

From Bench to Bedside: Multifunctional Nanoplatfoms in the Fight Against Non-alcoholic Fatty Liver Disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD) affects approximately 25% of the global adult population and represents a major public health burden, characterized by disease progression from steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and potentially hepatocellular carcinoma. Despite this high prevalence and serious clinical outcomes, no pharmacologic therapies are currently approved, and standard lifestyle interventions often prove ineffective. Therefore, there is a major unmet clinical need for innovative treatments. To overcome these limitations, nanomedicine has emerged as a promising approach, with multifunctional nanoplatfoms (MFNs) demonstrating distinctive advantages in tackling the complex pathology of NAFLD. For instance, MFNs enable targeted liver delivery, synergistic therapeutic effects (eg, reducing hepatic lipogenesis and fibrosis), and theranostic integration, thereby minimizing rapid clearance and adverse effects associated with conventional low-molecular-weight compounds. Consequently, this review comprehensively synthesizes the latest advances in MFNs for NAFLD management, critically analyzing their design strategies (eg, nanoencapsulation of bioactive compounds for enhanced bioavailability) and mechanistic roles in ameliorating inflammation, fibrosis, and steatosis. Furthermore, it explores challenges such as optimizing organ-specific targeting and personalized applications, while outlining future research directions to accelerate clinical translation and address coexisting conditions like chronic hepatitis B infection. By bridging current knowledge gaps, this work aims to inform the development of effective nanotherapeutic strategies for NAFLD.

Keywords: non-alcoholic fatty liver disease, multifunctional nanoplatfoms, synergistic therapy, theranostic nanoplatfoms, clinical translation

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent liver disease globally, affecting approximately 25% of the adult population.¹ With the global obesity epidemic, the incidence of NAFLD has exhibited a significant upward trend and is closely associated with manifestations of metabolic syndrome, such as type 2 diabetes and cardiovascular diseases.^{2,3} The disease spectrum can progress from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), ultimately leading to end-stage liver diseases including cirrhosis and hepatocellular carcinoma.^{4,5} Notably, the demand for liver transplantation related to NAFLD is rapidly increasing, making it the second most important indication for transplantation after viral hepatitis.⁶ This epidemiological shift poses a severe challenge to public health systems, underscoring the urgent need for developing novel therapeutic strategies.²

The spectrum of NAFLD encompasses a range of stages from simple steatosis to NASH with inflammation and fibrosis.⁷ Although controversies exist in the academic community regarding disease terminology, such as the proposal of the new name

MAFLD,⁸ the core pathological features consistently center around disturbances in hepatocyte lipid metabolism, oxidative stress, and inflammatory responses.^{9,10} Currently, the main clinical challenge lies in the absence of any formally approved pharmacological agents for NAFLD treatment,^{11,12} with existing interventions like lifestyle modifications exhibiting poor adherence and limited efficacy.¹³ More critically, approximately 20–30% of NASH patients progress to advanced fibrosis, underscoring an urgent need for therapeutic strategies that simultaneously target multiple pathological mechanisms.^{7,9} This unmet clinical need motivates researchers to explore innovative treatment paradigms, including nanotechnology-based approaches.^{14,15}

Nanomedicine presents a revolutionary potential for the treatment of NAFLD. Compared to traditional small molecule drugs, nano-delivery systems offer several distinct advantages: they can protect bioactive components,¹⁶ achieve liver-targeted delivery,¹⁷ synergistically co-load multiple therapeutic agents,¹⁸ and integrate diagnostic and therapeutic functions (“theranostics”).¹⁹ Particularly, the development of biomimetic nanoplastforms, such as those featuring ROS-responsive properties, significantly enhances drug accumulation and release efficiency within fibrotic livers.¹⁸ Nanotechnology also effectively overcomes the limitation of low bioavailability associated with natural bioactive compounds (eg, ginsenoside), enabling the development of long-term and low-toxic nano-formulations of ginsenoside.²⁰ These innovations address the critical bottlenecks of low therapeutic efficacy and significant organ toxicity observed with current drug treatments.^{20,21} Furthermore, nanomedicine provides the crucial technological platform needed to implement novel therapeutic strategies, including metabolic reprogramming and microbiome modulation.^{22,23} This multi-targeted and precise therapeutic philosophy embodied by nanomedicine is actively reshaping the overall paradigm of NAFLD management^{19,20} (Figure 1). Several recent reviews have explored the application of

