



# Emerging metabolic hormone therapeutics for metabolic dysfunction-associated steatohepatitis: incretin-based drugs, fibroblast growth factor analogs, and liver-targeting strategies

Sukwoo Han<sup>1</sup> · Jaehee Shin<sup>2</sup> · Jae Cheon Kim<sup>1</sup> · Dong Hee Na<sup>1,2,3</sup> 

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## Abstract

**Background** As the prevalence of metabolic dysfunction-associated steatohepatitis (MASH) continues to rise, drug development has accelerated, with growing interest in therapeutic strategies that harness metabolic hormones. Metabolic hormone-based approaches, particularly those originally developed for obesity and diabetes, have shown potential to mitigate MASH. Notably, the glucagon-like peptide-1 receptor (GLP-1R) agonist semaglutide received accelerated approval for MASH in 2025. In addition, GLP-1R-based multi-agonists and candidates leveraging the metabolic actions of fibroblast growth factor (FGF) 21 are in active clinical development for liver disease.

**Area covered** This review provides an overview of metabolic hormone-based therapies, including incretin-based drugs and FGF analogs, that are currently under clinical development for MASH. It also discusses liver-targeting strategies to achieve selective hepatic delivery, which may vary according to the expression of liver-specific receptors and fibrosis degree.

**Expert opinion** Within the MASH therapeutic landscape, incretin-based therapies are evolving from GLP-1R mono-agonist to multi-agonist approaches that aim to combine weight loss-mediated benefits with mechanisms that directly modulate hepatic lipid handling and inflammation. Moreover, the therapeutic actions of metabolic hormones in MASH, together with the expression profiles of their corresponding receptors, play a critical role in determining targeting strategies. Stage-specific and liver-selective delivery strategies will likely distinguish next-generation candidates. This review summarizes the pharmacological mechanisms and delivery strategies of each agent class and further explores these receptors as potential targets to inform the development of precision therapeutic approaches.

**Keywords** Metabolic dysfunction-associated steatohepatitis · Glucagon-like peptide-1 receptor agonist · Fibroblast growth factor · Liver targeting

## Introduction

Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), is the progressive inflammatory phenotype of metabolic dysfunction-associated steatotic liver disease (MASLD), histologically defined by steatosis, lobular inflammation, and hepatocyte ballooning, with or without fibrosis (Rinella et al. 2023). As MASLD progresses to MASH, the risks of cirrhosis, liver failure, hepatocellular carcinoma, and death increase, and among disease features, the fibrosis stage is the main determinant of mortality (Schwabe et al. 2020). The global prevalence of MASLD is currently about 38% and is projected to rise to 55.7% by 2040 (Le et al. 2022; Stefan et al. 2025). In the United States, MASH prevalence

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Sukwoo Han and Jaehee Shin contributed equally to this work.

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✉ Dong Hee Na  
dhna@cau.ac.kr

<sup>1</sup> Department of Global Innovative Drugs, The Graduate School of Chung-Ang University, Seoul 06974, Republic of Korea

<sup>2</sup> Department of Pharmaceutical Regulatory Sciences, The Graduate School of Chung-Ang University, Seoul 06974, Republic of Korea

<sup>3</sup> College of Pharmacy, Chung-Ang University, 84 Heukseok-ro, Dongjak-gu, Seoul 06974, Republic of Korea

among adults was about 5.8% in 2020 and is projected to increase to 7.9% by 2050 (Le et al. 2025).

Despite the disease's clinical burden, until recently, no therapy for MASH had been approved; however, the therapeutic landscape has shifted rapidly. Resmetirom (Rezdiffra®) received accelerated approval in March 2024 for noncirrhotic MASH with stage F2–F3 fibrosis based on liver histology results. In August 2025, semaglutide (2.4 mg, Wegovy®) likewise received accelerated approval for adults with MASH and moderate-to-advanced fibrosis based on interim liver histology results, with follow-up in confirmatory phase 3 outcomes trials ongoing (Keam, 2024; U.S. Food and Drug Administration, 2025).

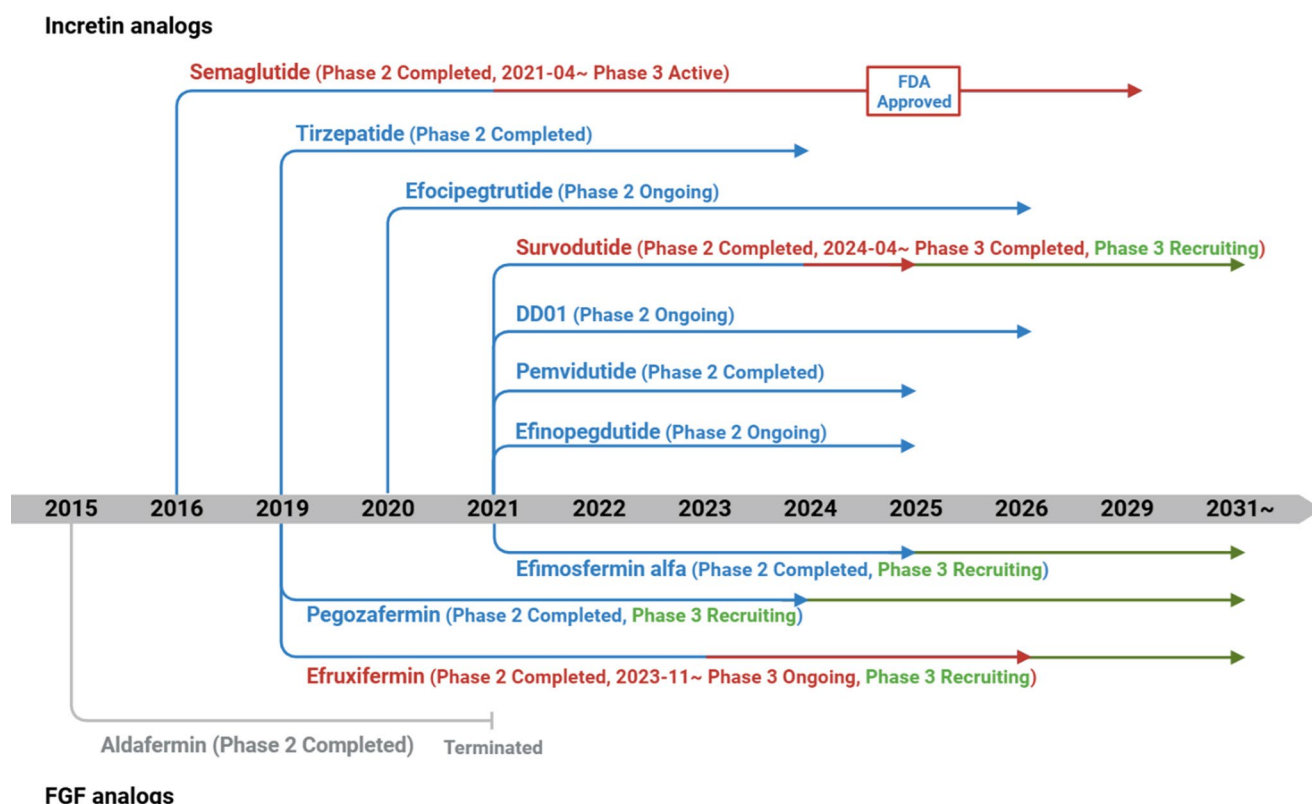
To address the heterogeneous and multifactorial pathophysiology of MASH, various therapeutic agents with different mechanisms of action are currently under development for the treatment of MASH. MASLD pathogenesis and its progression to MASH and cirrhosis are closely associated with metabolic imbalance and insulin resistance (Llovet et al. 2023). Individuals with type 2 diabetes mellitus (T2DM) show a greater tendency toward liver fibrosis progression (Huang et al. 2023). Obesity is also linked to both the development and progression of MASLD, and increasing body mass index correlates with a higher incidence of MASLD and progressive hepatic fibrosis (Koliaki

et al. 2025). This overlapping pathophysiology underscores the need for therapies that address obesity, T2DM, and MASH simultaneously. Accordingly, incretin-based therapies such as glucagon-like peptide-1 receptor (GLP-1R) agonists and fibroblast growth factor (FGF) family analogs, which were originally developed for the treatment of T2DM and obesity, are now being explored as potential treatments for MASH (Fig. 1). These agents may exert both direct and indirect effects on the liver, offering the potential to improve metabolic dysfunction and attenuate fibrogenesis. In addition, thyroid hormone receptor- $\beta$  (THR- $\beta$ ) agonists, farnesoid X receptor (FXR) agonists, and oligonucleotide-based therapeutics are under development. This review introduces the therapeutic mechanisms of metabolic hormones, summarizes clinical advances, and discusses delivery strategies for MASH therapies.

## Incretin analogs for MASH treatment

### GLP-1R agonists

GLP-1R agonists have been approved for the treatment of T2DM and obesity (Park et al. 2016; Holst, 2024). Recently, semaglutide received accelerated approval for MASH treatment, expanding the class's clinical relevance. GLP-1 is



**Fig. 1** Clinical development of metabolic hormone-based MASH therapies. MASH/NASH therapeutics in development, organized by year through those with active phase 3 status. Created with BioRender.com

secreted from intestinal L-cells and acts on pancreatic  $\beta$ -cells to increase insulin secretion in a glucose-dependent manner (Kjems et al. 2003; Meloni et al. 2013). GLP-1 also suppresses  $\alpha$ -cell glucagon release, thereby improving glycemic control. In energy balance, GLP-1 signaling regulates appetite and caloric intake via receptors expressed in several brain regions that govern satiety. Circulating GLP-1R agonists bind to GLP-1 receptors in the myenteric plexus, delaying gastric emptying (Halim et al. 2018). They also reduce leptin resistance, thereby enhancing leptin signaling, which increases satiety, reduces food intake, and elevates energy expenditure (Elmqvist et al. 1998; Ronveaux et al. 2015). GLP-1R agonists also suppress appetite through actions on the central nervous system. The binding of GLP-1R agonists to receptors in the nucleus tractus solitarius of the brainstem activates serotonergic neurons, which induces satiety and reduces food intake (van Bloemendaal et al. 2014). In addition, activation of GLP-1 receptors in the area postrema of the brainstem decreases appetite via dopaminergic signaling (Rinaman, 2010). Activation of hypothalamic GLP-1 receptors increases the secretion of anorexigenic peptides while decreasing the secretion of orexigenic peptides (Secher et al. 2014; Geloneze et al. 2017). Moreover, GLP-1R agonists reduce inflammation, thereby improving adipose tissue function and enabling the appropriate regulation of fat storage and release, which ultimately reduces ectopic fat deposition and body weight (Alharbi, 2024). Through these mechanisms, GLP-1R agonists slow gastric emptying and lower body weight. For treatment of MASH in humans, however, the precise mechanism of action is not fully understood and likely involves multiple pathways mediated by weight loss and other factors.

In MASH, most of the observed clinical benefits of GLP-1R agonists appear to be largely mediated by weight loss. However, whether GLP-1R agonists have clinically meaningful direct hepatocellular actions remains uncertain. Some preclinical work suggests enhanced fatty-acid oxidation, whereas other datasets report minimal hepatocyte GLP-1R expression and no direct hepatic actions. Evidence supporting direct hepatic actions of GLP-1R agonists includes studies demonstrating GLP-1R expression in hepatocytes. Gupta et al. reported that GLP-1R mRNA and protein are expressed in both primary human hepatocytes and Huh-7 cells, and that GLP-1 induces GLP-1R internalization in these cells (Gupta et al. 2010). In the same study, treatment with the GLP-1R agonist exendin-4 (EX-4) activated GLP-1R signaling. Ben-Shlomo et al. showed that GLP-1 treatment in primary hepatocytes increased intracellular cAMP levels and regulated hepatic lipogenesis via AMPK signaling activation (Ben-Shlomo et al. 2011). Lee et al. demonstrated that treatment of palmitic acid-loaded HepG2 cells with the GLP-1R agonist dulaglutide significantly increased

both protein levels and mRNA expression of FAM3A, a factor promoting fatty acid oxidation, thereby confirming that GLP-1R agonists enhance fatty acid  $\beta$ -oxidation (Lee et al. 2022). Additionally, De Mesquita et al. demonstrated that treatment with liraglutide decreased  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) and collagen I expression in human primary hepatic stellate cells (HSCs) and reduced  $\alpha$ -SMA and platelet-derived growth factor receptor  $\beta$  expression in chronic liver disease rats (De Mesquita et al. 2017).

Conversely, other studies have reported limited GLP-1R expression in hepatocytes. In a positron emission tomography imaging study with the GLP-1R tracer  $^{68}\text{Ga}$ -exendin-4, Eriksson et al. reported high pancreatic uptake and minimal uptake in other abdominal tissues, consistent with negligible hepatic GLP-1R expression (Eriksson et al. 2019). Consistently, GLP-1R was not detected in monkey liver cells (Pyke et al. 2014). Seo et al. found that GLP-1 and EX-4 showed limited hepatic distribution in diet-induced obesity rats (Seo et al. 2017). Furthermore, da Silva Lima et al. reported that treatment of human hepatocytes and HSCs with the GLP-1R agonist liraglutide failed to improve fibrotic markers or activate insulinotropic signaling pathways (Da Silva Lima et al. 2024).

Clinically, weight reduction correlates with histologic response in steatohepatitis, supporting guideline targets  $\geq 7$ –10% weight loss for histologic benefit (Tacke et al. 2024). The therapeutic effects of GLP-1R agonists in MASH appear to be predominantly indirect and mediated by weight loss. Indeed, RNA sequencing of liver tissue from healthy participants, patients with MAFLD, and patients with MASH showed minimal GLP-1R expression (Da Silva Lima et al. 2024). Collectively, GLP-1R agonists may improve MASH through indirect, weight-loss-driven mechanisms rather than through direct hepatocyte actions.

### GLP-1R/GIPR dual agonist

Secreted from K-cells, glucose-dependent insulinotropic polypeptide (GIP) enhances insulin secretion through direct activation of GIPR on pancreatic  $\beta$ -cells in a glucose-dependent manner and promotes nutrient uptake into adipose tissue (Seino et al. 2010; Seino & Yamazaki, 2022). Additionally, GIP can increase glucagon secretion from pancreatic  $\alpha$ -cells, which may secondarily augment its insulinotropic activity at lower glucose levels (Lewandowski et al. 2024). The body weight-reducing effects of GIPR agonists are more pronounced when these agents are co-administered with GLP-1R agonists than when they are used alone (Finan et al. 2013). Similar to GLP-1Rs, GIP receptors are also expressed in brain regions involved in appetite regulation (Samms et al. 2021). Therefore, GLP-1R/GIPR dual

agonists have been developed for the treatment of diabetes and obesity.

The mechanism underlying GIPR agonism in the treatment of MASH remains unclear (Newsome & Ambery, 2023), and its therapeutic effects appear to be indirect, similar to those of GLP-1R agonists. RNA sequencing of liver tissue from healthy individuals, individuals with MAFLD, and individuals with MASH revealed minimal GIPR expression (Da Silva Lima et al. 2024). Despite this limited mechanistic understanding, clinical evaluation of GLP-1R/GIPR dual agonists in MASH is ongoing. In patients with diabetes, the GLP-1R/GIPR dual agonist tirzepatide improved biomarkers relevant to MASH, including alanine aminotransferase (ALT), aspartate aminotransferase, keratin 18, PRO-C3, a marker of type III collagen formation, as well as adiponectin (Hartman et al. 2020). Moreover, in adults with MASH and fibrosis, tirzepatide improved liver histology, with higher rates of MASH resolution and fibrosis improvement (Loomba et al. 2024).

### GLP-1R/GCGR dual agonists

Oxyntomodulin is an endogenous peptide hormone that acts as an agonist at both the GLP-1R and glucagon receptor (GCGR) (Zimmermann et al. 2022), thereby mediating meaningful weight reduction and increased energy expenditure through its dual agonist activity (Wynne et al. 2005, 2006). However, its very short half-life, approximately 12 min, limits its therapeutic applicability (Schjoldager et al. 1988). Nevertheless, it provided the conceptual basis for GLP-1R/GCGR dual agonism and thereby motivated the development of long-acting GLP-1R/GCGR dual agonists.

