Gene therapy for non-alcoholic steatohepatitis and associated liver fibrosis

Unmet Need
Driven by the rising tide of obesity and lack of medical treatment, it is estimated that 1 out of 4 adults in the US has non-alcoholic fatty liver disease or non-alcoholic steatohepatitis (NAFLD/NASH). Although these are prevalent diseases, the cause is complex, and there is currently no approved treatment other than lifestyle change or liver transplant. Therefore, there is a great unmet need to develop treatment methods for NAFLD/NASH that can simultaneously target all the effected pathways in liver fibrosis.

Technology
Duke inventors have developed a gene therapy for Nonalcoholic steatohepatitis (NASH) and associated disorders. This is intended to treat patients with severe obesity and liver fibrosis. Specifically, microRNA 375 (miR-375), a little-studied modulator for a number of downstream gene expression pathways, has been observed to be enriched in livers in severely obese individuals carrying the PNPLA3 risk allele for NASH that are resistant to the disease. By introducing genetic material coding for the upregulation or expression of miR-375 or a mimic, a gene therapy approach could be used to treat NAFLD/NASH and severe obesity. The enrichment of miR-375 has been demonstrated in both human liver biopsy data and validated with small RNA-seq. Treatment with AAV encoding miR-375 reversed liver inflammation and lowered total liver mass and lipid content in mice with established NASH.

Other Applications
This technology could also apply to patients with other associated conditions such as hepatic fibrosis, hepatocellular carcinoma, hepatitis C induced NAHS,
drug induced NASH, and NASH risk factors such as obesity-related diabetes, heart failures, and clotting disorders.

Advantages

- There are currently no effective treatment methods for NAFLD/NASH, as the only options for patients are lifestyle change and liver transplant, so there is no approved market competition
- This therapy has the potential to treat several related disorders
- As miR-375 can mediate several genes, this may remove the need for using several different drugs in combination