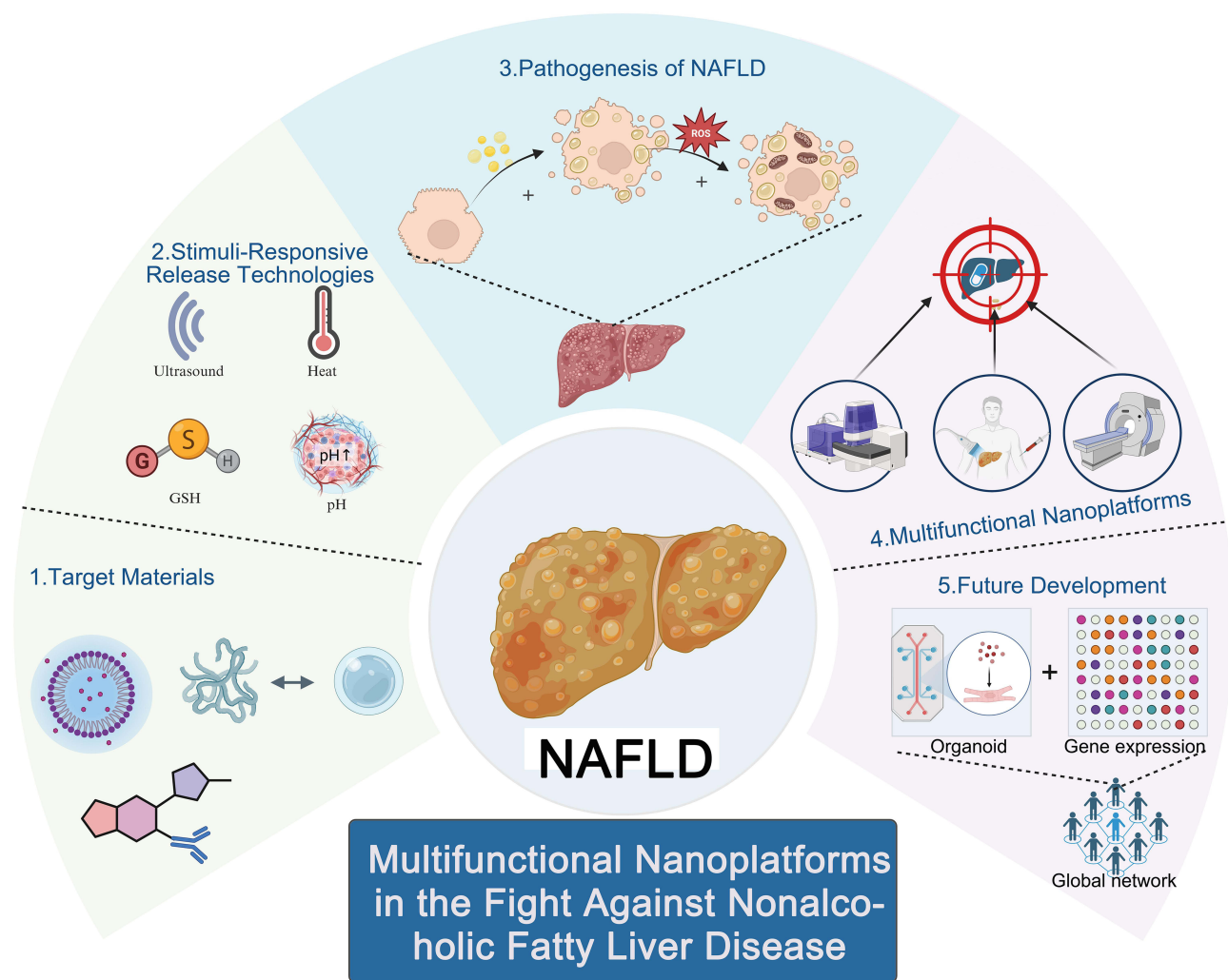


Figure 1 The schematic illumination of the multifunctional nanoplastforms in the fight against non-alcoholic fatty liver disease.

nanomedicine in NAFLD, focusing primarily on individual aspects such as the design of liver-targeted delivery systems, the use of natural product-based nanocarriers, or the potential of specific nanomaterials for anti-inflammatory or anti-fibrotic therapy. In contrast, the present review provides a comprehensive and systematic overview of multifunctional nanoplatfoms (MFNs) that integrate multiple therapeutic and diagnostic functions within a single system. Specifically, we critically analyze the design strategies—including material selection, stimuli-responsive release, and biomimetic surface engineering—that enable MFNs to simultaneously address the complex pathological features of NAFLD, such as steatosis, inflammation, and fibrosis. Moreover, we extend beyond preclinical development by offering an in-depth discussion of translational challenges, including scalable manufacturing, long-term biosafety, patient heterogeneity, and innovative clinical trial paradigms. The inclusion of a comprehensive table summarizing nanomaterial-based therapies and diagnostic platforms further distinguishes this review, providing a practical reference for researchers in the field. By bridging these interdisciplinary perspectives, this review aims to inform the rational design and clinical translation of next-generation nanotherapeutics for NAFLD.

Pathogenesis and Therapeutic Targets of NAFLD

Core Pathways of Hepatocyte Lipid Metabolism Dysregulation

The core pathological feature of NAFLD is abnormal lipid accumulation within hepatocytes, involving dysregulation of complex metabolic networks as shown in Figure 2. In the context of obesity and insulin resistance, the hepatic de novo lipogenesis (DNL) pathway is aberrantly activated, while fatty acid beta-oxidation is simultaneously suppressed.^{24,25} Sterol regulatory element-binding proteins (SREBPs), as key transcriptional regulators, drive upregulated expression of lipid synthesis-related enzymes, leading to excessive deposition of triglycerides in hepatocytes.^{25–27} Additionally, insulin resistance enhances peripheral adipose tissue lipolysis, flooding the liver with free fatty acids and further aggravating hepatic lipid burden.^{27,28} These metabolic disruptions constitute the initial pathological insult within the contemporary “multiple-hit” framework, setting the stage for subsequent inflammation and fibrosis.^{27,29,30} In this model, multiple parallel and interacting