Mechanistically, GLP-1 induces weight loss by suppressing appetite and delaying gastric emptying (Moiz et al. 2025), while glucagon exerts anorectic effects and promotes energy expenditure (Al-Massadi et al. 2019). Accordingly, dual agonism offers the potential for synergistic benefits in the treatment of obesity. Moreover, glucagon may contribute to improved glycemic control by potentiating  $\beta$ -cell insulinotropic signaling, especially in the presence of GLP-1 (Finan et al. 2020). Consistent with this proposed mechanism, co-administration of GLP-1 and glucagon resulted in a 2.4-fold increase in insulin secretion compared with GLP-1 monotherapy (Tan et al. 2013). Furthermore, the GLP-1R/GCGR dual agonist cotadutide demonstrated superior effects on insulin sensitivity compared with those of liraglutide and the GCGR agonist g1437 (Laker et al. 2025). Specifically, dual agonism improved the glucose infusion rate and produced greater improvements in insulin sensitivity, supporting its therapeutic potential in diabetes.

Glucagon receptor engagement promotes hepatic fatty acid oxidation and reduces liver fat, but excessive activation

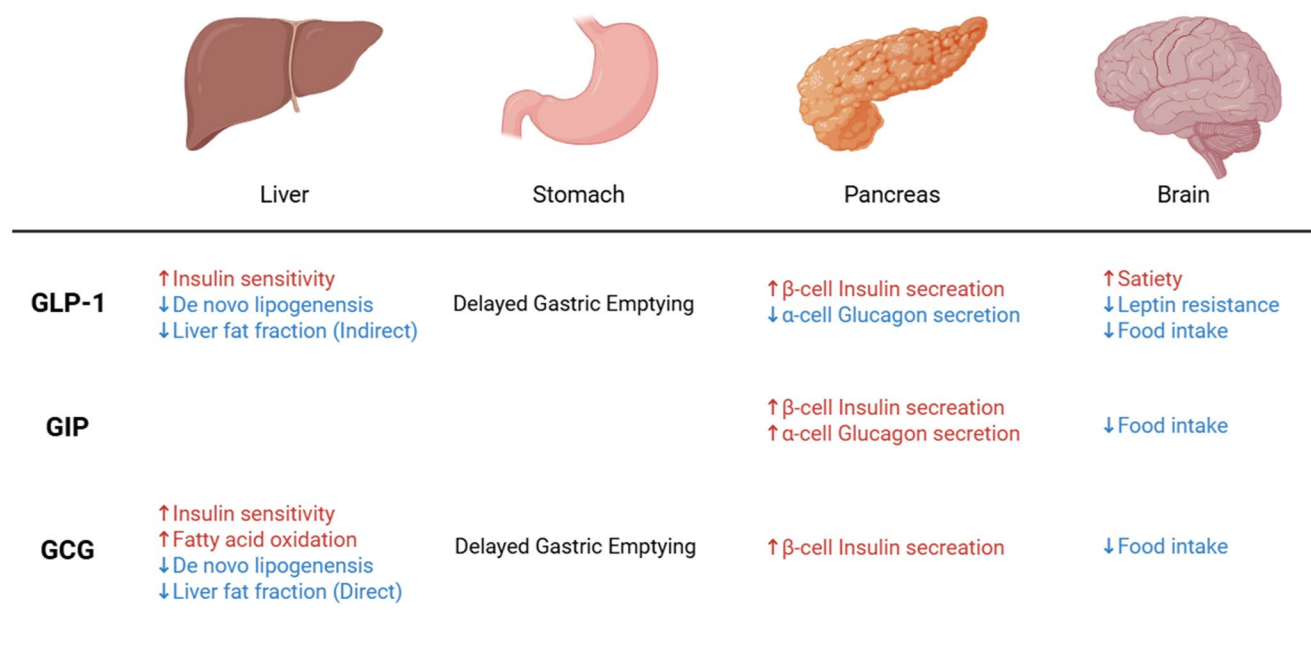
can also increase blood glucose levels. Dual GLP-1R/GCGR agonism is designed to preserve these hepatic lipid-lowering effects while reducing caloric intake and increasing energy expenditure, with GLP-1-mediated insulinotropic activity helping offset the glycemic liability associated with GCGR activation. The overall benefit depends on the GLP-1R:GCGR activity ratio, dose, exposure profile, and background metabolic control. As many patients with MASH have comorbid T2DM, and hyperglycemia can accelerate MASH progression, careful optimization of this balance is essential to capture hepatic benefit while maintaining glycemic control. Unlike GLP-1R or GIPR, GCGR is abundantly expressed in the liver (Svoboda et al. 1994). Therefore, combined targeting of GCGR and GLP-1R offers the potential for direct hepatic pharmacology in addition to weight-loss-mediated benefit. Glucagon promotes hepatic fatty acid oxidation while suppressing de novo lipogenesis (Wang et al. 2016), and it can modulate glycogen flux and improve mitochondrial turnover and function, thereby reducing hepatic lipid content (Boland et al. 2020). This liver-predominant expression profile makes GCGR an attractive target for the active targeting strategies discussed later. In rodent MASH models, GLP-1R/GCGR dual agonists such as pemvidutide and NN1177 improved liver enzyme levels, body weight, steatosis, inflammation, and fibrosis (Nestor et al. 2022; Monfeuga et al. 2024; Harrison et al. 2025). In addition, cotadutide inhibited hepatic lipogenesis and showed superior antifibrotic effects compared with a GLP-1R agonist and an FXR agonist (Boland et al. 2020).

### GLP-1R/GIPR/GCGR triple agonists

GLP-1R/GIPR/GCGR triple agonists are being developed for obesity and T2DM, combining the incretin-mediated benefits of GLP-1R and GIPR agonism on glycemic control and appetite suppression with GCGR agonism to increase energy expenditure (Fig. 2). Their potential in MASLD/MASH is also being explored. Finan et al. demonstrated that investigational unimolecular triple agonists produced superior effects on weight loss and glycemic control compared with mono or dual agonist approaches (Finan et al. 2015).

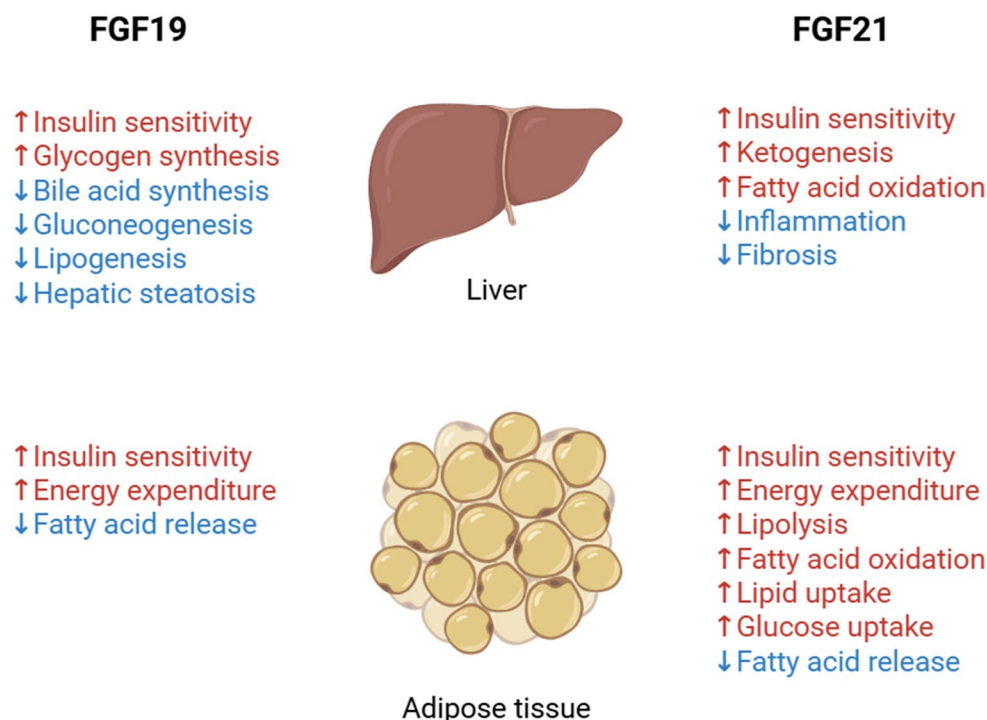
### FGF analogs for MASH treatment

Among the FGF family, FGF19 and FGF21 function as metabolic hormones that influence energy homeostasis (Zhang et al. 2015). Although no FGF-based therapies have been approved to date, multiple FGF analogs for MASH are being developed based on their metabolic effects (Fig. 3).



**Fig. 2** Therapeutic mechanisms of GLP-1, GIP, and glucagon in the liver, stomach, pancreas, and brain. Created with BioRender.com

**Fig. 3** Therapeutic mechanisms of FGF19 and FGF21 in the liver and adipose tissue. Created with BioRender.com



### FGF19

FGF19 (the human ortholog of rodent FGF15) is a hormone produced in the ileum (Talukdar & Kharitonov, 2021) in response to FXR activation. FGF signaling requires fibroblast growth factor receptors (FGFRs) and the co-receptor β-Klotho (KLB) (Kurosu et al. 2007). FGFRs belong to the

receptor tyrosine kinase family, whereas KLB is a membrane protein that functions as a co-receptor (Lemmon & Schlessinger, 2010). In humans, KLB is expressed in the liver, adipose tissue, pancreas, small intestine, and muscle (Harrison et al. 2024).

Initially, FGF19 was developed for bile acid regulation, T2DM, and obesity (Wu & Li, 2011). FGF19 was

investigated as a therapeutic agent for diabetes by suppressing gluconeogenesis, promoting glycogen synthesis (Kir et al. 2011; Potthoff et al. 2011), and improving insulin sensitivity (Tomlinson et al. 2002). In MASH, the therapeutic effects of FGF19 are mediated primarily through the regulation of bile acid synthesis. Accumulation of excess bile acids promotes HSCs activation, contributing to hepatic fibrosis (Svegliati-Baroni et al. 2005), inflammation, and liver injury (Li et al. 2017). FGF19 engages the hepatic FGFR4/KLB complex and suppresses CYP7A1, thereby reducing bile acid synthesis (Henriksson & Andersen, 2020), thereby decreasing hepatotoxic lipids, such as diacylglycerols, ceramides, and free cholesterol (Zhou et al. 2017). In addition, FGF19 enhances insulin sensitivity, allowing insulin to inhibit free fatty acid release from adipose tissue, limiting their accumulation in hepatocytes (Tomlinson et al. 2002). Moreover, FGF19-mediated inhibition of lipogenic enzymes and transcriptional activators suppresses de novo lipogenesis (Bhatnagar et al. 2009). Beyond lipid regulation, FGF19 may also contribute to the treatment of MASH through increased energy expenditure and subsequent weight reduction (Fu et al. 2004).

A key liability of native FGF19 is its mitogenic FGFR4 signaling observed in preclinical systems, which prompted engineering of FGF19-based analogs designed to retain metabolic activity while minimizing mitogenic potential, which is an essential consideration for chronic use in MASH (Zhou et al. 2017).

## FGF21

FGF21 is under development for hypertriglyceridemia, dyslipidemia, T2DM, and obesity, and is also being increasingly evaluated in MASH (Harrison et al. 2024). FGF21 is predominantly synthesized and activated in the liver and adipose tissue (Dolegowska et al. 2019). Similar to FGF19, FGF21 binds to the FGFR-KLB receptor complex, with the highest affinity for FGFR1c-KLB, while engaging FGFR3c (Suzuki et al. 2008). Within the C-terminal tail of FGF21, two sites interact with the KL1 and KL2 domains of KLB (Shi et al. 2018). The amino acid sequence spanning P158–S181 binds a broad surface within the extracellular domain of KLB (Aaldijk et al. 2023), the DP and SPS motifs mediating direct interactions (Kuzina et al. 2019). Compared with FGF19, FGF21 displays higher specificity for KLB than  $\alpha$ -Klotho, thereby conferring greater receptor selectivity (Shi et al. 2018). Recent studies have further suggested that, in addition to FGFR and KLB, heparin is required for FGF21 signaling (Suzuki et al. 2008; An et al. 2023).

FGF21 secretion is regulated by dietary composition. Its secretion increases under conditions of low protein intake or high fructose or carbohydrate consumption (Dushay et

al. 2015), as well as during fasting (Inagaki et al. 2007). Following secretion, FGF21 enhances insulin sensitivity, thereby suppressing free fatty acid release from adipose tissue and limiting free fatty acid accumulation within hepatocytes (Dushay et al. 2015). Furthermore, FGF21 promotes lipolysis in white adipose tissue and stimulates ketogenesis in the liver (Inagaki et al. 2007). It also promotes the uptake of glucose and lipids in adipose tissue (Kharitonov et al. 2005; Schlein et al. 2016). Consequently, FGF21 reduces blood glucose, triglyceride, and cholesterol levels, as well as body weight (Hecht et al. 2012). Beyond its peripheral actions, FGF21 can modulate central circuits by acting on glutamatergic neurons, leading to reduced hepatic triglyceride levels and improved fibrosis (Rose et al. 2025). Through its ability to suppress fibrosis and lipid accumulation, FGF21 demonstrates therapeutic potential for the treatment of MASH. As proven by F21 knockout mice, compared with wild-type mice, as they exhibit reduced hepatic fatty acid activation and  $\beta$ -oxidation, elevated free fatty acid levels, and more severe hepatic steatosis, fibrosis, inflammation, and peroxidative damage (Fisher et al. 2014).

While the metabolic benefits have made FGF21 an attractive target, multiple rodent studies, including FGF21-overexpression models, have shown reduced bone mass, with mechanisms involving PPAR $\gamma$ -mediated suppression of osteoblastogenesis and increased osteoclast activity (Wei et al. 2012). These preclinical bone-loss risks warrant prospective monitoring in clinical programs, including dual-energy X-ray absorptiometry and procollagen type I N-terminal propeptide/C-terminal telopeptide of type I collagen assessment, especially in long-duration studies and in patients with baseline osteopenia or osteoporosis. Available human data over short-to-mid-term treatment are generally reassuring, but multi-year safety remains to be established (Loomba et al. 2023).

## Ongoing clinical trials for MASH therapies

Table 1 summarizes incretin analogs, FGF analogs, oligonucleotide, and small molecules in clinical trials for MASH therapies.

