Weill Cornell Medicine

MicroRNA Mimics for the Treatment of Cardiometabolic Diseases

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Background & Unmet Need

- Impaired cholesterol and fat metabolism contributes to many cardiometabolic diseases, including obesity, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD) and atherosclerosis.
- Numerous regulatory factors have been found to modulate metabolic regulation of lipids, and are thus attractive therapeutic targets
- The sterol regulatory element-binding protein-2 (SREBP-2) directed transcription of low-density lipoprotein (LDL) receptor is essential for the removal of atherogenic LDL from circulation
- Post-translationally, LDLR-mediated cholesterol uptake is limited by SREBP-2- and LXR-induced counter mechanisms
- However, coordinated cellular mechanisms that restrict or prevent LDLR from degradation upon transcription remain uncharacterized
- **Unmet Need:** Improved understanding of LDLR regulation to inform development of novel treatments

Technology Overview

- **The Technology:** miRNA-33a-3p mimics that lower LDL and reduced hepatic steatosis for the treatment of cardiometabolic diseases such as NAFLD
- **The Discovery:** miRNA-33a, encoded within the *SREBP-2* gene, acts to promote LDLR expression and LDL-uptake through direct targeting of *PCSK9, IDOL and ANGPTL3.*
- **PoC Data:** Liver-targeted delivery of miRNA-33a-3p mimics into mouse models of diet-induced obesity resulted in reduced hepatic and circulating PCSK9 levels as well as serum ANGPTL3 levels
- miRNA-33a-3p mimics significantly lower LDL, and ameliorate hepatic steatosis while increasing HDL
- miRNA-33a-3p mimics therefore represent alternative therapeutic inhibitors of PCSK9, ANGPTL3, and LDL-cholesterol for reducing hypercholesterolemia and steatohepatitis

Inventors:
S. Hani Najafi-Shoushtari
Vimal Ramachandran

Patents:
PCT Application Filed

Publications:
Ramachandran et al. *Atherosclerosis*. 2022 (abstract)

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Technology Applications

- Treatment and prevention of cardiometabolic diseases and NAFLD/NASH
- Reduction of hypercholesterolemia and hypertriglyceridemia in patients with atherosclerosis and insufficient response to statins and dietary changes alone

Technology Advantages

- miRNAs can regulate multiple genes in the same biological process with as individual ~22 nucleotide transcripts
- miRNAs can be administered in a tissue-targeted manner to enhance specificity and efficacy while minimizing side effects
- miRNA-33a-3p successfully reduced LDL-cholesterol and hepatic steatosis in a mouse model of obesity

Supporting Data / Figures

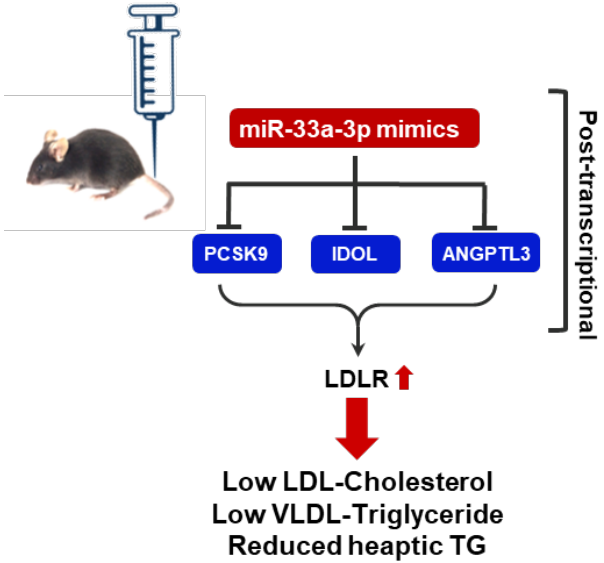

Figure 1: miR-33a-3p mimics are potent inhibitors targeting PCSK9, IDOL and ANGPTL3 expression.

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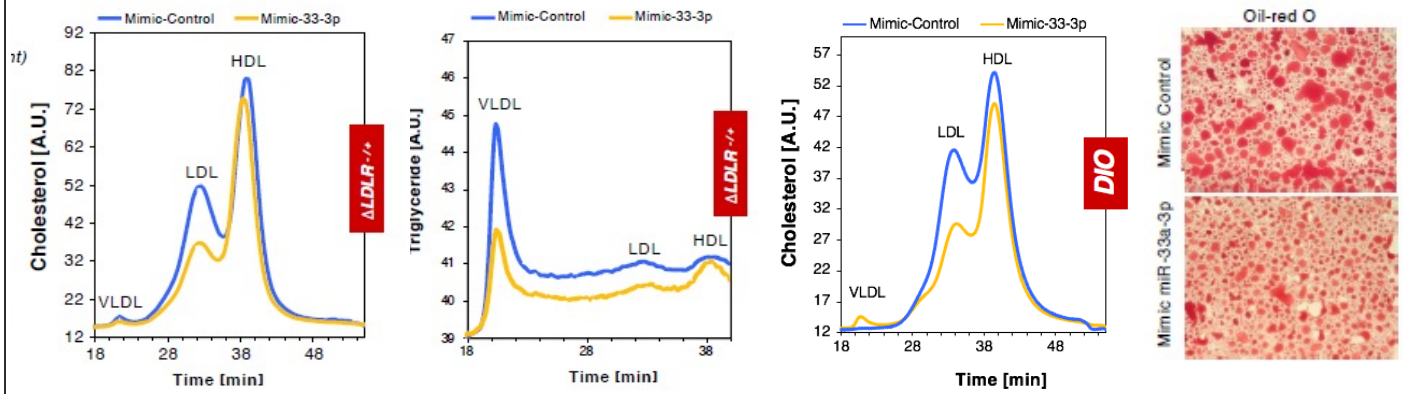

Figure 2: miRNA-33a-3p lowers plasma LDL-cholesterol and VLDL triglyceride levels and attenuates hepatic steatosis in diet-induced obese mice and heterozygous LDLR KO mice.

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