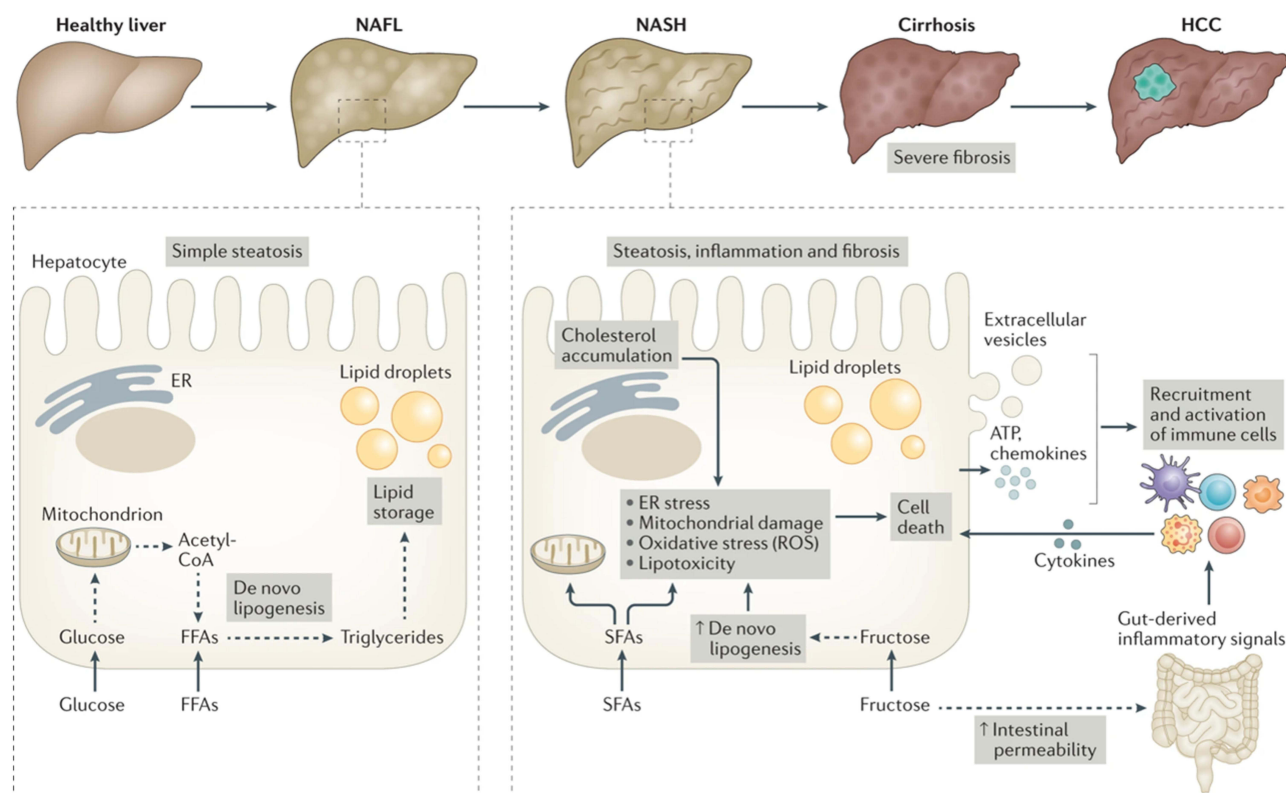


Figure 2 Pathophysiological schematic of hepatocellular carcinoma associated with non-alcoholic fatty liver disease. Reproduced with permission from Ref.³¹ Copyright 2022, Springer Nature.

factors—including insulin resistance, adipose tissue dysfunction, gut-derived metabolites, and genetic susceptibility—collectively contribute to disease initiation and progression, rather than a linear sequence of discrete hits.

Gut-Liver Axis and Gut Microbiome Dysbiosis

The gut microbiome plays a pivotal role in NAFLD pathogenesis through the gut-liver axis. Dietary patterns and exposure to environmental toxins can induce gut dysbiosis, disrupting intestinal barrier function and enabling microbial products like bacterial endotoxin (LPS) to enter the liver via the portal vein.^{32–35} These metabolites activate Toll-like receptors (TLRs) on hepatic Kupffer cells, triggering pro-inflammatory signaling pathways.^{33,36,37} Crucially, gut dysbiosis disrupts bile acid metabolism, interfering with the farnesoid X receptor (FXR) signaling pathway and impairing hepatic lipid homeostasis.^{38–40} It has long been known that antibiotic exposure alters gut microbiota-derived metabolites,^{41–43} further exacerbating liver metabolic dysregulation by affecting hepatic phospholipid biosynthesis.^{37,44} Beyond the activation of inflammatory pathways, gut-derived metabolites directly influence hepatic lipid metabolism. For instance, short-chain fatty acids (SCFAs), produced by commensal bacteria through dietary fiber fermentation, can regulate hepatic de novo lipogenesis by modulating sterol regulatory element-binding protein (SREBP) activity. Conversely, metabolites such as secondary bile acids and lipopolysaccharide (LPS) may exacerbate lipid accumulation by impairing insulin signaling and promoting pro-inflammatory cytokine release. These interactions underscore the critical role of the gut-liver axis not only in inflammation but also in the metabolic dysregulation that defines NAFLD.