### GLP-1R agonist

#### Semaglutide

Semaglutide, a GLP-1R agonist developed by Novo Nordisk, is approved as a once-weekly subcutaneous injection, marketed as Ozempic® for T2DM and as Wegovy® for chronic weight management and cardiovascular risk reduction, and as a once-daily oral tablet, marketed as Rybelsus®

**Table 1** MASH therapies in clinical trials

| Drug Class       | Drug /Company /Development stage              | Mechanism                | Trial phase and identifier | Dosing    | Size/duration                                                                                          | Primary end point                                                                                                                                                                                         | Results                                                                                                                                                                                                                                                          | Reference            |
|------------------|-----------------------------------------------|--------------------------|----------------------------|-----------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Incretin analogs | Semaglutide/Novo Nordisk/Accelerated approval | GLP-1R agonist           | Phase III (NCT04822181)    | Weekly sc | Part 1: Planned interim analysis in first 800 patients for 72 weeks<br>Part 2: 1205 patients/240 weeks | Part 1: Histology (Resolution of steatohepatitis with no worsening of liver fibrosis and a reduction in liver fibrosis with no worsening of steatohepatitis)<br>Part 2: Outcome (cirrhosis-free survival) | Part 1<br>Resolution of steatohepatitis without worsening of fibrosis<br>2.4 mg: 62.9%<br>Placebo: 34.3%<br>$p < 0.001$<br>Reduction in liver fibrosis without worsening of steatohepatitis<br>2.4 mg: 36.8%<br>Placebo: 22.4%<br>$p < 0.001$<br>Part 2: Ongoing | (Sanyal et al. 2025) |
|                  | Tirzepatide/Eli Lilly/Phase II                | GLP-1R/GIPR dual-agonist | Phase II (NCT04166773)     | Weekly sc | 190 patients/52 weeks                                                                                  | Resolution of MASH without worsening of fibrosis                                                                                                                                                          | Resolution of MASH without worsening of fibrosis<br>5 mg: 44%<br>10 mg: 56%<br>15 mg: 62%<br>placebo: 10%<br>$p < 0.001$                                                                                                                                         | (Loomba et al. 2024) |
|                  | Survodutide/Boehringer Ingelheim/Phase III    | GLP-1R/GCGR dual-agonist | Phase II (NCT04771273)     | Weekly sc | 293 patients/48 weeks                                                                                  | Histological improvement in MASH and no worsening of fibrosis                                                                                                                                             | Improvement in MASH with no worsening of fibrosis<br>2.4 mg: 47%<br>4.8 mg: 62%<br>6.0 mg: 43%<br>placebo: 14%<br>$p < 0.001$                                                                                                                                    | (Sanyal et al. 2024) |
|                  | Pemvidutide/Altimmune/Phase II                | GLP-1R/GCGR dual-agonist | Phase II (NCT05989711)     | Weekly sc | 190 patients/48 weeks                                                                                  | MASH resolution without worsening of fibrosis or Fibrosis improvement without worsening of MASH at week 24                                                                                                | MASH resolution without worsening of fibrosis<br>1.2 mg: 59%<br>1.8 mg: 52%<br>placebo: 19%<br>$p < 0.0001$<br>Fibrosis improvement without MASH worsening<br>1.2 mg: 32%<br>1.8 mg: 35%<br>placebo: 26%<br>NS                                                   | (Altimmune, 2025)    |

Table 1 (continued)

| Drug Class  | Drug /Company /Development stage                | Mechanism                       | Trial phase and identifier | Dosing                     | Size/duration          | Primary end point                                                                                                     | Results                                                                                                                                                                                                                                                     | Reference              |
|-------------|-------------------------------------------------|---------------------------------|----------------------------|----------------------------|------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| FGF analogs | DD01/D&D Pharmatech/Phase II                    | GLP-1R/GCGR dual-agonist        | Phase II (NCT06410924)     | Weekly sc                  | 67 patients/48 weeks   | ≥30% reduction in liver fat by MRI-PDFF at week 12                                                                    | ≥30% reduction in liver fat by MRI-PDFF at week 12<br>Placebo: 12%<br>$p<0.0001$<br>Ongoing                                                                                                                                                                 | (D&D Pharmatech, 2025) |
|             | Efinopegdutide/Merck Sharp & Dohme LLC/Phase II | GLP-1R/GCGR dual-agonist        | Phase II (NCT05877547)     | Weekly sc                  | 360 patients/52 weeks  | Resolution without worsening of fibrosis at week 52                                                                   | Ongoing                                                                                                                                                                                                                                                     |                        |
|             | Efocipegrutide/Hanmi Pharmaceutical/Phase II    | GLP-1R/GIPR/GCGR triple-agonist | Phase II (NCT04505436)     | Weekly sc                  | 215 patients/12 months | Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis                 | Ongoing                                                                                                                                                                                                                                                     |                        |
|             | Aldafermin/NGM Biopharmaceuticals/Discontinued  | FGF19 analog                    | Phase II (NCT04210245)     | Daily sc                   | 160 patients/48 weeks  | Change in the ELF score from baseline to week 48 with aldafermin versus placebo                                       | Fibrosis improvement<br>1 mg: 21%<br>3 mg: 23%<br>placebo: 15%<br>NS                                                                                                                                                                                        | (Rinella et al. 2024)  |
|             | Efruxifermin/Akero Therapeutics/Phase III       | Fc-fused FGF21 analog           | Phase II (NCT04767529)     | Weekly sc                  | 128 patients/96 weeks  | Improvement of fibrosis without worsening of MASH at week 24                                                          | Fibrosis improvement<br>28 mg: 39%<br>50 mg: 41%<br>placebo: 20%<br>$p<0.05$                                                                                                                                                                                | (Harrison et al. 2023) |
|             | Pegozafermin/89bio/Phase III                    | PEGylated FGF21 analog          | Phase II (NCT04929483)     | Weekly sc/Every 2 weeks sc | 219 patients/52 weeks  | Fibrosis improvement without worsening of MASH at week 24<br>MASH resolution without worsening of fibrosis at week 24 | Fibrosis improvement without worsening MASH<br>15 mg QW: 22%<br>30 mg QW: 26%<br>44 mg Q2W: 27%<br>Placebo: 7%<br>$p<0.01$<br>MASH resolution without worsening of fibrosis<br>15 mg QW: 37%<br>30 mg QW: 23%<br>44 mg Q2W: 26%<br>Placebo: 2%<br>$p<0.001$ | (Loomba et al. 2023)   |

**Table 1** (continued)

| Drug Class      | Drug /Company /Development stage                   | Mechanism               | Trial phase and identifier | Dosing                            | Size/duration         | Primary end point                                                                                                                                         | Results                                                                                                                                                                                                  | Reference            |
|-----------------|----------------------------------------------------|-------------------------|----------------------------|-----------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Oligonucleotide | Efimosfermin alfa/Boston Pharmaceuticals/Phase III | Fe-fused FGF21 analog   | Phase II (NCT04880031)     | Every 2 weeks sc/Every 4 weeks sc | 231 patients/12 weeks | Number of participants with TEAEs and TSEAEs                                                                                                              | MASH resolution without fibrosis worsening 300 mg Q4W: 68%<br>Placebo: 29%<br>$p < 0.01$<br>$\geq 1$ -stage fibrosis improvement without MASH worsening in 300 mg Q4W: 45%<br>Placebo: 21%<br>$p < 0.05$ | (Alkhour, 2024)      |
|                 | AZD2693/AstraZeneca/Discontinued                   | GalNAc conjugated ASO   | Phase II (NCT05809934)     | Monthly sc                        | 220 patients/52 weeks | Resolution without worsening of fibrosis based on histology                                                                                               | Data not disclosed                                                                                                                                                                                       |                      |
|                 | ION224/Ionis Pharmaceuticals/Phase II              | Ligand conjugated ASO   | Phase II (NCT04932512)     | Monthly sc                        | 160 patients/49 weeks | $\geq 2$ -point reduction in NAS with $\geq 1$ -point improvement in hepatocellular ballooning or lobular inflammation, and without worsening of fibrosis | (% of participants)<br>90 mg: 46%<br>120 mg: 59%<br>placebo: 18.7%<br>$p < 0.01$                                                                                                                         | (Loomba et al. 2025) |
|                 | ALN-HSD/Regeneron Pharmaceuticals/Phase II         | GalNAc conjugated siRNA | Phase II (NCT05519475)     | Every 12 weeks sc                 | 90 patients/52 weeks  | Change in the continuous quantitative liver fibrosis (qFibrosis) score                                                                                    | Ongoing                                                                                                                                                                                                  |                      |

Table 1 (continued)

| Drug Class     | Drug/Company/Development stage                            | Mechanism            | Trial phase and identifier | Dosing   | Size/duration                   | Primary end point                                                                                                                                                                                                      | Results                                                                                                                                                                                                                                                                                         | Reference               |
|----------------|-----------------------------------------------------------|----------------------|----------------------------|----------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Small molecule | Resmetirone/Madrigal Pharmaceuticals/Accelerated approval | THR- $\beta$ agonist | Phase III (NCT03900429)    | Daily po | 1759 patients/ $\leq$ 54 months | Week 52: Resolution with no worsening of fibrosis, and an improvement in fibrosis by at least one stage with no worsening of the NAS<br>Week 54: All-cause mortality, liver transplant, and significant hepatic events | Week 52: Resolution with no worsening of fibrosis<br>80 mg qd: 25.9%<br>100 mg qd: 29.9%<br>Placebo: 9.7%<br>$p < 0.001$<br>Fibrosis improvement by at least one stage without worsening the NAS<br>80 mg qd: 24.2%<br>100 mg qd: 25.9%<br>Placebo: 14.2%<br>$p < 0.001$<br>Month 54<br>Ongoing | (Harri-son et al. 2024) |
|                | Obeticholic acid/Intercept Pharmaceuticals/Discontinued   | FXR agonist          | Phase III (NCT03439254)    | Daily po | 919 patients/ $\leq$ 18 months  | Improvement in Fibrosis by at Least 1 Stage Without Worsening of MASH                                                                                                                                                  | 10 mg: 11.1%<br>25 mg: 11.9%<br>placebo: 9.9%<br>NS                                                                                                                                                                                                                                             | (Wang et al. 2024)      |
|                | Cilofexor/Gilead Sciences/Phase II                        | FXR agonist          | Phase II (NCT02854605)     | Daily po | 140 patients/ $\leq$ 24 weeks   | Overall safety as assessed by percentage of participants with TEAE                                                                                                                                                     | $\geq$ 30% reduction in liver fat by MRI-PDFF<br>100 mg: 39%<br>30 mg: 14%<br>Placebo: 13%<br>$p < 0.05$ for 100 mg                                                                                                                                                                             | (Patel et al. 2020)     |

Trials were retrieved from ClinicalTrials.gov; NCT identifiers correspond to registry records. ELF, enhanced liver fibrosis; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; NAS, NAFLD Activity Score; po, per os injection; NS, not significant

for T2DM. In August 2025, Wegovy® received accelerated approval in the USA for the treatment of noncirrhotic MASH with moderate-to-advanced liver fibrosis (F2–F3) in adults, as an adjunct to a reduced-calorie diet and increased physical activity. The MASH indication remains contingent on confirmatory outcome data.

The phase 3 ESSENCE program (NCT04822181) randomized adults with biopsy-proven MASH and F2–F3 fibrosis 2:1 to semaglutide 2.4 mg SC weekly or placebo for 240 weeks. Part 1, a planned interim analysis at week 72 in the first approximately 800 participants, evaluated coprimary histologic endpoints: resolution of steatohepatitis without worsening of fibrosis and at least 1-stage improvement in fibrosis without worsening of steatohepatitis. Part 2 continues through week 240, with cirrhosis-free survival as the primary endpoint (Sanyal et al. 2025).

In Part 1, semaglutide met both histologic primary endpoints: 62.9% achieved MASH resolution without fibrosis worsening, whereas it was 34.3% with placebo, and 36.8% achieved fibrosis improvement without MASH worsening, whereas it was 22.4% with placebo. Mean body-weight change at week 72 was −10.5% with semaglutide whereas it was −2.0% with placebo (Sanyal et al. 2025). For context, weight loss with semaglutide 2.4 mg in general obesity (STEP1) averaged −14.9% at 68 weeks, suggesting that weight reduction may be smaller in the MASH population, likely reflecting disease-specific characteristics and differences in trial design (Wilding et al. 2021). Therefore, Wegovy® received accelerated approval, and its indication was expanded to include noncirrhotic MASH with moderate-to-advanced liver fibrosis in adults.

## GLP-1R/GIPR dual agonist

### Tirzepatide

Tirzepatide is a once-weekly GLP-1R/GIPR dual agonist developed by Eli Lilly and is the first agent in this class to receive FDA approval. It is marketed as Mounjaro® for T2DM (May 13, 2022) (Eli Lilly and Company, 2022), as Zepbound® for chronic weight management (November 8, 2023) and for moderate-to-severe obstructive sleep apnea in adults with obesity (December 20, 2024) (Eli Lilly and Company, 2025).

In the phase 2 SYNERGY-NASH trial (NCT04166773), adults with biopsy-confirmed MASH and F2–F3 fibrosis were randomized to receive tirzepatide at doses of 5, 10, or 15 mg or placebo once-weekly for 52 weeks. The primary endpoint was resolution of MASH without worsening of fibrosis, and a key secondary endpoint was  $\geq 1$ -stage fibrosis improvement without worsening of MASH. Tirzepatide produced dose-dependent benefits: 44, 56, and 62% met the

primary endpoint in the 5, 10, and 15 mg groups, respectively, compared with that of placebo at 10%; 55, 51, and 51% achieved fibrosis improvement in the corresponding dose groups, compared with that of placebo at 30%. Mean body weight change at week 52 was −10.7%, −13.3%, and −15.6% for 5, 10, and 15 mg, respectively, compared with that of placebo at −0.8% (Loomba et al. 2024).

## GLP-1R/GCGR dual agonist

### Survodutide

Survodutide (BI 456906) is a once-weekly GLP-1R/GCGR dual agonist being developed for MASH and obesity by Boehringer Ingelheim, and it was originally licensed from Zealand Pharma.

Under conditions of 100% human plasma, survodutide exhibits  $EC_{50}$  values of 1.0 and 8.3 nM for GLP-1R and GCGR, respectively, corresponding to a potency ratio of approximately 8:1 (Zimmermann et al. 2022). Based on this receptor balance, survodutide produced significant reductions in hepatic fat and improved glycemic control in rodent disease models. Clinical development has advanced through phase 2 trials for obesity, T2DM, and MASH (NCT04667377, NCT04153929, NCT04771273). Phase 3 trials are underway for MASH with moderate or advanced fibrosis (NCT06632444), MASH with cirrhosis (NCT06632457), and obesity (NCT06066515).

In a phase 2 study in MASH, adults with biopsy-proven MASH (F1–F3) were randomized 1:1:1:1 to receive survodutide 2.4, 4.8, or 6.0 mg or placebo once weekly for 48 weeks, including a titration phase. The primary endpoint was histologic improvement in MASH, defined as a  $\geq 2$ -point decrease in the NAFLD Activity Score, without worsening fibrosis. In the planned treatment analysis, response rates were 47, 62, and 43% for 2.4, 4.8, and 6.0 mg, respectively, compared with that of placebo at 14% with placebo. Key secondary analyses showed fibrosis improvement  $\geq 1$  stage in 34, 36, and 34%, respectively, compared with that of placebo at 22% (Sanyal et al. 2024). These findings did not show a clear dose-response pattern. However, actual-treatment analyses, based on the received maintenance dose, were also reported in the Supplementary Appendix accompanying the original phase 2 study, and showed a more pronounced dose-response pattern, because participants who could not tolerate gastrointestinal adverse events (AEs) were allowed to down-titrate during escalation (Sanyal et al. 2024). The most frequent AEs were gastrointestinal; treatment discontinuation occurred in 20% with survodutide compared with that of placebo at 3%, predominantly during the dose-escalation phase, suggesting that slower titration might improve tolerability.

## Pemvidutide

Pemvidutide (ALT-801) is a once-weekly GLP-1R/GCGR dual agonist under development by Altimimmune, with a balanced potency at both GLP-1R and GCGR (Klein et al. 2022). Clinical development has progressed through completion of phase 2 trials in obesity (NCT05295875) and MASH (NCT05989711).

Recently, the IMPACT phase 2b trial in adults with biopsy-confirmed MASH and F2–F3 fibrosis ( $N=212$ ; 1:2:2 randomization to weekly 1.2 mg, 1.8 mg, or placebo for 24 weeks) was completed, and topline results were reported (Altimimmune, 2025). At the 24-week topline analysis, MASH resolution without fibrosis worsening was achieved in 59.1% and 52.1% of participants receiving pemvidutide 1.2 and 1.8 mg, respectively, compared with that of placebo at 19.1%. Fibrosis improvement  $\geq 1$  stage without worsening of MASH occurred in 31.8% and 34.5%, respectively, compared with that of placebo at 25.9%. A supplemental artificial intelligence-based histology analysis showed significantly greater fibrosis reduction, including a  $\geq 60\%$  reduction in fibrosis in 30.6% of patients receiving 1.8 mg, compared with that of patients receiving placebo at 8.2%. Mean weight loss was  $-5.0\%$  and  $-6.2\%$  with pemvidutide 1.2 and 1.8 mg, respectively (placebo,  $-1.0\%$ ), with no plateau at 24 weeks.

Owing to its balanced GLP-1:GCG activity, glycemic control was maintained, with minimal HbA1c changes regardless of diabetes status. The safety profile was favorable, with AE-related discontinuation rates of 0.0% (1.2 mg) and 1.2% (1.8 mg) compared with that of placebo at 2.4%; no drug-related serious adverse events (SAEs) were reported. The IMPACT phase 2b trial of pemvidutide was completed on November 25, 2025, and the topline 48-week results for key secondary endpoints have been reported.

