Novel MicroRNA-30c Analogs to Reduce Secretion of Apolipoprotein B in Human Hepatoma Cells

Therapeutic agents for lowering plasma lipid levels without causing the steatosis associated to microsomal transfer protein inhibitors.

Technology Overview

This invention describes the development of potent microRNA-30c (miR-30c) analogs that are expected to be superior therapeutic agents for lowering plasma lipid levels with high efficacy and specificity and without causing the steatosis associated to microsomal transfer protein (MTP) inhibitors. Chemical modifications introduced on miR-30c improve stability and delivery to hepatic cells without the aid of viral vectors or lipid emulsions.

After having shown that increasing cellular levels of miR-30c reduces MTP, plasma lipids and atherosclerosis without further increasing hepatic lipid synthesis, the inventors have synthesized potent miR-30c analogs that allow targeted hepatic delivery. miR-30c analogs contain N-acetyl-galactosamine (GalNAc) modifications in the passenger strand of the miR duplex to improve their stability and hepatic delivery while retaining the potency of the sense strand.

Background

Hypercholesterolemia is a major risk factor for cardiovascular disease, a leading cause of morbidity and mortality in the US and globally, and costs the US health system ~$363 billion yearly. Current treatment options include statins, PCSK9 neutralizing antibodies, and MTP inhibitors. However, many patients do not tolerate or do not completely respond to these strategies. In addition, while offering an alternative for patients irresponsive to statins and PCSK9 inhibitors (i.e. those with familial hypercholesterolemia), MTP inhibitors often cause hepatic steatosis. Hence, there is an unmet need for therapeutics that can effectively reduce levels of MTP and plasma lipids without damaging the liver.

Development Status

In unpublished work, some of the novel analogs have demonstrated ***in vivo* efficacy** in a hypercholesterolemic mouse model.

Benefits

- Efficient method to inhibit MTP activity and apoB secretion without cellular toxicity
- Enhanced stability and delivery without the need of lipid emulsions or viral vectors
- A safer alternative for patients resistant to statins and PCSK9 inhibitors
  - By additionally targeting genes involved in lipid synthesis in the liver, miR-30c analogs may circumvent the steatosis seen with current MTP inhibitors

Technology ID

HUS02-03

Category

Life Sciences/Therapeutics/Cardiovas
Disease

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Applications

Novel targeted therapeutic approach for hyperlipidemia and cardiovascular disease as an alternative or in combination with existing lipid lowering drugs.

IP Status

US patent pending

References

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2. Yadav PK, Haruehanroengra P, Irani S, Wang T, Ansari A, Sheng J, Hussain MM.(Mar 10, 2022) , https://pubmed.ncbi.nlm.nih.gov/35278429/