Key Regulatory Nodes in Inflammation and Fibrosis Progression

The progression from NAFLD to NASH involves a “second hit” characterized by lipotoxicity-induced inflammation and fibrosis. Excessive lipid accumulation causes endoplasmic reticulum stress and mitochondrial dysfunction, generating reactive oxygen species (ROS) that activate pro-inflammatory pathways like NF- κ B and JNK.^{25,45,46} This inflammatory milieu activates hepatic stellate cells (HSCs), promoting extracellular matrix deposition and liver fibrosis.^{25,27,46} Notably, genetic factors such as 17 β -hydroxysteroid dehydrogenase 13 (HSD17B13) modulate disease progression, offering insights into NAFLD heterogeneity.^{46–48} Insulin resistance serves as a critical amplifier of inflammatory signaling in NAFLD. Hyperinsulinemia promotes the activation of NF- κ B and JNK pathways in both hepatocytes and Kupffer cells, enhancing the production of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). Moreover, insulin resistance impairs autophagy, leading to the accumulation of damaged mitochondria and sustained reactive oxygen species (ROS) production, which further perpetuates the inflammatory milieu. This vicious cycle creates a self-sustaining environment that drives the transition from simple steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis.

Limitations of Current Pharmacotherapies

Despite NAFLD/NASH being the most prevalent chronic liver disease globally, no FDA-approved drugs specifically target the pathways causing NAFLD/NASH.^{39,49–52} Current strategies focus mainly on metabolic comorbidities: *eg* insulin sensitizers for insulin resistance or lipid-lowering agents for dyslipidemia.^{51,53,54} However, these approaches target single pathological facets and fail to address NAFLD’s multisystem complexity.^{25,55,56} Preclinical studies suggest promising therapies targeting gut microbiota (*eg* fecal microbiota transplantation) or bile acid metabolism (*eg* FXR agonists),^{33,39,40} yet challenges remain in translation to clinical practice: significant inter-individual variability, unclear long-term safety, and difficulties in clinical trial design due to disease heterogeneity.^{25,55,56} Taken together, the pathophysiology of NAFLD is now understood as a complex, multi-faceted process involving the simultaneous interplay of metabolic, inflammatory, and fibrotic pathways. The limitations of current pharmacotherapies stem largely from their single-target nature, which fails to address this integrated pathology. This underscores the urgent need for multi-targeted therapeutic strategies—such as multifunctional nanoplatforms—that can concurrently modulate lipid metabolism, resolve inflammation, and halt fibrosis progression. The subsequent sections of this review will discuss how nanotechnology offers a promising platform to achieve such integrated therapeutic effects.

Design Principles of Multifunctional Nanoplatforms

The design of multifunctional nanoplatforms for NAFLD must account for the unique pathophysiological features of the diseased liver, including enhanced vascular permeability, activated hepatic stellate cells, increased oxidative stress, and dysregulated immune cell infiltration. Unlike oncology applications where enhanced permeability and retention (EPR) effects

dominate, NAFLD targeting strategies often leverage receptor upregulation on hepatocytes (eg, asialoglycoprotein receptor, LDLR), activated hepatic stellate cells (eg, PDGFR β , integrins), or infiltrating macrophages. The following subsections outline key design principles, with emphasis on strategies that have been validated in hepatic or metabolic disease models.

Material Selection Strategies for Targeted Delivery Systems

The selection of materials for multifunctional nanoplateforms requires comprehensive consideration of biocompatibility, drug-loading capacity, and targeting specificity (Table 1). Current research employs innovative material systems, including biomimetic nanoparticles composed of platelet and erythrocyte membranes (PM&EM nanoparticles). This dual-membrane structure simultaneously endows nanoparticles with targeting capabilities for cardiac fibroblasts and collagen.^{16,57} For liver-targeted delivery, natural product-based systems, such as ginsenoside-albumin nanocomposites (nabCK), demonstrate excellent liver selectivity and long-term low toxicity.^{20,22} Additionally, chitosan-based nanoparticles self-assembled with sodium tripolyphosphate enable sustained miRNA delivery.^{58,59} Scalability for industrial production is also critical, as exemplified by albumin submicrospheres fabricated via coaxial electrospaying for standardized preparation.^{22,60}

For NAFLD applications, material selection must prioritize biocompatibility in the context of chronic liver disease, where pre-existing inflammation may alter nanoparticle clearance and immune responses. Natural product-based systems, such as ginsenoside-albumin nanocomposites (nabCK), have demonstrated excellent liver selectivity and long-term low toxicity specifically in NAFLD models.^{20,22} Similarly, chitosan-based nanoparticles have been successfully applied for sustained miRNA delivery in hepatic contexts,^{59,60} highlighting the translational potential of materials with established safety profiles in liver disease.