## DD01

DD01 is a once-weekly dual GLP-1 and glucagon receptor agonist being developed by D&D Pharmatech for MASH. The molecule is PEG-conjugated, supporting prolonged systemic exposure; the sponsor describes DD01 as a liver-targeted agent with a half-life of approximately 7–8 d and slow absorption ( $T_{\max}$  approximately 6 d), enabling true once-weekly dosing without lengthy titration (D&D Pharmatech, 2025). DD01's GLP-1:GCG potency ratio of approximately 11:1, together with its prolonged pharmacokinetic profile, is proposed to support rapid liver fat reduction while maintaining favorable metabolic effects, including reductions in body weight and HbA1c.

Phase 2 development is ongoing in a 48-week, double-blind trial in overweight or obese adults with MASLD/

MASH (NCT06410924). After 2 weeks at 20 mg, participants continue with 40 mg once weekly. At the planned 12-week analysis reported in June 2025, the study met its primary endpoint: 75.8% of DD01-treated participants achieved at least a 30% reduction in liver fat by magnetic resonance imaging–proton density fat fraction (MRI-PDFF) compared with that in placebo at 11.8%; mean liver fat decreased by 62.3% with DD01 compared with placebo at 8.3%, and 48.5% reached  $\leq 5\%$  liver fat, indicating normalization. Noninvasive fibrosis markers also improved, including magnetic resonance elastography (MRE), PRO-C3, and enhanced liver fibrosis (ELF). Reported AEs were predominantly gastrointestinal and generally mild-to-moderate, with few discontinuations (three participants at database lock for the week 12 primary analysis). Notably, achieving at least a 30% MRI-PDFF reduction is associated with higher odds of histologic response in MASH across trials (Stine et al. 2021), underscoring the clinical relevance of the 12-week readout while awaiting biopsy data. The trial includes a 48-week histologic assessment of MASH resolution and fibrosis (Stine et al. 2021).

## Efinopegdutide

Efinopegdutide (MK-6024) is a GLP-1R/GCGR dual agonist that was initially advanced as JNJ-64565111 by Janssen for obesity. In August 2020, Merck (MSD) licensed global rights from Hanim Pharmaceutical and is now developing efinopegdutide for MASH. In a randomized phase 2a study in MASH, once-weekly efinopegdutide 10 mg reduced liver fat content more than semaglutide at 1 mg over 24 weeks, supporting its potential for steatohepatitis indications (Romero-Gómez et al. 2023).

Efinopegdutide is a modified oxyntomodulin peptide that is site-specifically linked via an approximately 10 kDa PEG moiety to the constant (Fc) region of human IgG4, which prolongs systemic exposure and enables once-weekly subcutaneous dosing. Its reported terminal half-life in humans is on the order of approximately 112–276 h, consistent with weekly administration. The in vitro potency ratio for GLP-1R and GCGR is 2:1 (Romero-Gómez et al. 2023).

Earlier trials in obesity, including studies in populations with and without T2DM, showed dose-dependent weight loss but no HbA1c reduction in the T2DM dose-ranging study, despite a higher incidence of GI AEs than placebo and liraglutide (Alba et al. 2021). A phase 2b, placebo-controlled study in precirrhotic MASH is ongoing (NCT05877547), with histologic endpoints including MASH resolution without fibrosis worsening; the study also includes an open-label semaglutide (Wegovy®) arm for contextualization.

## GLP-1R/GIPR/GCGR triple agonist

### Efocipegtrutide

Efocipegtrutide (HM15211) is a long-acting triple agonist of GLP-1, GIP, and glucagon that is being developed by Hanmi Pharmaceutical for MASH. It is designed as a peptide-PEG-IgG Fc domain conjugate, which prolongs systemic exposure and supports once-weekly dosing. In preclinical models, efocipegtrutide improved steatohepatitis and fibrosis. In MCD-diet mice, it improved liver injury and fibrosis, as evidenced by reductions in ALT and hydroxyproline (Choi et al. 2018). Furthermore, in AMLN-diet mice, 8 weeks of efocipegtrutide treatment produced a significant improvement in liver fibrosis (Kim et al. 2021). A randomized, double-blind phase 2 clinical trial in adults with biopsy-confirmed MASH is ongoing over 52 weeks and includes histologic endpoints (NCT04505436).

### FGF analog

#### Aldafermin

Aldafermin (NGM282, M70) is a non-tumorigenic analog of FGF19 that acts on the FGFR1c-KLB and FGFR4-KLB (Harrison et al. 2021). Unlike wild-type FGF19, it contains N-terminal modifications that retain CYP7A1 suppression while reducing FGF19-induced hepatocarcinogenic potential through inhibition of signal transducer and activator of transcription 3 (Zhou et al. 2017). Activation of the FGFR1c-KLB complex reduces liver steatosis and improves insulin sensitivity, whereas activation of the FGFR4-KLB complex suppresses CYP7A1 expression, leading to reduced bile acid synthesis.

Aldafermin has completed phase 2 clinical evaluation. After 48 weeks of daily subcutaneous administration, fibrosis improvement was observed in 23 and 21% of patients receiving 3 and 1 mg, respectively, compared with that in the placebo group at 15% (Rinella et al. 2024). However, despite these findings, the development of aldafermin for MASH was discontinued after earlier clinical studies failed to meet the primary endpoint (Ngm Biopharmaceuticals, 2021).

#### Efruxifermin

Efruxifermin (EFX) is a long-acting Fc-FGF21 analog being developed by Akero Therapeutics for MASH. EFX is a bivalent fusion protein comprising two engineered human FGF21 polypeptides linked to an IgG1 Fc scaffold, and is designed to deliver sustained, balanced signaling through FGFR1c/2c/3c with  $\beta$ -Klotho in the liver and adipose tissue.

Therefore, this addresses steatosis, inflammation, and fibrosis while supporting once-weekly dosing (Harrison et al. 2021).

In the phase 2b HARMONY trial (adults with F2–F3 fibrosis and MASH, 24 weeks; NCT04767529), in the liver-biopsy analysis set, the primary endpoint of at least 1-stage fibrosis improvement without MASH worsening was achieved by 39% of patients receiving EFX 28 mg, 41% receiving EFX 50 mg, and 20% in the placebo. In the full analysis set, wherein missing biopsies were counted as a nonresponse, rates were 36% (28 mg) and 33% (50 mg) compared against the 19% of the placebo. Gastrointestinal AEs, notably diarrhea and nausea, were the most frequent and were generally mild-to-moderate (Harrison et al. 2023).

Phase 3 development, through the SYNCHRONY program, is ongoing and comprises three randomized, placebo-controlled studies: SYNCHRONY Histology (biopsy-confirmed F2–F3), SYNCHRONY Outcomes (compensated cirrhosis, F4), and SYNCHRONY Real-World (noninvasively diagnosed MASLD/MASH, F1–F4).

#### Pegozafermin

Pegozafermin (BIO89-100) is a long-acting glycoPE-Gylated FGF21 analog engineered for sustained activation of  $\beta$ -Klotho-dependent FGFR1c/2c/3c signaling in the liver and adipose tissue. Site-specific O-linked glycoPEGylation, involving an approximately 20-kDa linear PEG, extends the terminal half-life to about 55–100 h, thereby enabling once-weekly (QW) or every-2-weeks (Q2W) subcutaneous dosing (Rosenstock et al. 2023; Mansbach & Margalit, 2024). In KLB-expressing cell systems, pegozafermin has shown higher potency than native FGF21.

In the phase 2b ENLIVEN trial, patients with biopsy-confirmed MASH received pegozafermin 44 mg Q2W, 30, or 15 mg QW for 24 weeks. Histologic outcomes favored pegozafermin: MASH resolution without fibrosis worsening occurred in 37% (15 mg QW), 23% (30 mg QW), and 26% (44 mg Q2W), compared with that of placebo at 2%;  $\geq$ 1-stage fibrosis exhibiting significant improvement without MASH worsening was observed in 26% (30 mg QW) and 27% of patients (44 mg Q2W), compared with that of placebo at 7%. The most common AEs were gastrointestinal and generally mild-to-moderate, and discontinuations were infrequent (Loomba et al. 2023).

Phase 3 development is underway (ENLIGHTEN-Fibrosis and ENLIGHTEN-Cirrhosis).

#### Efimosfermin alfa

Efimosfermin alfa (BOS-580) is a once-monthly Fc-FGF21 analog under development for MASH. The molecule

comprises an engineered FGF21 moiety fused to human IgG1 Fc and incorporates stabilizing design elements, including an additional disulfide bond, point mutations to reduce aggregation and proteolysis, and an effector-silent Fc with LALA substitutions. These features produce about 21-d half-life, supporting monthly SC dosing and balanced FGFR1c/2c/3c- $\beta$ -Klotho signaling in the liver and adipose tissue (Rader et al. 2022).

In a randomized, double-blind phase 2a study in participants with phenotypic MASH, efimosfermin achieved large MRI-PDFF reductions after 12 weeks and showed a favorable, predominantly gastrointestinal safety profile (Loomba et al. 2025). In a separate 24-week study in adults with biopsy-confirmed F2–F3 MASH, efimosfermin 300 mg every 4 weeks (Q4W) met prespecified histologic endpoints, with MASH resolution without fibrosis worsening in 68% compared with placebo at 29%, and  $\geq$ 1-stage fibrosis exhibiting improvement without MASH worsening in 45% vs 21% in the biopsy analysis set. Additionally, noninvasive assessments, including MRI-PDFF, ELF, and vibration-controlled transient elastography liver stiffness measurement, improved, and gastrointestinal AEs were generally mild-to-moderate, with low discontinuation rates (Alkhouri, 2024).

### Oligonucleotide

Oligonucleotides are short nucleic acid molecules, typically comprising 8–50 nucleotides, that regulate target RNA expression through Watson–Crick base pairing (Lakhia et al. 2019). For the treatment of MASH, antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) are under development as possible treatments for MASH. ASOs bind to target mRNA and induce RNase H-mediated cleavage or suppress protein expression through steric blockade or splice modulation (Li et al. 2024). siRNAs silence target gene expression by promoting the degradation of mature mRNA (Hu et al. 2020; Alshaer et al. 2021). While ASOs bind to mRNA or pre-mRNA as single strands, siRNAs are incorporated into the RNA-induced silencing complex, which retains the guide strand and directs binding to complementary mRNA targets (Watts & Corey, 2012).

AZD2693 is a PNPLA3-targeting ASO designed to treat hepatic steatosis, inflammation, and fibrosis associated with the I148M mutation (isoleucine-to-methionine substitution at position 148 in PNPLA3) (Armisen et al. 2025). The molecule uses GalNAc conjugation for liver targeting, but phase 2 development was terminated because efficacy was insufficient. ION224, another ASO targeting DGAT2 for MASH, has completed a phase 2 trial. In a study involving monthly subcutaneous injections of 90 or 120 mg, 46.2% and 58.8% of participants, respectively, achieved the primary endpoint, compared with that in the placebo at 18.7%

(NCT04932512) (Loomba et al. 2025). ARO-PNPLA3 (JNJ-75220795), a GalNAc-conjugated siRNA targeting the PNPLA3 mutation, has completed phase 1 studies (Jeon et al. 2025). ALN-HSD (an siRNA targeting HSD17B13) is a GalNAc-conjugated siRNA currently being evaluated in a phase 2 trial for MASH treatment (NCT05519475).

## Small molecules

### THR- $\beta$ agonist

THR- $\beta$  is a nuclear receptor predominantly expressed in the liver (Xue & Wei, 2024). Resmetirom, a selective THR- $\beta$  agonist, became the first FDA-approved therapy for adults with noncirrhotic MASH with moderate-to-advanced fibrosis in 2024 (Keam, 2024). Resmetirom exerts its therapeutic effects through THR- $\beta$  binding, promoting mitochondrial fatty acid oxidation and suppressing de novo lipogenesis (Petta et al. 2024). Additionally, it enhances the conversion of free thyroxine (T4) to triiodothyronine (T3), thereby increasing THR- $\beta$  binding and stimulating hepatic FGF21 expression via T3-mediated THR- $\beta$  activation (Adams et al. 2010). These metabolic effects support its development as a treatment for MASH. Selective targeting of THR- $\beta$  is critical for THR agonists, as activation of THR- $\alpha$  may lead to AEs in the heart, skeletal muscle, and other tissues (Xue & Wei, 2024). Resmetirom incorporates a chemical moiety that confers selective binding to THR- $\beta$ , demonstrating 28-fold selectivity over THR- $\alpha$  (Kelly et al. 2014).

In the 52-week biopsy analysis of the phase 3 MAE-STRO-NASH trial, resmetirom 80 and 100 mg met both histologic primary endpoints against placebo: MASH resolution without fibrosis worsening (approximately 25.9% and 29.9% vs 9.7%, respectively) and  $\geq$ 1-stage fibrosis improvement without MASH worsening (approximately 24.2% and 25.9% vs 14.2%, respectively), along with improvements in lipids, including low-density lipoprotein cholesterol (Harrison et al. 2024).

### FXR agonist

FXR is a bile acid-activated nuclear receptor that regulates bile acid homeostasis, suppresses inflammatory responses, inhibits fibrogenesis, and prevents HSCs activation (Zhang et al. 2013; Ferrell et al. 2019; Clifford et al. 2021; Bertolini et al. 2022; Wang et al. 2024). FXR agonists have been developed for MASH treatment; however, concerns regarding AEs have limited their clinical progress.

Obeticholic acid (OCA), a steroidal bile acid derivative, was the first FXR agonist to enter phase 3 clinical development for MASH (Wang et al. 2024). In the phase 3 REGENERATE trial, the primary histologic endpoint was  $\geq$ 1-stage

improvement in fibrosis without worsening of MASH after 18 months of treatment. Published analyses showed that fibrosis improvement without worsening of MASH was achieved in 22.4% of patients receiving OCA 25 mg compared to those receiving placebo at 9.6%. Meanwhile, MASH resolution without worsening of fibrosis occurred in 6.5% compared with those in the placebo group at 3.5% (NCT03439254). In terms of safety, pruritus was the most common treatment-emergent AE, and OCA was also associated with increases in low-density lipoprotein cholesterol (Ng et al. 2023).

GW4064, a nonsteroidal FXR agonist, was developed as a selective FXR activator (Maloney et al. 2000). However, its clinical potential was limited by low bioavailability, short half-life, and stilbene-related photolability and toxicity. To overcome these limitations, GS-9674 (cilofexor) was developed by replacing the stilbene structure with a cyclopropyl group, thereby improving photostability, the toxicity profile, FXR affinity, and pharmacokinetics (Li et al. 2020). Cilofexor has completed a phase 2 trial. In addition, liver fat content was assessed using MRI-PDFF after 24 weeks of once-daily oral administration. Treatment-emergent AEs occurred in 89.3%, 76.8%, and 67.9% of patients in the cilofexor 100 mg, 30 mg, and placebo groups, respectively, whereas discontinuation due to treatment-emergent AEs occurred in 1.8%, 8.9%, and 7.1% of patients in the respective groups.  $\geq 30\%$  reduction in MRI-PDFF was observed in 39% of the 100 mg group, 14% of the 30 mg group, and 13% of the placebo group. Median relative percentage changes in liver fat content were  $-22.7\%$ ,  $-1.8\%$ , and  $+1.9\%$ , respectively (Patel et al. 2020).

### Delivery strategies for liver-selective therapy in MASLD/MASH

MASLD/MASH therapeutics may benefit from hepatic targeting regarding both efficacy and safety. For instance, nonselective THR activation can induce thyrotoxicosis-associated AEs, including tachycardia, muscle wasting, and bone impairment (Saponaro et al. 2020). In contrast, resmetirom is a substrate of the hepatocyte-enriched membrane transporters OATP1B1 and OATP1B3, enabling preferential hepatic delivery, and it exhibits high THR- $\beta$  selectivity to enhance hepatic metabolic regulation while minimizing off-target effects (Hönes et al. 2022). Therefore, liver-targeting strategies are likely to be particularly important for drug classes whereby extrahepatic adverse effects represent a key safety concern.

