 eaal2722. 15 Aug. 2017, doi:10.1126/scisignal.aal2722
- Christoffersen, Christina, and Lars Bo Nielsen. “Apolipoprotein M: bridging HDL and endothelial function.” Current opinion in lipidology vol. 24,4 (2013): 295-300.
- Christoffersen, Christina, et al. “Endothelium-Protective Sphingosine-1-Phosphate Provided by HDL-Associated Apolipoprotein M.” Proceedings of the National Academy of Sciences, vol. 108, no. 23, June 2011, pp. 9613 LP – 9618.

Benefits

- ApoM-Fc has increased in vivo stability with half-life of 93.5 hours
- ApoM-Fc does not activate immune and hematopoietic S1P receptors, hence circulating numbers of lymphocytes, white blood cells, red blood cells and platelets not altered

Applications

- Treatment of of hypertension, ischemia of the heart and brain, accelerated atherosclerosis and peripheral vascular disease
- Reducing the side effect of Fingolimod (S1P agonist) in patients being treated with it.

Patents

- Patent granted US10870689 B2

IP Status

- Patented