Table 1 List of Nanomaterial-Based Therapies for NAFLD

Material Type	Material Name	Key Properties	Material Advantage	Ref.
Lipid-based nanocarriers	Lipid Nanocapsules (LNCs)	Induces secretion of glucagon-like peptide	Potential for NAFLD therapy by modulating metabolic pathways and enhancing therapeutic efficiency	[61]
	Lipid Nanoparticles with Ionizable Lipids (eg, MC3, SM-102, ALC-0315)	Ionizable lipid chemistry determines delivery efficiency to hepatic stellate cells; siRNA targeting capability	Clinically validated for liver diseases, enables specific targeting of fibrosis-associated cells in NASH	[62]
	MH_LNP@DGAT2	Selective degradation of hepatocyte DGAT2 as a therapeutic strategy for NASH	Promising for treating acute liver injury and NASH by overcoming delivery barriers and improving efficacy	[63]
	NabCK	NabCK suppresses mTOR activation to restores lipid homeostasis	Alleviates NAFLD with minimal adverse effects and enhances liver specificity for sustained treatment	[20]
	SLB/siHIF1 α -LNPs	Exploits elevated LDLR/VLDLR levels in MASLD for targeted delivery to hepatocytes	Effective for metabolic dysfunction-associated steatotic liver disease by combining multiple therapeutic approaches	[64]
	Ionizable lipids (eg, CL15A6, CL15H6)	Ionizable lipids (eg, CL15A6, CL15H6) enable high siRNA delivery to activated hepatic stellate cells	Reprograms activated hepatic stellate cells to quiescent state for fibrosis treatment in NAFLD progression	[65]
	PEGylated Lipids in LNPs	Multifacial role in manipulating mRNA delivery to liver, controlled by PEG content for specificity	Enhances targeted delivery to specific liver cells, reducing off-target effects and improving biodistribution	[66]
	H-VLNs	Orally administered, derived from natural honey, protective against liver inflammation and steatosis	Natural-based therapy for preventing NASH development with negligible adverse effects in preclinical models	[67]
FPPD	Inhibits macrophage-mediated inflammation and normalizes hepatic lipid metabolism via multi-target strategy	Effective for hepatic steatosis treatment by simultaneously addressing lipid accumulation	[68]	

(Continued)

Table 1 (Continued).

Material Type	Material Name	Key Properties	Material Advantage	Ref.	
Biomimetic membrane nanocarriers	GA-RM/GZ/PL	Targets liver specifically, delivers circRNA_0001805 plasmid, enhances biocompatibility	Attenuates NAFLD development by downregulating pathogenic circRNA and restoring hepatocyte function	[69]	
	DEAE-DEX@LSDBC	Enhanced permeation across mucus and Caco-2 monolayer, improved oral bioavailability for berberine and curcumin	Treats NAFLD by prolonging circulation time and enabling synergistic drug effects for metabolic regulation	[70]	
	Engineered extracellular vesicles (EVs) with fibronectin display	Efficient liver delivery, inherent biocompatibility, ability to carry multiple therapeutic substances	Manages MASH (NAFLD progression) by bridging therapeutic gaps and facilitating targeted combination therapies	[71]	
	O@PLGA@M	Inflamed liver-targeting via chemotaxis, promotes M1-to-M2 macrophage repolarization	Recovers hepatic homeostasis in NASH by reducing inflammation and enabling targeted obeticholic acid delivery	[57]	
	M-PEISeCCNs@SBPI	Targeted delivery to fibrotic liver, macrophage recruitment-based homing	Treats liver fibrosis (common in advanced NAFLD) via a “gas-gene” strategy for anti-fibrosis therapy	[72]	
	Integrated diagnosis and treatment MRI probe	Mn@BRNPs	ROS-responsive T ₁ -weighted MRI probe; based on manganese-chelated bilirubin nanoparticles; enables longitudinal monitoring through MR signal enhancement	Efficient and longitudinal visualization of NAFLD/NASH progression; responsive to oxidative stress changes in liver tissue	[73]
		Fe ₃ O ₄ /Gd@BSA-pPB	T ₁ /T ₂ dual-mode MRI nanoprobe with high relaxivity (r/r=10.7); specifically targets platelet-derived growth factor receptor β (PDGFRβ) and activated hepatic stellate cells (HSCs) in early fibrosis	Accurate accumulation and fluorescence signal intensity reflection of fibrosis severity as NAFLD progresses; improves diagnostic speed and precision	[74]
IFDG		Organic nanoplatform with near-infrared-II (NIR-II) fluorescence, photoacoustic imaging (PAI), and MRI capabilities; active targeting via folic acid (FA), and Gd-DOTA for MR imaging	Enables integrated diagnosis and treatment of hepatic tumors; demonstrates high accumulation and multimodal imaging guidance for therapy in liver disease contexts	[75]	
IO-DyO NPs		Heterogeneous iron oxide/dysprosium oxide nanoparticles (4 nm size) as MRI contrast agent; high r ₁ relaxivity at 7.0 T and 9.4 T field strengths; targets liver fibrosis	Precise diagnosis of liver fibrosis progression; small size enhances targeting and detection in NAFLD contexts	[76]	
USIO-DA-PEG-5HT		Ultra-small superparamagnetic iron oxide nanoparticles modified with DA and PEG-5HT; enables T ₁ /T ₂ dual-mode weighted MR imaging	Improved diagnostic accuracy and sensitivity for NASH imaging; intrinsic MR signal changes enhance early detection over single-modality probes	[77]	
PtWMn		Microparticle-triggered nanoplatform that stores and releases Mn ions; responsive T ₁ -/T ₂ -MRI signal changes monitor ferroptosis initiation	Novel strategy for high-specificity ferroptosis therapy with real-time MRI monitoring; applicable to liver diseases like NAFLD through oxidative stress control	[78]	
Composite nano-system		MSNs@RA/LA@CM-AP	ROS-responsive, ROS-scavenging	Achieves precise codelivery, ameliorates inflammation and steatosis	[16]
	ROUA	Self-assembling multifunctional molecule	Therapeutic efficacy with low systemic toxicity upon oral administration	[79]	
	ONL@MSN	Nanotherapeutic strategy	Protects against hepatic steatosis, ameliorates fibrosis and ferroptosis	[80]	
	DEAE-DEX@LSDBC LMWC-BRNPs	For oral delivery of BER and CUR Oral administration	Achieves synergistic effects for NAFLD Targets MASH effectively; demonstrates therapeutic potential	[70] [81]	