Tuning passive design features to match hepatic micro-anatomy and its disease-associated remodeling enhances liver-selective delivery. For instance, hydrodynamic size needs to be appropriately adjusted. In the healthy liver,

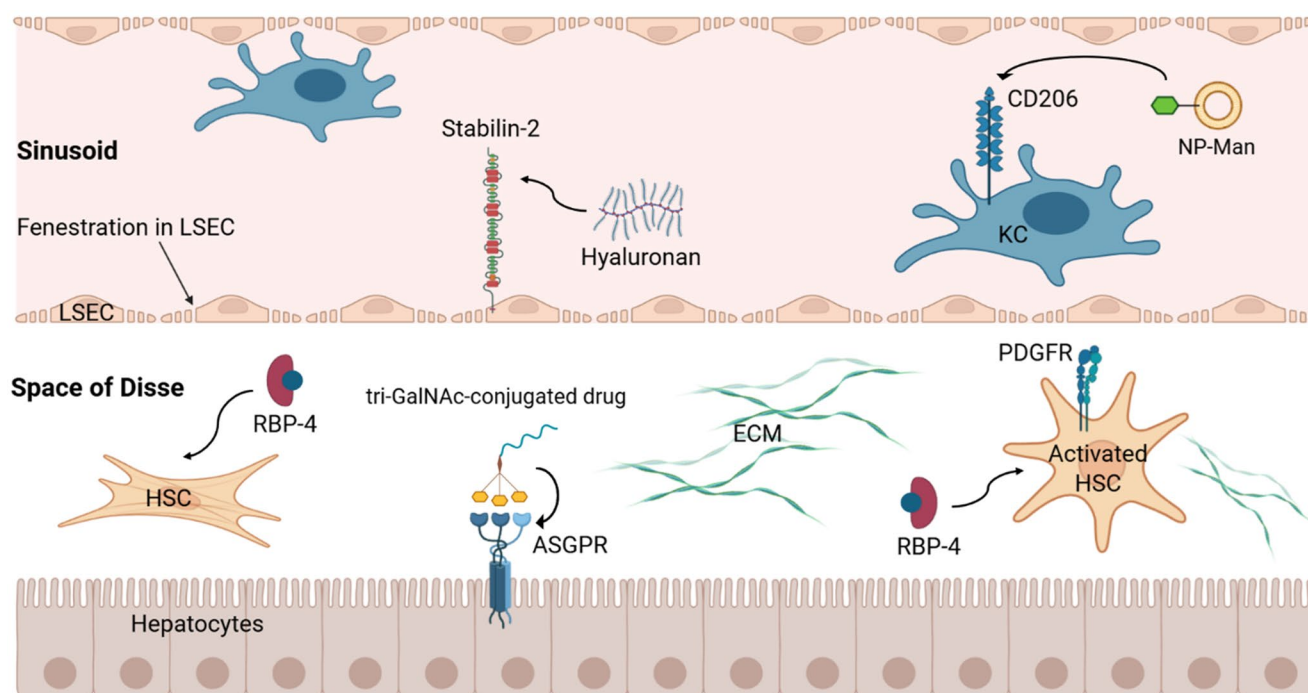
fenestrated liver sinusoidal endothelial cells (LSECs; typically  $\sim 100\text{--}150\text{ nm}$  pores; broader range  $\sim 50\text{--}300\text{ nm}$ ) allow sub- $\sim 150\text{ nm}$  constructs to access the Space of Disse (Deleve, 2015; Szafranska et al. 2021). With MASLD/MASH progression, defenestration and capillarization reduce parenchymal access and tend to increase reticuloendothelial capture by Kupffer cells (KCs) (Qu et al. 2024). Small-sized entities ( $\lesssim 10\text{ nm}$ ) are predominantly cleared renally, whereas larger particles ( $\gtrsim 150\text{--}200\text{ nm}$ ) more readily undergo hepato-splenic sequestration and experience slower interstitial transport (Choi et al. 2011; Colino et al. 2020). In earlier disease, tuning size within roughly  $\sim 30\text{--}120\text{ nm}$  can often balance liver exposure with parenchymal access; as fenestrations close, smaller and/or longer-circulating formats may be required to sustain hepatocyte and HSC delivery without overwhelming KC uptake.

PEGylation can confer beneficial effects, such as reduced opsonization, enhanced stability and prolonged half-life (Pasut & Veronese, 2012; Park et al. 2019; Jin et al. 2025). Moreover, conjugating PEGs of appropriate size and architecture (linear vs branched) can shift intrahepatic distribution toward or away from KC uptake (Suk et al. 2016). For peptide/peptide-like biologics, moderate PEGylation often achieves long-acting profiles while preserving receptor engagement. In addition, in a liver-fibrosis model, PEGylation of interferon- $\gamma$  increased hepatic uptake and antifibrotic efficacy, consistent with distributional shifts associated with enlarged hydrodynamic size (Bansal et al. 2011).

Beyond passive features, active targeting is required to achieve liver-specific delivery. This can be accomplished using ligands that bind receptors enriched in specific hepatic cell types (Fig. 4). Taken together, receptor-guided delivery combined with rational physicochemical tuning offers a promising approach to achieving cell-selective exposure in MASLD/MASH.

### Targeting hepatocytes

The asialoglycoprotein receptor (ASGPR) is highly expressed on hepatocytes and rapidly internalizes ligands through clathrin-mediated endocytosis (Spiess, 1990). Tri-antennary N-acetylgalactosamine (GalNAc) has emerged as a clinical standard for hepatocyte delivery of siRNA and ASO payloads, and this strategy can be extended to other payloads, including small-molecule conjugates and polymeric or lipid nanoparticles with surface-displayed GalNAc (Setten et al. 2019; Kasiewicz et al. 2023). ASGPR targeting is well-suited to silencers or degraders designed to address hepatocyte-intrinsic drivers, such as lipotoxic stress pathways and bile-acid dysregulation (Debacker et al. 2020). Important design variables include GalNAc valency



**Fig. 4** Schematic representation of the hepatic sinusoid and potential liver-targeting candidates. Abbreviations: LSEC, liver sinusoidal endothelial cell; KC, Kupffer cell; NP-Man, mannose-functionalized

nanoparticle; HSC, hepatic stellate cell; ASGPR, asialoglycoprotein receptor; ECM, extracellular matrix; RBP-4, retinol binding protein 4. Created with BioRender.com

and spatial presentation, linker stability, and ligand density, which together modulate receptor avidity, endocytic flux, and endosomal escape (Holland et al. 2021).

### Targeting hepatic stellate cells

Upon activation, HSCs upregulate PDGFR- $\beta$  and  $\alpha$ v-class integrins, notably  $\alpha$ v $\beta$ 3 and  $\alpha$ v $\beta$ 5, which can be engaged by antibodies, antibody fragments or RGD/cRGD peptides to concentrate antifibrotic cargoes, such as TGF- $\beta$  pathway modulators, lysyl oxidase (LOX/LOXL) inhibitors, and siRNA against collagen-processing enzymes, within the fibrotic niche (Friedman, 2008; Henderson et al. 2013; Giannelli et al. 2016; Chen et al. 2020). An orthogonal strategy leverages HSC vitamin A handling. Retinol-binding protein 4 (RBP4) is a protein predominantly expressed in hepatocytes, secreted into the bloodstream, and forms a complex with retinol (vitamin A) to transport it as a retinol-RBP4 holoprotein (holo-RBP) (Maher, 2013). HSCs, as retinol-storing cells, can take up holo-RBP (GjØen et al. 1987; Lee et al. 2015). By coupling retinol/retinoid motifs or RBP-mimetic ligands, delivery can be enriched in lipid-droplet-containing HSCs while minimizing off-target uptake by hepatocytes (Chen et al. 2020).

### Targeting Kupffer cells

Targeting KCs is a key strategy for treating liver diseases through the use of surface receptors, such as the mannose (CD206) and scavenger receptors, to deliver anti-inflammatory payloads, including NF- $\kappa$ B modulators or siRNA (Van Der Heide et al. 2019). The main obstacle is off-target drug accumulation in other macrophage populations, particularly in the spleen, where similar receptors are also expressed (De Souza et al. 2025). To improve liver selectivity, current research focuses on optimizing nanoparticle characteristics, such as ligand density and surface charge, and employing pharmacological strategies, such as dose fractionation, to saturate the mononuclear phagocyte system. In addition to using advanced bio-inspired approaches, such as “don’t-eat-me” (CD47) signals and hepatic blood-flow-tuned infusion profiles (Alexis et al. 2008; Elias et al. 2013).

### Targeting liver sinusoidal endothelial cells

Targeting LSECs is inherently stage-dependent, and two complementary strategies have emerged. An early, restorative approach exploits the Stabilin-2 (hyaluronan receptor for endocytosis) scavenger receptor, which is abundantly expressed on healthy LSECs, to ferry hyaluronan (HA)-decorated carriers that deliver endothelial-protective or anti-inflammatory payloads, such as S1P-axis modulators and

NO-dependent cytoskeletal regulators (Harris et al. 2008). HA valency, molecular weight, and surface density tune Stabilin engagement and endocytic flux, and can improve parenchymal access when fenestrations are preserved (Liu et al. 2019; Kaps et al. 2023). This pathway narrows with MASLD/MASH progression: capillarization with defenestration and basement-membrane deposition limits exchange and impairs HA uptake. Therefore, this diminishes the utility of Stabilin-directed delivery in advanced fibrosis; off-liver uptake via Stabilin-expressing endothelia and reticuloendothelial tissues also warrants attention to dose and corona management (Deleve, 2015; Qu et al. 2024).

As capillarization and inflammation progress, an alternative strategy is to leverage inducible adhesion molecules such as Intercellular adhesion molecule-1 (ICAM-1). In inflamed or cholestatic states, LSECs maintain these molecules, thereby allowing carriers modified with antibodies, peptides, or aptamers to undergo cell adhesion molecule (CAM)-mediated adhesion and endocytosis despite reduced fenestrations (Gulubova, 1998; Muro et al. 2003). Key development challenges for this approach center on optimizing affinity and avidity to ensure firm capture under sinusoidal shear, tuning carrier size and deformability to prevent microvascular obstruction, and managing exposure to mitigate extrahepatic endothelial uptake, such as in the lung and systemic vasculature (Muro et al. 2008).

Thus, HA/Stabilin targeting is best suited to earlier disease stages with preserved fenestration, whereas ICAM-1-directed approaches may retain function as capillarization advances. The optimal approach is disease-state dependent, requiring patient stratification, such as noninvasive fibrosis staging, together with passive design levers, including size, charge and corona, to bias hepatic over splenic deposition while safeguarding endothelial function.

### Targeting fibrotic lesions/extracellular matrix

Fibrotic septa expose accessible binding sites on fibrillar collagens I/III and other extracellular matrix components within the Space of Disse; these sites can therefore be exploited to localize carriers to fibrotic lesions (Mcquitty et al. 2020). Matrix-binding ligands, such as collagen-binding peptides or domains, including vWF-A3 or other CBD motifs, as well as collagen-reactive antibodies, can prolong tissue residence and increase local concentrations within lesions even without strict cell specificity. Therefore, complementing HSC/Kupffer-directed strategies and mitigating washout in high-flow sinusoids (Healing 2000; Wahyudi et al. 2016). Liver-focused examples include collagen-binding nanoparticle probes that preferentially accumulate in fibrotic liver, supporting the translational feasibility of collagen anchoring as a strategy for intralesional retention (Zhang et al. 2023).

Enzyme-responsive (“smart”) linkers cleavable by matrix-associated proteases, such as MMP-2/9 substrate sequences including GPLGIAGQ, PLGLAG, and GPVGLIGK, can trigger on-site cargo release, thereby improving on-target activation while limiting parenchymal exposure (Vrettos et al. 2018). As MMP expression and activity in liver fibrosis vary with etiology and disease stage, cleavage kinetics and specificity should be validated for the intended disease stage to avoid under- or over-release (Duarte et al. 2015; Geervliet & Bansal, 2020).

### Future perspective

With the recent USA approvals of a THR- $\beta$  agonist (resmetirom) in 2024 and GLP-1R agonist (semaglutide) in 2025 for adults with MASH and moderate-to-advanced fibrosis, the field is shifting from generalized metabolic control toward multi-mechanism targeting and stage-aware, liver-selective interventions. Early multi-mechanism approaches are exemplified by the GLP-1R/GIPR/GCGR triple agonist (retatrutide) (Sanyal et al. 2024) and GLP-1R/GCGR dual agonist (survodutide), which extend metabolic debulking beyond GLP-1 monotherapy.

Systematic evaluation of combination and sequencing strategies is now a critical priority. Combination strategies may pair upstream metabolic debulking agents (GLP-1 monotherapy, GLP-1R/GCGR dual agonists, and next-generation triple agonists) with liver-directed therapies, including THR- $\beta$  agonists, FXR agonists, FGF21 analogs, and antifibrotic agents that more directly target fibrosis and intrahepatic pathology. Such an approach may facilitate early improvements in body weight, insulin resistance, and steatosis, while subsequently promoting more durable histologic improvements. In addition, a sequential treatment strategy may offer further advantages, whereby initial metabolic debulking establishes a more favorable hepatic environment before introducing agents specifically designed to target activated HSCs, fibrotic lesions, or other intrahepatic drivers of persistent fibrosis. Early clinical signals support GLP-1 + FGF21 strategies under evaluation, informing rational co-administration or sequence designs with pre-specified safety architectures (Harrison et al. 2025).

Beyond selecting therapeutic mechanisms and treatment sequences, optimizing the delivery of these agents will also be essential for the long-term management of MASH. Given that MASH requires chronic treatment, and that most incretin- and FGF-based therapies are being developed as repeatedly administered subcutaneous injectable formulations, the development of long-acting drug delivery systems (DDSs) may improve treatment durability, reduce dosing frequency, enhance patient adherence, and stabilize systemic exposure. For GLP-1-based therapies, a rapid increase in peak plasma

concentration resulting from excessive initial burst release may contribute to gastrointestinal adverse events, such as nausea and vomiting. Therefore, sustained-release depot formulations require careful optimization of release kinetics to minimize the initial burst and maintain stable systemic exposure (Kim et al. 2024; Maharjan et al. 2024).

Stage-specific selection of liver-targeting strategies is also critical in MASH. In earlier disease stages, relatively preserved fenestration may facilitate access to hepatocytes and LSECs, making GalNAc-mediated ASGPR targeting of hepatocytes or LSEC-restorative approaches more feasible. As MASH progresses, fenestration loss and capillarization increasingly affect intrahepatic drug distribution. In advanced fibrotic stages, activated HSCs may represent a more suitable target, as illustrated by vitamin-A-modified lipid nanoparticles carrying HSP47 siRNA (BMS-986263; phase 1/2 in hepatic fibrosis), which exploit the retinoid uptake pathway enriched in activated HSCs (Qosa et al. 2023). Together, these examples highlight the importance of tailoring ligand selection and carrier design to disease stage and target cell type.

Alongside advances in delivery, efficient assessment of therapeutic efficacy remains a critical challenge in MASH. While the definitive endpoint for MASH remains long-term liver-related outcomes, which necessitate large and lengthy trials, the field relies on histologic improvement as a surrogate endpoint for accelerated approval, as seen with resmetirom and semaglutide. However, liver biopsy constitutes a significant bottleneck because of its invasive nature, patient risk, sampling variability, and challenges with pathologist concordance. This limitation underscores the urgent need for robust, noninvasive tests (NITs). A significant effort is underway to validate NITs, including MRI-PDFF, MRE, corrected T1, Fibroscan, ELF, and PRO-C3, against histologic data and long-term outcomes. As these NITs gain regulatory acceptance, they may evolve from exploratory markers to primary endpoints. The successful validation and integration of these tools are expected to streamline patient stratification and accelerate future MASH therapeutic development (Sanyal et al. 2023). Ultimately, the next wave of MASH therapeutics will be defined not only by what they target but also by where and how they act within the liver, and by the quality of evidence linking those actions to fibrosis and clinical benefit.

## Conclusion

The therapeutic landscape for MASH is rapidly evolving. The pharmacological paradigm is shifting from indirect-acting incretins (GLP-1R, GIPR agonists) toward multi-agonist strategies that harness direct hepatic actions

(GCGR, FGFR). Looking forward, integrating these potent metabolic hormones with advanced, liver-selective delivery strategies will be crucial. Optimizing cell-specific targeting (e.g., hepatocyte vs HSC) and tailoring strategies to fibrosis stage will be essential for maximizing therapeutic efficacy while minimizing systemic off-target effects. This convergence of mechanism-based pharmacology and precision delivery will be essential for halting and ultimately reversing liver fibrosis in this complex disease.

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**Data availability** All data generated or analyzed during this study are included in this published article.

