Chimeric FGF21: Treatment of NAFLD, NASH and Hepatic Steatosis

New and efficacious versions of fibroblast growth factor 21 (FGF21) for metabolic liver diseases

Technology

Dr. Mohammadi and colleagues have designed chimeric versions of Fibroblast growth factor 21 (FGF21) with enhanced stability but no (greater) antigenicity compared to native FGF21. These fusion proteins show greater affinity to βKlotho, a co-receptor required for FGF21-βKlotho-FGF receptor (FGFR) complex formation and downstream signaling activities associated with Type 2 diabetes and obesity. In proof-of-concept studies (Zhao et al. EBioMedicine 2019), they compared the effects of FGF21 chimera and FGF21WTon fatty liver in diabetic dyslipedimia mice (db/db) and showed considerable reduction in liver mass, a greater attenuation of hepatic steatosis, and reduction in the liver triglycerides compared to the WT. The study also saw greater corresponding reductions in serum levels of ALT and AST in mice.

Background

During the past century, dramatic modifications in lifestyle have radically changed the health priorities in most areas of the world, owing to a growing incidence of noncommunicable disease. The new epidemic in chronic liver disease is related to the burden of NAFLD, paralleling the worldwide increase of obesity. The global prevalence of NAFLD is currently estimated to be 24%. NAFLD, particularly its histological phenotype NASH, can potentially progress to advanced liver disease, cirrhosis and hepatocellular carcinoma (HCC). FGF21 analogs and FGF21 receptor agonists (FGF1RAs) that mimic FGF21 ligand activity constitute the new “FGF21-class” of anti-obesity and anti-diabetic molecules that improve insulin sensitivity, ameliorate hepatosteatosis and promote weight loss. The metabolic actions of FGF21-class proteins in obese mice are attributed to stimulation of brown fat thermogenesis and increased secretion of adiponectin. The therapeutic utility of FGF21-class molecules is under active investigation in clinical trials for the treatment of Type 2 diabetes and non-alcoholic steatohepatitis (NASH). However, native FGF21 has poor pharmacokinetics and there is an unmet need for enhanced, efficacious versions of FGF21.

Applications

- NAFLD
- Non-alcoholic steatohepatitis (NASH)
- Hepatic steatosis
- Type 2 Diabetes
- Obesity
- Related metabolic disorders

IP Status

This technology is protected by issued U.S. patents:

Category

Life Sciences/Biologics
Life Sciences/Therapeutics/Metabolic Diseases
Life Sciences/Therapeutics/Liver Disease
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Learn more

- US9475856B2
- US10174090B2

References

1. Dr. Moosa Mohammadi, et al. , Paracrine-endocrine FGF chimeras as potent therapeutics for metabolic diseases