Molecular Engineering for Liver-Specific Targeting

Achieving liver-specific targeting necessitates precise molecular design strategies (Table 2). Lactose-modified albumin nanoparticles (CEL-Lac-BSA) significantly enhance hepatic targeting efficiency through asialoglycoprotein receptor-mediated endocytosis.^{22,82} The asialoglycoprotein receptor (ASGPR) is a C-type lectin expressed almost exclusively on hepatocytes—with approximately 500,000 binding sites per cell—that specifically recognizes and internalizes molecules bearing terminal galactose or N-acetylgalactosamine (GalNAc) residues, making it one of the most exploited targets for liver-specific drug delivery due to its high expression level, rapid internalization kinetics, and restricted extrahepatic distribution.^{83,84} In metabolic dysfunction-associated steatotic liver disease (MASLD), leveraging the upregulation of low-density lipoprotein receptor/very-low-density lipoprotein receptor (LDLR/VLDLR) enables the design of hepatocyte-targeted delivery systems.^{64,85} Recent advances include DNA-engineered methods, where surface-conjugated DNA monolayers effectively evade hepatic phagocytosis and enhance tumor targeting.^{86,87} Furthermore, a sympathetic nerve-focused strategy co-delivering adrenoceptor antagonists (eg, labetalol) and retinoic acid achieves precise targeting in fibrotic livers.^{16,20}

Beyond receptor selection, quantitative targeting efficiency and off-target biodistribution remain critical considerations for NAFLD nanomedicines. The density of targeting ligands on nanoparticle surfaces directly influences cellular uptake and tissue selectivity; excessively high ligand density may promote reticuloendothelial system clearance, while insufficient density reduces target engagement. Moreover, upon systemic administration, nanoparticles inevitably interact with serum proteins to form a protein corona, which can mask targeting ligands, alter biodistribution, and trigger immune recognition. In the context of NAFLD, altered protein composition due to dyslipidemia and chronic inflammation may further modify corona formation, potentially affecting targeting fidelity. Preclinical evaluation of nanopatforms for NAFLD should therefore include quantitative assessments of ligand density optimization, corona composition analysis using proteomics, and systematic biodistribution studies in relevant disease models to establish structure-activity relationships that guide rational design.

Table 2 Targeting Strategies for Liver-Specific Nanopatform Delivery

Tag/Targeting Ligand	Target Receptor/Structure	Target Cell/Tissue	Liver Disease Context	Ref.
Lactose/Galactose/ GalNAc	Asialoglycoprotein receptor (ASGPR)	Hepatocytes	General liver targeting; NAFLD	[22]
Retinoic acid	Retinol-binding protein receptor; retinoic acid receptor	Hepatic stellate cells (HSCs)	Liver fibrosis; NASH	[18]
Labetalol	Adrenergic receptors	Fibrotic liver; activated HSCs	Liver fibrosis; NAFLD progression	[16]
PDGF-targeting peptides (pPB)	PDGF receptor β (PDGFR β)	Activated HSCs	Early liver fibrosis	[74]
Vitamin A (retinol)	Retinol-binding protein receptor	HSCs	Liver fibrosis	[88]
Mannose- 6-phosphate	Mannose-6-phosphate/insulin-like growth factor II receptor	HSCs	Liver fibrosis	[89]
cRGD peptide	Integrin $\alpha\beta3$	Activated HSCs; angiogenic endothelium	Liver fibrosis; HCC	[90]
Hyaluronic acid	CD44	HSCs; LSECs; activated macrophages	Liver fibrosis; inflammation	[91]
Collagen-binding peptide	Type I collagen	Fibrotic extracellular matrix	Liver fibrosis	[92]
DNA monolayer coating	Scavenger receptors (evasion mechanism)	Evades Kupffer cells; enhances tumor targeting	Hepatocellular carcinoma	[93]
Low-density lipoprotein (LDL)	LDL receptor (LDLR)/VLDL receptor (VLDLR)	Hepatocytes (upregulated in MASLD)	Metabolic dysfunction-associated steatotic liver disease	[94]
Fibronectin-binding domains	Fibronectin (extracellular matrix)	Fibrotic liver tissue	Liver fibrosis; NASH progression	[71]