## Declarations

**Research involving human and/or animal participants** This work does not contain any studies with human participants or animals performed by any of the authors.

**Conflict of interest** Dong Hee Na was the Editor-in-Chief of the Journal of Pharmaceutical Investigation while conducting this study. Editor status has no bearing on editorial considerations. The other authors (S. Han, J. Shin, and J.C. Kim) declare that they have no conflict of interest.

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## References

Aaldijk AS, Verzijl CRC, Jonker JW, Struik D (2023) Biological and pharmacological functions of the FGF19- and FGF21-coreceptor

- beta-klotho. *Front Endocrinol*. 14:1150222. <https://doi.org/10.3389/fendo.2023.1150222>
- Adams AC, Astapova I, Fisher FM, Badman MK, Kurgansky KE, Flier JS, Hollenberg AN, Maratos-Flier E (2010) Thyroid hormone regulates hepatic expression of fibroblast growth factor 21 in a PPAR $\alpha$ -dependent manner. *J Biol Chem* 285(19):14078–14082. <https://doi.org/10.1074/jbc.C110.107375>
- Al-Massadi O, Fernø J, Diéguez C, Nogueiras R, Quiñones M (2019) Glucagon control on food intake and energy balance. *Int J Mol Sci* 20(16):3905. <https://doi.org/10.3390/ijms20163905>
- Alba M, Yee J, Frustaci ME, Samtani MN, Fleck P (2021) Efficacy and safety of glucagon-like peptide-1/glucagon receptor co-agonist JNJ-64565111 in individuals with obesity without type 2 diabetes mellitus: a randomized dose-ranging study. *Clin Obes* 11(2):e12432. <https://doi.org/10.1111/cob.12432>
- Alexis F, Pridgen E, Molnar LK, Farokhzad OC (2008) Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol Pharm* 5:505–515
- Alharbi SH (2024) Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications. *Ther Adv Endocrinol Metab* 15:20420188231222367
- Alkhouri N (2024) Once-Monthly Efimosfermin Alfa (BOS-580) in Metabolic Dysfunction-Associated Steatohepatitis With F2/F3 Fibrosis: Results From a 24-Week, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial. *Gastroenterology & Hepatology* 20
- Alshaer W, Zureigat H, Al Karaki A, Al-Kadash A, Gharaibeh L, Hatmal MM, Aljabali AA, Awidi A (2021) siRNA: Mechanism of action, challenges, and therapeutic approaches. *Eur J Pharmacol* 905:174178
- Altimmune, I. (2025) Altimmune announces positive topline results from the IMPACT phase 2b trial of Pemvidutide in the treatment of MASH. <https://ir.altimmune.com/news-releases/news-release-details/altimmune-announces-positive-topline-results-impact-phase-2b>
- An SJ, Mohanty J, Tome F, Suzuki Y, Lax I, Schlessinger J (2023) Heparin is essential for optimal cell signaling by FGF21 and for regulation of  $\beta$ Klotho cellular stability. *Proc Natl Acad Sci USA* 120:e2219128120
- Armisen J, Rauschecker M, Sarv J, Liljeblad M, Wernevik L, Niazi M, Knöchel J, Eklund O, Sandell T, Sherwood J, Bergenholm L, Hallén S, Wang S, Kamble P, Bhat M, Maxvill I, Wang Y, Lee RG, Bhanot S, Guo S, Romeo S, Lawitz E, Fjellström O, Lindén D, Blau JE, Loomba R (2025) AZD2693, a PNPLA3 antisense oligonucleotide, for the treatment of MASH in 148 M homozygous participants: Two randomized phase I trials. *J Hepatol* 83:31–42
- Bansal R, Post E, Proost JH, De Jager-Krikken A, Poelstra K, Prakash J (2011) PEGylation improves pharmacokinetic profile, liver uptake and efficacy of Interferon gamma in liver fibrosis. *J Controlled Release* 154:233–240
- Ben-Shlomo S, Zvibel I, Shnell M, Shlomai A, Chepurko E, Halpern Z, Barzilai N, Oren R, Fishman S (2011) Glucagon-like peptide-1 reduces hepatic lipogenesis via activation of AMP-activated protein kinase. *J Hepatol* 54:1214–1223
- Bertolini A, Fiorotto R, Strazzabosco M (2022) Bile acids and their receptors: modulators and therapeutic targets in liver inflammation. *Semin Immunopathol* 44:547–564
- Bhatnagar S, Damron HA, Hillgartner FB (2009) Fibroblast growth factor-19, a novel factor that inhibits hepatic fatty acid synthesis. *J Biol Chem* 284:10023–10033
- Boland ML, Laker RC, Mather K, Nawrocki A, Oldham S, Boland BB, Lewis H, Conway J, Naylor J, Guionaud S, Feigh M, Veidal SS, Lantier L, McGuinness OP, Grimsby J, Rondinone CM, Jermutus L, Larsen MR, Trevaskis JL, Rhodes CJ (2020) Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist Cotadutide via modulating mitochondrial function and lipogenesis. *Nat Metab* 2:413–431
- Chen W, Yang A, Jia J, Popov YV, Schuppan D, You H (2020) Lysyl oxidase (LOX) family members: rationale and their potential as therapeutic targets for liver fibrosis. *Hepatology* 72:729–741
- Choi CHJ, Zuckerman JE, Webster P, Davis ME (2011) Targeting kidney mesangium by nanoparticles of defined size. *Proceedings of the National Academy of Sciences* 108:6656–6661
- Choi IY, Kim JK, Lee JS, Park E, Kim YH, Jung SY, Kim SJ (2018) Effect of a novel long-acting GLP-1/GIP/glucagon triple agonist (HM15211) in a NASH and fibrosis animal model. *Diabetes* 67:1106–1110P
- Clifford BL, Sedgeman LR, Williams KJ, Morand P, Cheng A, Jarrett KE, Chan AP, Brearley-Sholto MC, Wahlström A, Ashby JW, Barshop W, Wohlschlegel J, Calkin AC, Liu Y, Thorell A, Meikle PJ, Drew BG, Mack JJ, Marschall HU, Tarling EJ, Edwards PA (2021) & De Aguiar Vallim TQ FXR activation protects against NAFLD via bile-acid-dependent reductions in lipid absorption. *Cell Metab* 33:1671–1684.e1674
- Colino CI, Lanao JM, Gutierrez-Millan C (2020) Targeting of hepatic macrophages by therapeutic nanoparticles. *Front Immunol* 11:218
- D&D Pharmatech (2025) DD-Pharmatech announces positive phase 2 results for DD01 in MASH with robust reductions in liver fat accompanied by improvements in liver and metabolic health. <https://www.businesswire.com/news/home/20250616477730/en/DD-Pharmatech-Announces-Positive-Phase-2-Results-for-DD01-in-MASH-with-Robust-Reductions-in-Liver-Fat-Accompanied-by-Improvements-in-Liver-and-Metabolic-Health>
- Da Silva Lima N, Cabaleiro A, Novoa E, Riobello C, Knerr PJ, He Y, Esquinas-Román EM, González-García I, Prevot V, Schwaninger M, Dieguez C, López M, Müller TD, Varela-Rey M, Douros JD, Nogueiras R (2024) GLP-1 and GIP agonism has no direct actions in human hepatocytes or hepatic stellate cells. *Cell Mol Life Sci* 81:468
- De Mesquita FC, Guixé-Muntet S, Fernández-Iglesias A, Maeso-Díaz R, Vila S, Hide D, Ortega-Ribera M, Rosa JL, García-Pagán JC, Bosch J, De Oliveira JR, Gracia-Sancho J (2017) Liraglutide improves liver microvascular dysfunction in cirrhosis: Evidence from translational studies. *Sci Rep* 7:3255
- De Souza TL, Santiago MDA, Ribeiro FN, Figueiredo FB, Junior AVM, Menezes RC, Porrozi R, Morgado FN (2025) Splenic macrophage functional profile and its role in the immunopathogenesis of canine visceral leishmaniasis. *Front Immunol* 16:1617751
- Debacker AJ, Voutilä J, Catley M, Blakey D, Habib N (2020) Delivery of oligonucleotides to the liver with GalNAc: from research to registered therapeutic drug. *Mol Ther* 28:1759–1771
- Deleve LD (2015) Liver sinusoidal endothelial cells in hepatic fibrosis. *Hepatology* 61:1740–1746
- Dolegowska K, Marchelek-Mysliwiec M, Nowosiad-Magda M, Slawinski M, Dolegowska B (2019) FGF19 subfamily members: FGF19 and FGF21. *J Physiol Biochem* 75:229–240
- Duarte S, Baber J, Fujii T, Coito AJ (2015) Matrix metalloproteinases in liver injury, repair and fibrosis. *Matrix Biol* 44:147–156
- Dushay JR, Toschi E, Mitten EK, Fisher FM, Herman MA, Maratos-Flier E (2015) Fructose ingestion acutely stimulates circulating FGF21 levels in humans. *Mol Metab* 4:51–57
- Eli Lilly and Company (2022). MOUNJARO (tirzepatide) injection, for subcutaneous use: Prescribing Information Silver Spring (MD): U.S. Food and Drug Administration
- Eli Lilly and Company (2025). ZEPBOUND (tirzepatide) injection, for subcutaneous use: prescribing information. Silver Spring (MD): U.S. Food and Drug Administration
- Elias DR, Poloukhina A, Popik V, Tsourkas A (2013) Effect of ligand density, receptor density, and nanoparticle size on cell targeting. *Nanomed Nanotechnol Biol Med* 9:194–201

- Elmqvist JK, Maratos-Flier E, Saper CB, Flier JS (1998) Unraveling the central nervous system pathways underlying responses to leptin. *Nat Neurosci* 1:445–450
- Eriksson O, Velikyan I, Haack T, Bossart M, Evers A, Laitinen I, Larsen PJ, Plettenburg O, Takano A, Halldin C (2019) Assessment of glucagon receptor occupancy by Positron Emission Tomography in non-human primates. *Sci Rep* 9:14960
- Ferrell JM, Pathak P, Boehme S, Gilliland T, Chiang JYL (2019) Deficiency of Both Farnesoid X Receptor and Takeda G Protein-Coupled Receptor 5 Exacerbated Liver Fibrosis in Mice. *Hepatology* 70:955–970
- Finan B, Ma T, Ottaway N, Müller TD, Habegger KM, Heppner KM, Kirchner H, Holland J, Hembree J, Raver C, Lockie SH, Smiley DL, Gelfanov V, Yang B, Hofmann S, Bruemmer D, Drucker DJ, Pfluger PT, Perez-Tilve D, Gidda J, Vignati L, Zhang L, Hauptman JB, Lau M, Brecheisen M, Uhles S, Riboulet W, Hainaut E, Sebokova E, Conde-Knape K, Konkar A, Dimarchi RD, Tschöp MH (2013) Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. *Sci Transl Med* 5:209ra151
- Finan B, Yang B, Ottaway N, Smiley DL, Ma T, Clemmensen C, Chabenne J, Zhang L, Habegger KM, Fischer K, Campbell JE, Sandoval D, Seeley RJ, Bleicher K, Uhles S, Riboulet W, Funk J, Hertel C, Belli S, Sebokova E, Conde-Knape K, Konkar A, Drucker DJ, Gelfanov V, Pfluger PT, Müller TD, Perez-Tilve D, Dimarchi RD, Tschöp MH (2015) A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nat Med* 21:27–36
- Fisher FM, Chui PC, Nasser IA, Popov Y, Cunniff JC, Lundasen T, Kharitonov A, Schuppan D, Flier JS, Maratos-Flier E (2014) Fibroblast growth factor 21 limits lipotoxicity by promoting hepatic fatty acid activation in mice on methionine and choline-deficient diets. *Gastroenterology* 147:1073–1083e1076
- Friedman SL (2008) Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. *Physiol Rev* 88:125–172
- Fu L, John LM, Adams SH, Yu XX, Tomlinson E, Renz M, Williams PM, Soriano R, Corpuz R, Moffat B, Vandlen R, Simmons L, Foster J, Stephan JP, Tsai SP, Stewart TA (2004) Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. *Endocrinology* 145:2594–2603
- Geervliet E, Bansal R (2020) Matrix metalloproteinases as potential biomarkers and therapeutic targets in liver diseases. *Cells* 9:1212
- Geloneze B, De Lima-Júnior JC, Velloso LA (2017) Glucagon-Like Peptide-1 Receptor Agonists (GLP-IRAs) in the Brain-Adipocyte Axis. *Drugs* 77:493–503
- Giannelli G, Mikulits W, Dooley S, Fabregat I, Moustakas A, Ten Dijke P, Portincasa P, Winter P, Janssen R, Leporatti S (2016) The rationale for targeting TGF- $\beta$  in chronic liver diseases. *Eur J Clin Invest* 46:349–361
- Gjøn T, Bjerkelund T, Blomhoff HK, Norum KR, Berg T, Blomhoff R (1987) Liver takes up retinol-binding protein from plasma. *J Biol Chem* 262:10926–10930
- Gulubova MV (1998) Intercellular adhesion molecule-1 (ICAM-1) expression in the liver of patients with extrahepatic cholestasis. *Acta Histochem* 100:59–74
- Gupta NA, Mells J, Dunham RM, Grakoui A, Handy J, Saxena NK, Anania FA (2010) Glucagon-like peptide-1 receptor is present on human hepatocytes and has a direct role in decreasing hepatic steatosis in vitro by modulating elements of the insulin signaling pathway. *Hepatology* 51:1584–1592
- Halim MA, Degerblad M, Sundbom M, Karlbom U, Holst JJ, Webb DL, Hellström PM (2018) Glucagon-Like Peptide-1 Inhibits Prandial Gastrointestinal Motility Through Myenteric Neuronal Mechanisms in Humans. *J Clin Endocrinol Metab* 103:575–585
- Harris EN, Weigel JA, Weigel PH (2008) The human hyaluronan receptor for endocytosis (HARE/Stabilin-2) is a systemic clearance receptor for heparin. *J Biol Chem* 283:17341–17350
- Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM, Abdelmalek MF, Younossi Z, Baum SJ, Francque S, Charlton MR, Newsome PN, Lanthier N, Schiefke I, Mangia A, Pericàs JM, Patil R, Sanyal AJ, Noureddin M, Bansal MB, Alkhouri N, Castera L, Rudraraju M, Ratzliff V (2024) A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. *N Engl J Med* 390:497–509
- Harrison SA, Browne SK, Suschak JJ, Tomah S, Gutierrez JA, Yang J, Roberts MS, Harris MS (2025) Effect of pemvidutide, a GLP-1/glucagon dual receptor agonist, on MASLD: A randomized, double-blind, placebo-controlled study. *J Hepatol* 82:7–17
- Harrison SA, Frias JP, Lucas KJ, Reiss G, Neff G, Bollepalli S, Su Y, Chan D, Tillman EJ, Moulton A, De Temple B, Zari A, Shringarpure R, Rolph T, Cheng A, Yale K (2025) Safety and Efficacy of Efruxifermin in Combination With a GLP-1 Receptor Agonist in Patients With NASH/MASH and Type 2 Diabetes in a Randomized Phase 2 Study. *Clin Gastroenterol Hepatol* 23:103–113
- Harrison SA, Frias JP, Neff G, Abrams GA, Lucas KJ, Sanchez W, Gogia S, Sheikh MY, Behling C, Bedossa P, Shao L, Chan D, Fong E, De Temple B, Shringarpure R, Tillman EJ, Rolph T, Cheng A, Yale K (2023) Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Gastroenterol Hepatol* 8:1080–1093
- Harrison SA, Neff G, Guy CD, Bashir MR, Paredes AH, Frias JP, Younes Z, Trotter JF, Gunn NT, Moussa SE, Kohli A, Nelson K, Gottwald M, Chang WCG, Yan AZ, Depaoli AM, Ling L, Lieu HD (2021) Efficacy and Safety of Aldafermin, an Engineered FGF19 Analog, in a Randomized, Double-Blind, Placebo-Controlled Trial of Patients With Nonalcoholic Steatohepatitis. *Gastroenterology* 160:219–231.e211
- Harrison SA, Rolph T, Knott M, Dubourg J (2024) FGF21 agonists: An emerging therapeutic for metabolic dysfunction-associated steatohepatitis and beyond. *J Hepatol* 81:562–576
- Harrison SA, Ruane PJ, Freilich BL, Neff G, Patil R, Behling CA, Hu C, Fong E, De Temple B, Tillman EJ, Rolph TP, Cheng A, Yale K (2021) Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat Med* 27:1262–1271
- Hartman ML, Sanyal AJ, Loomba R, Wilson JM, Nikooienejad A, Bray R, Karanikas CA, Duffin KL, Robins DA, Haupt A (2020) Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes. *Diabetes Care* 43:1352–1355
- Healing MET (2000) Growth factors engineered for super-affinity to the extracellular. *J Clin Microbiol* 38:1053–1057
- Hecht R, Li YS, Sun J, Belouski E, Hall M, Hager T, Yie J, Wang W, Winters D, Smith S, Spahr C, Tam LT, Shen Z, Stanislaus S, Chinooskowsong N, Lau Y, Sickmier A, Michaels ML, Boone T, Véniant MM, Xu J (2012) Rationale-Based Engineering of a Potent Long-Acting FGF21 Analog for the Treatment of Type 2 Diabetes. *PLoS ONE* 7:e49345
- Henderson NC, Arnold TD, Katamura Y, Giacomini MM, Rodriguez JD, McCarty JH, Pellicoro A, Raschperger E, Betsholtz C, Rumin PG (2013) Targeting of  $\alpha$ v integrin identifies a core molecular pathway that regulates fibrosis in several organs. *Nat Med* 19:1617–1624
- Henriksson E, Andersen B (2020) FGF19 and FGF21 for the Treatment of NASH—Two Sides of the Same Coin? Differential and Overlapping Effects of FGF19 and FGF21 From Mice to Human. *Front Endocrinol (Lausanne)* 11:601349

