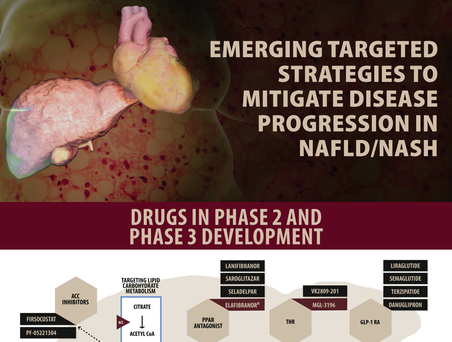
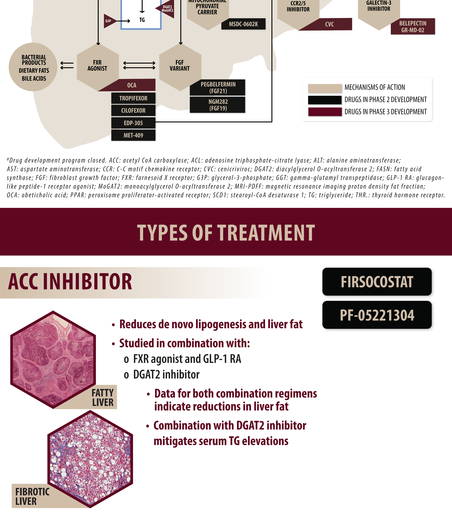


EMERGING TARGETED STRATEGIES TO MITIGATE DISEASE PROGRESSION IN NAFLD/NASH

DRUGS IN PHASE 2 AND PHASE 3 DEVELOPMENT



*Drug development program closed. *ACC: acetyl CoA carboxylase; ACL: adenosine triphosphate-citrate lyase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CCR: C-C motif chemokine receptor; CVC: cenicriviroc; DGAT2: diacylglycerol O-acyltransferase 2; FASN: fatty acid synthase; FGF: fibroblast growth factor; FXR: farnesoid X receptor; G3P: glycerol-3-phosphate; GGT: gamma-glutamyl transpeptidase; GLP-1 RA: glucagon-like peptide-1 receptor agonist; MoGAT2: monoacylglycerol O-acyltransferase 2; MRI-PDFF: magnetic resonance imaging proton density fat fraction; OCA: obeticholic acid; PPAR: peroxisome proliferator-activated receptor; SCD1: stearoyl-CoA desaturase 1; TG: triglyceride; THR.: thyroid hormone receptor.*

TYPES OF TREATMENT

ACC INHIBITOR

FIRSOCOSTAT

PF-05221304

- **Reduces de novo lipogenesis and liver fat**
- **Studied in combination with:**
  - FXR agonist and GLP-1 RA
  - DGAT2 inhibitor
    - **Data for both combination regimens indicate reductions in liver fat**
    - **Combination with DGAT2 inhibitor mitigates serum TG elevations**

FXR AGONIST

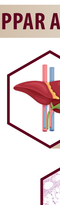
OCA

TROPIFEXOR

CILOFEXOR

EDP-305

MET-409



- **FXRs are nuclear receptors that bind bile acids**
  - Receptors are highly expressed in the liver and small intestine
    - **FXR and bile acids work together to:**
      - Regulate lipid and/or glucose homeostasis
      - Promote insulin sensitivity
      - Potentially modulate liver fibrosis
- **Pharmacologic activation by FXR agonists improves fibrosis in non-alcoholic steatohepatitis (NASH)**

FGF ANALOGUE ALDAFERMIN/ NGM282

PEGBELFERMIN (FGF21)

NGM282 (FGF19)

- **FGF analogues are engineered to regulate:**
  - Bile acid synthesis
  - Glucose homeostasis
    - **FGF analogues have been shown to:**
      - Reduce relative liver fat content
      - Improve fibrosis without worsening NASH
      - Resolve NASH without worsening fibrosis

GLP-1 RA

LIRAGLUTIDE

SEMAGLUTIDE

TERZIPATIDE

DANUGLIPRON

- **GLP-1 RAs are incretin mimetics**
- **Improve hepatic and adipose insulin sensitivity**
- **Decrease hepatic fat deposition, inflammation, and fibrosis**
  - **Increase free fatty-acid synthesis and glucose uptake in adipose tissue**
  - **GLP-1 RAs have been shown to resolve NASH without worsening fibrosis**

PPAR AGONISTS

ELAFIBRANOR

SELADELPAR

SAROGLITAZAR

LANIFIBRANOR

- **PPARs are a family of ligand-activated transcription factors that regulate several metabolic processes**
  - PPARα
    - » Expressed in the liver and other metabolically active tissues
    - » Lowers lipid levels
    - » Drives expressions of genes that regulate fatty acid β-oxidation, lipid transport, and the hormone FGF21
  - PPARδ
    - » Highly expressed in hepatocytes
    - » Involved in fatty acid oxidation
    - » Decreases hepatic glucose production
    - » Improves insulin sensitivity
    - » Exerts anti-inflammatory activities in macrophages and Kupffer cells
  - PPARγ
    - » Highly expressed in adipose tissue where they:
      - Increase glucose uptake
      - Promote storage of TGs
      - Decrease plasma free fatty acids
      - Induce secretion of anti-inflammatory cytokines
    - » Increases insulin sensitivity in multiple organs
- **PPAR agonists have been shown to:**
  - **Resolve NASH without worsening fibrosis**
  - **Improve fibrosis without worsening NASH**

THR AGONISTS

MGL-3196

VK2809-201

- **THRβ is highly expressed in the liver**
  - Regulates liver TG and cholesterol metabolism
    - **Observations suggest that NASH could be associated with diminished THR levels**
    - **Liver-specific THR activation has been shown to:**
      - Reduce liver fat
      - Reduce liver fibrosis
      - Resolve NASH

References: Boubia B, et al. J Med Chem. 2018;61:2246-2265. Calle RA, et al. Nat Med. 2021;27:1836-1848. Francque SM, et al. AASLD TLMdX 2020. Abstract 12. Ghazanfar H, et al. Cureus. 2021;13:e15141. Harrison SA, et al. Hepatology. 2018;68 (1 suppl):9A. Harrison SA, et al. Lancet. 2019;394:2012-2024. Harrison SA, et al. Gastroenterology. 2021;160:219-231.e1. Loomba R, et al. EASL dILC 2020. Abstract A5073. Loomba R, et al. EASL dILC 2020. Abstract LB004. Newsome PN, et al. N Engl J Med. 2021;384:1113-1124. Noureddin M, et al. Endocrinol Diabetes Metab. 2019;2:e00105. Vuppalanchi R, et al. Nat Rev Gastroenterol Hepatol. 2021;18:373-392. Younossi ZM, et al. Lancet. 2019;394:2184-2196.