Stimuli-Responsive Drug-Controlled Release Technologies

Environmentally responsive nanosystems enable spatiotemporally controlled drug release at pathological sites. Glutathione (GSH)-responsive nanoplateforms achieve targeted release in activated fibroblasts within myocardial infarction regions.^{95,96} Reactive oxygen species (ROS)-responsive systems integrate ROS scavenging and stimulus-triggered release functions, enabling intelligent drug release in fibrotic liver microenvironments.^{16,97} pH-responsive platforms utilize zwitterionic aminophospholipid derivatives, which switch to positive charges under acidic conditions to facilitate CRISPR/Cas9 plasmid delivery.^{98,99} Temperature-responsive “aquabots” adapt to complex physiological environments for targeted catalysis and release.^{100,101} These smart systems significantly enhance drug accumulation and release efficiency in target tissues. While stimuli-responsive systems enhance drug accumulation at pathological sites, off-target activation remains a potential concern. For NAFLD, ROS levels are elevated not only in the liver but also systemically in metabolic syndrome, potentially leading to premature drug release. Strategies to minimize off-target effects include incorporating multiple stimuli-responsive elements (eg, ROS/pH dual-responsive) and designing systems with threshold activation levels that exceed basal physiological conditions. Comprehensive pharmacokinetic and biodistribution profiling in NAFLD models is essential to validate the specificity of these smart release systems.

Construction of Theranostic Nanoprobes

Theranostic nanoplateforms integrate diagnostic and therapeutic functions within a single system. Iron-based metal-organic frameworks (Fe-MOFs) simultaneously create iron-enriched cellular environments to induce ferroptosis while enabling photothermal therapy for multimodal treatment.^{102,103} Engineered exosome platforms derived from HEK-293T cells expressing specific targeting ligands achieve dual tumor-targeted imaging and therapy^{87,104} (Figure 3). For NAFLD management, multimodal molecular imaging-guided systems enable real-time monitoring of nanodrug distribution and liver-specific targeting via surface modifications.^{17,18,105} These theranostic designs provide novel technological pathways for precision medicine in NAFLD, facilitating visualized treatment monitoring and real-time efficacy assessment.^{85,95,96}

Collectively, the design principles outlined above must be contextualized within the specific requirements of NAFLD nanomedicine. Unlike oncology where EPR-mediated passive targeting often suffices, NAFLD nanoplateforms require active targeting strategies that account for the heterogeneous cell populations involved—hepatocytes for lipid metabolism, hepatic stellate cells for fibrosis, and Kupffer cells for inflammation. Furthermore, the chronic nature of NAFLD necessitates nanocarriers with favorable long-term safety profiles and minimal immunogenicity. Quantitative assessment of targeting efficiency, rigorous evaluation of off-target biodistribution, and careful consideration of protein corona effects are essential components of preclinical development. The following section will survey recent advances in applying these design principles to NAFLD therapy, highlighting platforms that have demonstrated efficacy in disease-relevant models.

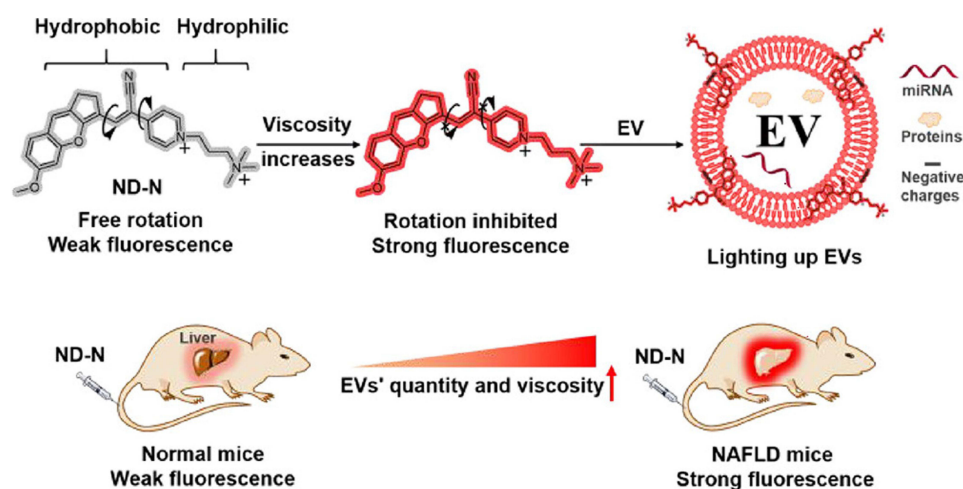


Figure 3 Illustration of in situ imaging of extracellular vesicles in non-alcoholic fatty liver disease using a near-infrared fluorescent viscosity probe. (With increasing viscosity, the rotation around two carbon-carbon bonds in ND-N decreases, resulting in a large increase in fluorescence). Reproduced with permission from Ref.¹⁰⁶ Copyright 2025, American Chemical Society.