- Holland RJ, Lam K, Ye X, Martin AD, Wood MC, Palmer L, Fraser D, Mcclintock K, Majeski S, Jarosz A (2021) Ligand conjugate SAR and enhanced delivery in NHP. *Mol Ther* 29:2910–2919
- Holst JJ (2024) GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. *Nat Metab* 6:1866–1885
- Hönes GS, Sivakumar RG, Hoppe C, König J, Führer D, Moeller LC (2022) Cell-Specific Transport and Thyroid Hormone Receptor Isoform Selectivity Account for Hepatocyte-Targeted Thyromimetic Action of MGL-3196. *Int J Mol Sci* 23
- Hu B, Zhong L, Weng Y, Peng L, Huang Y, Zhao Y, Liang XJ (2020) Therapeutic siRNA: state of the art. *Signal Transduct Target Ther* 5:101
- Huang DQ, Wilson LA, Behling C, Kleiner DE, Kowdley KV, Dasarathy S, Amangurbanova M, Terrault NA, Diehl AM, Chalasani N, Neuschwander-Tetri BA, Sanyal AJ, Tonascia J, Loomba R (2023) Fibrosis Progression Rate in Biopsy-Proven Nonalcoholic Fatty Liver Disease Among People With Diabetes Versus People Without Diabetes: A Multicenter Study. *Gastroenterology* 165:463–472 e465
- Inagaki T, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA (2007) Endocrine regulation of the fasting response by PPAR $\alpha$ -mediated induction of fibroblast growth factor 21. *Cell Metab* 5:415–425
- Jeon JY, Ayyar VS, Ouchi S, Fabbrini E, Koshkina A, Prusakiewicz JJ, Dallas J, Yang T, Jian W, Kang L, Cofsky K, Rady B, Tamamura R, Saito Y, Yamashita A, Vaughan T, Wendel S, Makimura H, Csonka D, Goyal N (2025) Preclinical and Clinical Pharmacokinetics of JNJ-75220795, an siRNA Therapeutic Targeting PNPLA3, for Metabolic Dysfunction-Associated Steatohepatitis. *J Clin Pharmacol* 65:644–653
- Jin L, Sim DI, Kim SH, Han S, Thein W, Na DH (2025) Poly (ethylene glycol) conjugation to glycyl-L-histidyl-L-lysine peptide enhances fibroblast proliferation and wound healing in rats. *J Drug Deliv Sci Technol* :107969
- Kaps L, Limeres MJ, Schneider P, Svensson M, Zeyn Y, Fraude S, Cacicado ML, Galle PR, Gehring S, Bros M (2023) Liver cell type-specific targeting by nanoformulations for therapeutic applications. *Int J Mol Sci* 24:11869
- Kasiewicz LN, Biswas S, Beach A, Ren H, Dutta C, Mazzola AM, Rohde E, Chadwick A, Cheng C, Garcia SP (2023) GalNAc-Lipid nanoparticles enable non-LDLR dependent hepatic delivery of a CRISPR base editing therapy. *Nat Commun* 14:2776
- Keam SJ (2024) Resmetimrom: First Approval. *Drugs* 84:729–735
- Kelly MJ, Pietranico-Cole S, Larigan JD, Haynes NE, Reynolds CH, Scott N, Vermeulen J, Dvornozniak M, Conde-Knape K, Huang KS, So SS, Thakkar K, Qian Y, Banner B, Mennona F, Danzi S, Klein I, Taub R, Tilley J (2014) Discovery of 2-[3,5-dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yloxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile (MGL-3196), a Highly Selective Thyroid Hormone Receptor  $\beta$  agonist in clinical trials for the treatment of dyslipidemia. *J Med Chem* 57:3912–3923
- Kharitononkov A, Shiyanova TL, Koester A, Ford AM, Micanovic R, Galbreath EJ, Sandusky GE, Hammond LJ, Moyers JS, Owens RA, Gromada J, Brozinick JT, Hawkins ED, Wroblewski VJ, Li DS, Mehrbod F, Jaskunas SR, Shanafelt AB (2005) FGF-21 as a novel metabolic regulator. *J Clin Invest* 115:1627–1635
- Kim JK, Lee JS, Lee SM, Choi JH, Kwon H, Park EJ, Bae SM, Kim DJ, Kim Y, Choi IY (2021) 656-P: Antifibrotic Potential of a Novel Long-Acting Glucagon/GIP/GLP-1 Triple Agonist (HM15211) in Preclinical Models of Fibrosis. *Diabetes* 70:656–P
- Kim SS, Ro SW, Na DH (2024) In vitro–in vivo correlation of microsphere formulations: recent advances and challenges. *J Pharm Invest* 54:37–49
- Kir S, Beddow SA, Samuel VT, Miller P, Previs SF, Suino-Powell K, Xu HE, Shulman GI, Kliewer SA, Mangelsdorf DJ (2011) FGF19 as a postprandial, insulin-independent activator of hepatic protein and glycogen synthesis. *Science* 331:1621–1624
- Kjems LL, Holst JJ, Vølund A, Madsbad S (2003) The influence of GLP-1 on glucose-stimulated insulin secretion: effects on  $\beta$ -cell sensitivity in type 2 and nondiabetic subjects. *Diabetes* 52:380–386
- Klein S, Nestor JJ Jr, Harris MS, Suyundikov A, Casper ROB, Steele SM, Payne JD, Krishnan V, Roberts MS, Browne SK (2022) 334-OR: pemvidutide (ALT-801), a balanced (1: 1) GLP-1/glucagon dual receptor agonist, induces rapid and marked weight loss without the need for dose titration in people with overweight/obesity. *Diabetes* 71:334–OR
- Koliaki C, Dalamaga M, Kakounis K, Liatis S (2025) Metabolically Healthy Obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Navigating the Controversies in Disease Development and Progression. *Curr Obes Rep* 14:46
- Kurosu H, Choi M, Ogawa Y, Dickson AS, Goetz R, Eliseenkova AV, Mohammadi M, Rosenblatt KP, Kliewer SA, Kuro OM (2007) Tissue-specific expression of  $\beta$ Klotho and fibroblast growth factor (FGF) receptor isoforms determines metabolic activity of FGF19 and FGF21. *J Biol Chem* 282:26687–26695
- Kuzina ES, Ung PM, Mohanty J, Tome F, Choi J, Pardon E, Steyaert J, Lax I, Schlessinger A, Schlessinger J, Lee S (2019) Structures of ligand-occupied  $\beta$ -Klotho complexes reveal a molecular mechanism underlying endocrine FGF specificity and activity. *Proc Natl Acad Sci U S A* 116:7819–7824
- Laker RC, Egolf S, Will S, Lantier L, McGuinness OP, Brown C, Bhargava N, Oldham S, Kuszpit K, Alfaro A, Li X, Kang T, Pellegrini G, Andréasson AC, Kajani S, Sitaula S, Larsen MR, Rhodes CJ (2025) GLP-1R/GCGR dual agonism dissipates hepatic steatosis to restore insulin sensitivity and rescue pancreatic  $\beta$ -cell function in obese male mice. *Nat Commun* 16:4714
- Lakhia R, Mishra A, Patel V (2019) Manipulation of renal gene expression using oligonucleotides. *Methods Cell Biol* 154:109–120
- Le MH, Yeo YH, Zou B, Barnet S, Henry L, Cheung R, Nguyen MH (2022) Forecasted 2040 global prevalence of nonalcoholic fatty liver disease using hierarchical bayesian approach. *Clin Mol Hepatol* 28:841–850
- Le P, Tatar M, Dasarathy S, Alkhouri N, Herman WH, Taksler GB, Deshpande A, Ye W, Adekunle OA, McCullough A, Rothberg MB (2025) Estimated Burden of Metabolic Dysfunction-Associated Steatotic Liver Disease in US Adults, 2020 to 2050. *JAMA Netw Open* 8:e2454707
- Lee H, Jeong H, Park S, Yoo W, Choi S, Choi K, Lee MG, Lee M, Cha D, Kim YS (2015) Fusion protein of retinol-binding protein and albumin domain III reduces liver fibrosis. *EMBO Mol Med* 7:819–830
- Lee J, Hong SW, Kim MJ, Moon SJ, Kwon H, Park SE, Rhee EJ, Lee WY (2022) Dulaglutide Ameliorates Palmitic Acid-Induced Hepatic Steatosis by Activating FAM3A Signaling Pathway. *Endocrinol Metab (Seoul)* 37:74–83
- Lemmon MA, Schlessinger J (2010) Cell signaling by receptor tyrosine kinases. *Cell* 141:1117–1134
- Lewandowski SL, El K, Campbell JE (2024) Evaluating glucose-dependent insulinotropic polypeptide and glucagon as key regulators of insulin secretion in the pancreatic islet. *Am J Physiol Endocrinol Metab* 327:E103–e110
- Li M, Cai SY, Boyer JL (2017) Mechanisms of bile acid mediated inflammation in the liver. *Mol Aspects Med* 56:45–53

- Li C, Yang J, Wang Y, Qi Y, Yang W, Li Y (2020) Farnesoid X Receptor Agonists as Therapeutic Target for Cardiometabolic Diseases. *Front Pharmacol* 11:1247
- Li S, Xiong F, Zhang S, Liu J, Gao G, Xie J, Wang Y (2024) Oligonucleotide therapies for nonalcoholic steatohepatitis. *Mol Ther Nucleic Acids* 35:102184
- Liu Q, Wang X, Liu X, Kumar S, Gochman G, Ji Y, Liao Y-P, Chang CH, Situ W, Lu J (2019) Use of polymeric nanoparticle platform targeting the liver to induce treg-mediated antigen-specific immune tolerance in a pulmonary allergen sensitization model. *ACS Nano* 13:4778–4794
- Llovet JM, Willoughby CE, Singal AG, Greten TF, Heikenwälder M, El-Serag HB, Finn RS, Friedman SL (2023) Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. *Nat Rev Gastroenterol Hepatol* 20:487–503
- Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, Brouwers B, Robins DA, Nikoobie A, Bunck MC, Haupt A, Sanjay AJ (2024) Tirzepatide for Metabolic Dysfunction-Associated Steatohepatitis with Liver Fibrosis. *N Engl J Med* 391:299–310
- Loomba R, Kowdley KV, Rodriguez J, Kim NJ, Alvarez AM, Morrow L, Jeglinski B, Clawson A, Chowdhury S, Bain G, Odriljin T (2025) Efimosfermin alfa (BOS-580), a long-acting FGF21 analogue, in participants with phenotypic metabolic dysfunction-associated steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet Gastroenterol Hepatol* 10:734–745
- Loomba R, Morgan E, Yousefi K, Li D, Geary R, Bhanot S, Alkhouiri N (2025) Antisense oligonucleotide DGAT-2 inhibitor, ION224, for metabolic dysfunction-associated steatohepatitis (ION224-CS2): results of a 51-week, multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 406:821–831
- Loomba R, Sanyal AJ, Kowdley KV, Bhatt DL, Alkhouiri N, Frias JP, Bedossa P, Harrison SA, Lazas D, Barish R, Gottwald MD, Feng S, Agollah GD, Hartsfield CL, Mansbach H, Margalit M, Abdelmalek MF (2023) Randomized, Controlled Trial of the FGF21 Analogue Pegozaferrin in NASH. *N Engl J Med* 389:998–1008
- Maharjan R, Lim DS, Baik HJ, Park HE, Kim M-S, Kim KH, Jeong SH (2024) Preparation of semaglutide long-acting injectable microcapsules with physicochemical properties, long-term stability, and pharmacokinetics and pharmacodynamics. *J Pharm Invest* 54:667–681
- Maher JJ (2013) Retinol binding protein 4 and fatty liver: A direct link? *Hepatology* 58:477–479
- Maloney PR, Parks DJ, Haffner CD, Fivush AM, Chandra G, Plunket KD, Creech KL, Moore LB, Wilson JG, Lewis MC, Jones SA, Willson TM (2000) Identification of a chemical tool for the orphan nuclear receptor FXR. *J Med Chem* 43:2971–2974
- Mansbach H, Margalit M (2024) Methods of treatment of NASH using mutant FGF-21 peptide conjugates. *WO patent WO2024044680A2*
- Mcquitty CE, Williams R, Chokshi S, Urbani L (2020) Immunomodulatory role of the extracellular matrix within the liver disease microenvironment. *Front Immunol* 11:574276
- Meloni AR, Deyoung MB, Lowe C, Parkes DG (2013) GLP-1 receptor activated insulin secretion from pancreatic  $\beta$ -cells: mechanism and glucose dependence. *Diabetes Obes Metab* 15:15–27
- Moiz A, Filion KB, Tsoukas MA, Yu OH, Peters TM, Eisenberg MJ (2025) Mechanisms of GLP-1 Receptor Agonist-Induced Weight Loss: A Review of Central and Peripheral Pathways in Appetite and Energy Regulation. *Am J Med* 138:934–940
- Monfeuga T, Norlin J, Bugge A, Gaalsgaard ED, Prada-Medina CA, Latta M, Veidal SS, Petersen PS, Feigh M, Holst D (2024) Evaluation of long acting GLP1R/GCGR agonist in a DIO and biopsy-confirmed mouse model of NASH suggest a beneficial role of GLP-1/glucagon agonism in NASH patients. *Mol Metab* 79:101850
- Muro S, Garnacho C, Champion JA, Leferovich J, Gajewski C, Schuchman EH, Mitragotri S, Muzykantov VR (2008) Control of endothelial targeting and intracellular delivery of therapeutic enzymes by modulating the size and shape of ICAM-1-targeted carriers. *Mol Ther* 16:1450–1458
- Muro S, Wiewrodt R, Thomas A, Koniaris L, Albelda SM, Muzykantov VR, Koval M (2003) A novel endocytic pathway induced by clustering endothelial ICAM-1 or PECAM-1. *J Cell Sci* 116:1599–1609
- Nestor JJ, Parkes D, Feigh M, Suschak JJ, Harris MS (2022) Effects of ALT-801, a GLP-1 and glucagon receptor dual agonist, in a translational mouse model of non-alcoholic steatohepatitis. *Sci Rep* 12:6666
- Newsome PN, Ambery P (2023) Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver. *J Hepatol* 79:1557–1565
- Ng CH, Tang ASP, Xiao J, Wong ZY, Yong JN, Fu CE, Zeng RW, Tan C, Wong GHZ, Teng M, Chee D, Tan DJH, Chan KE, Huang DQ, Chew NWS, Nah B, Siddiqui MS, Sanyal AJ, Nouredin M, Muthiah M (2023) Safety and tolerability of obeticholic acid in chronic liver disease: a pooled analysis of 1878 individuals. *Hepatology Commun* 7:e0005
- Ngm Biopharmaceuticals I (2021) *NGM Bio Reports Topline Results from 24-Week Phase 2b ALPINE 2/3 Study of Aldafermin in NASH*, <<https://ir.ngmbio.com/node/8481/pdf>>
- Park EJ, Choi J, Lee KC, Na DH (2019) Emerging PEGylated non-biologic drugs. *Expert Opin Emerg Drugs* 24:107–119
- Park EJ, Lim SM, Lee KC, Na DH (2016) Exendins and exendin analogs for diabetic therapy: a patent review (2012–2015). *Expert Opin Ther Pat* 26:833–842
- Pasut G, Veronese FM (2012) State of the art in PEGylation: the great versatility achieved after forty years of research. *J Control Release* 161:461–472
- Patel K, Harrison SA, Elkhachab M, Trotter JF, Herring R, Rojter SE, Kayali Z, Wong VW, Greenbloom S, Jayakumar S, Shiffman ML, Freilich B, Lawitz EJ, Gane EJ, Harting E, Xu J, Billin AN, Chung C, Djedjos CS, Subramanian GM, Myers RP, Middleton MS, Rinella M, Nouredin M (2020) Cilofexor, a Nonsteroidal FXR Agonist, in Patients With Noncirrhotic NASH: A Phase 2 Randomized Controlled Trial. *Hepatology* 72:58–71
- Petta S, Targher G, Romeo S, Pajvani UB, Zheng MH, Aghemo A, Valenti LVC (2024) The first MASH drug therapy on the horizon: Current perspectives of resmetirom. *Liver Int* 44:1526–1536
- Potthoff MJ, Boney-Montoya J, Choi M, He T, Sunny NE, Satapati S, Suino-Powell K, Xu HE, Gerard RD, Finck BN, Burgess SC, Mangelsdorf DJ, Kliewer SA (2011) FGF15/19 regulates hepatic glucose metabolism by inhibiting the CREB-PGC-1 $\alpha$  pathway. *Cell Metab* 13:729–738
- Pyke C, Heller RS, Kirk RK, Ørskov C, Reedtz-Runge S, Kastrup P, Hvelplund A, Bardram L, Calatayud D, Knudsen LB (2014) GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* 155:1280–1290
- Qosa H, De Oliveira C, Cizza G, Lawitz EJ, Colletti N, Wetherington J, Charles ED, Tiruchera GS (2023) Pharmacokinetics, safety, and tolerability of BMS-986263, a lipid nanoparticle containing HSP47 siRNA, in participants with hepatic impairment. *Clin Transl Sci* 16:1791–1802
- Qu J, Wang L, Li Y, Li X (2024) Liver sinusoidal endothelial cell: An important yet often overlooked player in the liver fibrosis. *Clin Mol Hepatol* 30:303
- Rader DJ, Maratos-Flier E, Nguyen A, Hom D, Ferriere M, Li Y, Kompa J, Martic M, Hinder M, Basson CT, Yowe D, Diener J, Goldfine AB (2022) LLF580, an FGF21 Analog, Reduces

- Triglycerides and Hepatic Fat in Obese Adults With Modest Hypertriglyceridemia. *J Clin Endocrinol Metab* 107:e57–e70
- Rinaman L (2010) Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Res* 1350:18–34
- Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, Arrese M, Bataller R, Beuers U, Boursier J, Bugianesi E, Byrne CD, Castro Narro GE, Chowdhury A, Cortez-Pinto H, Cryer DR, Cusi K, El-Kassas M, Klein S, Eskridge W, Fan J, Gawrich S, Guy CD, Harrison SA, Kim SU, Koot BG, Korenjak M, Kowdley KV, Lacaille F, Loomba R, Mitchell-Thain R, Morgan TR, Powell EE, Roden M, Romero-Gómez M, Silva M, Singh SP, Sookoian SC, Spearman CW, Tiniakos D, Valenti L, Vos MB, Wong VW, Xanthakos S, Yilmaz Y, Younossi Z, Hobbs A, Villota-Rivas M, Newsome PN (2023) A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 78:1966–1986
- Rinella ME, Lieu HD, Kowdley KV, Goodman ZD, Alkhouri N, Lawitz E, Ratziu V, Abdelmalek MF, Wong VW, Younes ZH, Sheikh AM, Brannan D, Freilich B, Membreno F, Sinclair M, Melchor-Khan L, Sanyal AJ, Ling L, Harrison SA (2024) A randomized, double-blind, placebo-controlled trial of aldafermin in patients with NASH and compensated cirrhosis. *Hepatology* 79:674–689
- Romero-Gómez M, Lawitz E, Shankar RR, Chaudhri E, Liu J, Lam RLH, Kaufman KD, Engel SS (2023) A phase IIa active-comparator-controlled study to evaluate the efficacy and safety of efinopegdutide in patients with non-alcoholic fatty liver disease. *J Hepatol* 79:888–897
- Ronveaux CC, Tomé D, Raybould HE (2015) Glucagon-like peptide 1 interacts with ghrelin and leptin to regulate glucose metabolism and food intake through vagal afferent neuron signaling. *J Nutr* 145:672–680
- Rose JP, Morgan DA, Sullivan AI, Fu X, Inigo-Vollmer M, Burgess SC, Meyerholz DK, Rahmouni K, Potthoff MJ (2025) FGF21 reverses MASH through coordinated actions on the CNS and liver. *Cell Metab* 37:1515–1529e1516
- Rosenstock M, Tseng L, Pierce A, Offman E, Chen CY, Charlton RW, Margalit M, Mansbach H (2023) The Novel GlycoPEGylated FGF21 Analog Pegzofermin Activates Human FGF Receptors and Improves Metabolic and Liver Outcomes in Diabetic Monkeys and Healthy Human Volunteers. *J Pharmacol Exp Ther* 387:204–213
- Samms RJ, Sloop KW, Gribble FM, Reimann F, Adriaenssens AE (2021) GIPR function in the central nervous system: implications and novel perspectives for GIP-based therapies in treating metabolic disorders. *Diabetes* 70:1938–1944
- Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, Anstee QM, Hussain SA, Newsome PN, Ratziu V, Hosseini-Tabatabaei A, Schattenberg JM, Nouredin M, Alkhouri N, Younes R (2024) A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. *N Engl J Med* 391:311–319
- Sanyal AJ, Castera L, Wong VW (2023) Noninvasive Assessment of Liver Fibrosis in NAFLD. *Clin Gastroenterol Hepatol* 21:2026–2039
- Sanyal AJ, Kaplan LM, Frias JP, Brouwers B, Wu Q, Thomas MK, Harris C, Schlott NC, Du Y, Mather KJ, Haupt A, Hartman ML (2024) Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat Med* 30:2037–2048
- Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, Cali AM, Bugianesi E, Rinella ME, Roden M (2025) Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med* 392:2089–2099
- Saponaro F, Sestito S, Runfola M, Rapposelli S, Chiellini G (2020) Selective Thyroid Hormone Receptor-Beta (TR $\beta$ ) Agonists: New Perspectives for the Treatment of Metabolic and Neurodegenerative Disorders. *Front Med (Lausanne)* 7:331
- Schjoldager BT, Baldissera FG, Mortensen PE, Holst JJ, Christiansen J (1988) Oxyntomodulin: a potential hormone from the distal gut. Pharmacokinetics and effects on gastric acid and insulin secretion in man. *Eur J Clin Invest* 18:499–503
- Schlein C, Talukdar S, Heine M, Fischer AW, Krott LM, Nilsson SK, Brenner MB, Heeren J, Scheja L (2016) FGF21 Lowers Plasma Triglycerides by Accelerating Lipoprotein Catabolism in White and Brown Adipose Tissues. *Cell Metab* 23:441–453
- Schwabe RF, Tabas I, Pajvani UB (2020) Mechanisms of Fibrosis Development in Nonalcoholic Steatohepatitis. *Gastroenterology* 158:1913–1928
- Secher A, Jelsing J, Baquero AF, Hecksher-Sørensen J, Cowley MA, Dalbøge LS, Hansen G, Grove KL, Pyke C, Raun K, Schäffer L, Tang-Christensen M, Verma S, Witgen BM, Vrang N (2014) & Bjerre Knudsen L The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest* 124:4473–4488
- Seino Y, Fukushima M, Yabe D (2010) GIP and GLP-1, the two incretin hormones: Similarities and differences. *J Diabetes Investig* 1:8–23
- Seino Y, Yamazaki Y (2022) Roles of glucose-dependent insulinotropic polypeptide in diet-induced obesity. *J Diabetes Investig* 13:1122–1128
- Seo D, Faintuch BL, Aparecida De Oliveira E, Faintuch J (2017) Pancreas and liver uptake of new radiolabeled incretins (GLP-1 and Exendin-4) in models of diet-induced and diet-restricted obesity. *Nucl Med Biol* 49:57–64
- Setten RL, Rossi JJ, Han S-P (2019) The current state and future directions of RNAi-based therapeutics. *Nat Rev Drug Discovery* 18:421–446
- Shi SY, Lu YW, Richardson J, Min X, Weiszmann J, Richards WG, Wang Z, Zhang Z, Zhang J, Li Y (2018) A systematic dissection of sequence elements determining  $\beta$ -Klotho and FGF interaction and signaling. *Sci Rep* 8:11045
- Spiess M (1990) The asialoglycoprotein receptor: a model for endocytic transport receptors. *Biochemistry* 29:10009–10018
- Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA (2025) Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. *Lancet Diabetes Endocrinol* 13:134–148
- Stine JG, Munaganuru N, Barnard A, Wang JL, Kaulback K, Argo CK, Singh S, Fowler KJ, Sirlin CB, Loomba R (2021) Change in MRI-PDFF and histologic response in patients with nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 19:2274–2283 e2275
- Suk JS, Xu Q, Kim N, Hanes J, Ensign LM (2016) PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. *Adv Drug Deliv Rev* 99:28–51
- Suzuki M, Uehara Y, Motomura-Matsuzaka K, Oki J, Koyama Y, Kimura M, Asada M, Komi-Kuramochi A, Oka S, Imamura T (2008) betaKlotho is required for fibroblast growth factor (FGF) 21 signaling through FGF receptor (FGFR) 1c and FGFR3c. *Mol Endocrinol* 22:1006–1014
- Svegliati-Baroni G, Ridolfi F, Hannivoort R, Saccomanno S, Homan M, De Minicis S, Jansen PL, Candelaresi C, Benedetti A, Moshage H (2005) Bile acids induce hepatic stellate cell proliferation via activation of the epidermal growth factor receptor. *Gastroenterology* 128:1042–1055
- Svoboda M, Tastenoy M, Vertongen P, Robberecht P (1994) Relative quantitative analysis of glucagon receptor mRNA in rat tissues. *Mol Cell Endocrinol* 105:131–137
- Szafranska K, Kruse LD, Holte CF, Mccourt P, Zapotoczny B (2021) The wHole story about fenestrations in LSEC. *Front Physiol* 12:735573

- Tacke F, Horn P, Wong VW-S, Ratzliff V, Bugianesi E, Francque S, Zelber-Sagi S, Valenti L, Roden M, Schick F (2024) EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 81:492–542
- Talukdar S, Kharitonov A (2021) FGF19 and FGF21: In NASH we trust. *Mol Metab* 46:101152
- Tan TM, Field BC, McCullough KA, Troke RC, Chambers ES, Salem V, Gonzalez Maffe J, Baynes KC, De Silva A, Viardot A, Alsafi A, Frost GS, Ghatei MA, Bloom SR (2013) Coadministration of glucagon-like peptide-1 during glucagon infusion in humans results in increased energy expenditure and amelioration of hyperglycemia. *Diabetes* 62:1131–1138
- Tomlinson E, Fu L, John L, Hultgren B, Huang X, Renz M, Stephan JP, Tsai SP, Powell-Braxton L, French D, Stewart TA (2002) Transgenic mice expressing human fibroblast growth factor-19 display increased metabolic rate and decreased adiposity. *Endocrinology* 143:1741–1747
- U.S. Food and Drug Administration (2025) FDA approves treatment for serious liver disease known as ‘MASH’. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-serious-liver-disease-known-mash>
- Van Bloemendaal L, Ten Kulve JS, La Fleur SE, Ijzerman RG, Diamant M (2014) Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. *J Endocrinol* 221:T1–16
- Van Der Heide D, Weiskirchen R, Bansal R (2019) Therapeutic targeting of hepatic macrophages for the treatment of liver diseases. *Front Immunol* 10:2852
- Vrettos EI, Mezö G, Tzakos AG (2018) On the design principles of peptide–drug conjugates for targeted drug delivery to the malignant tumor site. *Beilstein J Org Chem* 14:930–954
- Wahyudi H, Reynolds AA, Li Y, Owen SC, Yu SM (2016) Targeting collagen for diagnostic imaging and therapeutic delivery. *J Controlled Release* 240:323–331
- Wang H, Zhao M, Sud N, Christian P, Shen J, Song Y, Pashaj A, Zhang K, Carr T, Su Q (2016) Glucagon regulates hepatic lipid metabolism via cAMP and Insig-2 signaling: implication for the pathogenesis of hypertriglyceridemia and hepatic steatosis. *Sci Rep* 6:32246
- Wang K, Zhang Y, Wang G, Hao H, Wang H (2024) FXR agonists for MASH therapy: Lessons and perspectives from obeticholic acid. *Med Res Rev* 44:568–586
- Watts JK, Corey DR (2012) Silencing disease genes in the laboratory and the clinic. *J Pathol* 226:365–379
- Wei W, Dutchak PA, Wang X, Ding X, Wang X, Bookout AL, Goetz R, Mohammadi M, Gerard RD, Dechow PC (2012) Fibroblast growth factor 21 promotes bone loss by potentiating the effects of peroxisome proliferator-activated receptor  $\gamma$ . *Proceedings of the National Academy of Sciences* 109:3143–3148
- Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MT, Wadden TA (2021) Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 384:989–1002
- Wu X, Li Y (2011) Therapeutic utilities of fibroblast growth factor 19. *Expert Opin Ther Targets* 15:1307–1316
- Wynne K, Park AJ, Small CJ, Meeran K, Ghatei MA, Frost GS, Bloom SR (2006) Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. *Int J Obes (Lond)* 30:1729–1736
- Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, Wren AM, Frost GS, Meeran K, Ghatei MA, Bloom SR (2005) Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes* 54:2390–2395
- Xue F, Wei L (2024) THR- $\beta$  Agonist for Nonalcoholic Steatohepatitis Treatment: Challenges of a Promising Drug. *J Clin Transl Hepatol* 12:755–757
- Zhang F, Kong D, Lu Y, Zheng S (2013) Peroxisome proliferator-activated receptor- $\gamma$  as a therapeutic target for hepatic fibrosis: from bench to bedside. *Cell Mol Life Sci* 70:259–276
- Zhang F, Yu L, Lin X, Cheng P, He L, Li X, Lu X, Tan Y, Yang H, Cai L, Zhang C (2015) Minireview: Roles of Fibroblast Growth Factors 19 and 21 in Metabolic Regulation and Chronic Diseases. *Mol Endocrinol* 29:1400–1413
- Zhang J, Ning Y, Zhu H, Rotile NJ, Wei H, Diyabalanage H, Hansen EC, Zhou IY, Barrett SC, Sojoodi M (2023) Fast detection of liver fibrosis with collagen-binding single-nanometer iron oxide nanoparticles via T1-weighted MRI. *Proceedings of the National Academy of Sciences* 120:e2220036120
- Zhou M, Learned RM, Rossi SJ, Depaoli AM, Tian H, Ling L (2017) Engineered FGF19 eliminates bile acid toxicity and lipotoxicity leading to resolution of steatohepatitis and fibrosis in mice. *Hepatology* 1:1024–1042
- Zimmermann T, Thomas L, Baader-Pagler T, Haebel P, Simon E, Reindl W, Bajrami B, Rist W, Uphues I, Drucker DJ, Klein H, Santhanam R, Hamprecht D, Neubauer H, Augustin R (2022) BI 456906: Discovery and preclinical pharmacology of a novel GCGR/GLP-1R dual agonist with robust anti-obesity efficacy. *Mol Metab* 66:101633

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