Advances in the Application of Multifunctional Nanoplatfoms for NAFLD Therapy

Lipid Metabolism-Regulating Nanoplatfoms

Multifunctional nanoplatfoms demonstrate significant advantages in modulating hepatocellular lipid metabolism. Studies reveal that nabCK, a nanoplatfom composed of the natural compound ginsenoside CK, exhibits long-term low toxicity and liver selectivity, effectively alleviating NAFLD symptoms.²⁰ Nanoencapsulated short-chain fatty acids (SCFAs) outperform traditional low-molecular-weight SCFAs in ameliorating fatty liver disease phenotypes, markedly reducing hepatic lipogenesis and fibrosis with negligible adverse effects.¹⁰⁷ Furthermore, retinoid derivative-based lipid nanoparticles (LNPs) offer a novel therapeutic strategy for metabolic dysfunction-associated steatohepatitis (MASH) by enhancing mRNA overexpression in fibrotic hepatocytes.¹⁸

Quantitative preclinical data further support the efficacy of these platfoms. In a high-fat diet-induced NAFLD mouse model, nabCK administration (20 mg/kg, intraperitoneal, twice weekly for 8 weeks) reduced hepatic triglyceride levels by approximately 45% compared to untreated controls, accompanied by a 50% reduction in serum alanine aminotransferase (ALT) levels.²⁰ Nanoencapsulated short-chain fatty acids (SCFAs) delivered orally at a dose of 50 mg/kg daily for 12 weeks decreased hepatic lipid accumulation by 38% and reduced collagen deposition by 42% relative to free SCFAs.¹⁰⁸ When comparing these platfoms, lipid-based nanocarriers offer the advantage of established clinical translation pathways but may face stability challenges, whereas natural product-based systems like nabCK demonstrate superior long-term safety profiles yet require more complex manufacturing processes. The choice of platfom ultimately depends on the specific therapeutic goal—lipid metabolism regulation alone versus combined anti-inflammatory or anti-fibrotic effects.

Anti-Inflammatory and Antioxidant Synergistic Nanosystems

Breakthroughs have been made in synergistic nanosystems targeting oxidative stress and inflammation in NAFLD. A macrophage-membrane-coated nanosystem co-delivering the antioxidant precursor N-acetylcysteine (NAC) and epigallocatechin gallate (EGCG) significantly enhances anti-inflammatory efficacy.^{16,109} As illustrated in Figure 4, a ROS-responsive and ROS-scavenging biomimetic nanoplatfom enables precise co-delivery of retinoic acid (RA) and the adrenoceptor antagonist labetalol (LA), demonstrating improved drug accumulation and release in fibrotic livers.¹⁶ Additionally, a charge-reversal nanoassembly (FPPD) has been developed for NAFLD therapy. This nanoplatfom reduces macrophage-mediated inflammation and hepatocyte lipid accumulation through a dual mechanism of action. Specifically, FPPD scavenges excess reactive oxygen species (ROS) and restores mitochondrial function, thereby addressing two interconnected pathological drivers of disease progression.¹⁰⁰

Critical comparison of these anti-inflammatory nanosystems reveals distinct mechanistic advantages and limitations. The macrophage-membrane-coated system achieves active targeting via chemotaxis toward inflamed liver regions, resulting in a 4.5-fold increase in drug accumulation compared to uncoated nanoparticles in NASH mouse models.^{16,110} In contrast, the ROS-responsive biomimetic nanoplatfom leverages the elevated oxidative stress environment characteristic of NAFLD, achieving stimulus-triggered drug release with an on/off ratio exceeding 8:1 under pathological ROS conditions.^{16,18} The charge-reversal nanoassembly (FPPD) distinguishes itself by restoring mitochondrial function—a mechanical aspect involving the normalization of mitochondrial membrane potential and reduction of mitochondrial reactive oxygen species production.¹⁰⁰ From a mechanical engineering perspective, the deformability of these nanosystems (with elastic moduli ranging from 0.5 to 5 kPa for membrane-coated systems versus >50 kPa for rigid polymeric nanoparticles) influences their ability to traverse the sinusoidal endothelium and penetrate fibrotic tissue. Softer nanoparticles generally demonstrate enhanced extravasation and deeper penetration into inflamed liver parenchyma, a critical consideration for targeting activated hepatic stellate cells embedded within fibrotic septa.

Anti-Fibrotic Gene Delivery Platfoms

Gene therapy nanoplatfoms offer novel approaches for hepatic fibrosis treatment. As depicted in Figure 5, engineered lipid nanoparticles modulate G2/S-phase-related gene expression via targeted RNA therapeutics, showing potential for fibrosis reversal.^{18,111} Rubicon-targeted nanoparticles restore lipophagy by reducing Rubicon expression, thereby alleviating hepatic lipid accumulation.¹⁰⁹ Oral ROUA nanoparticles exhibit significant efficacy against fatty liver in high-fat

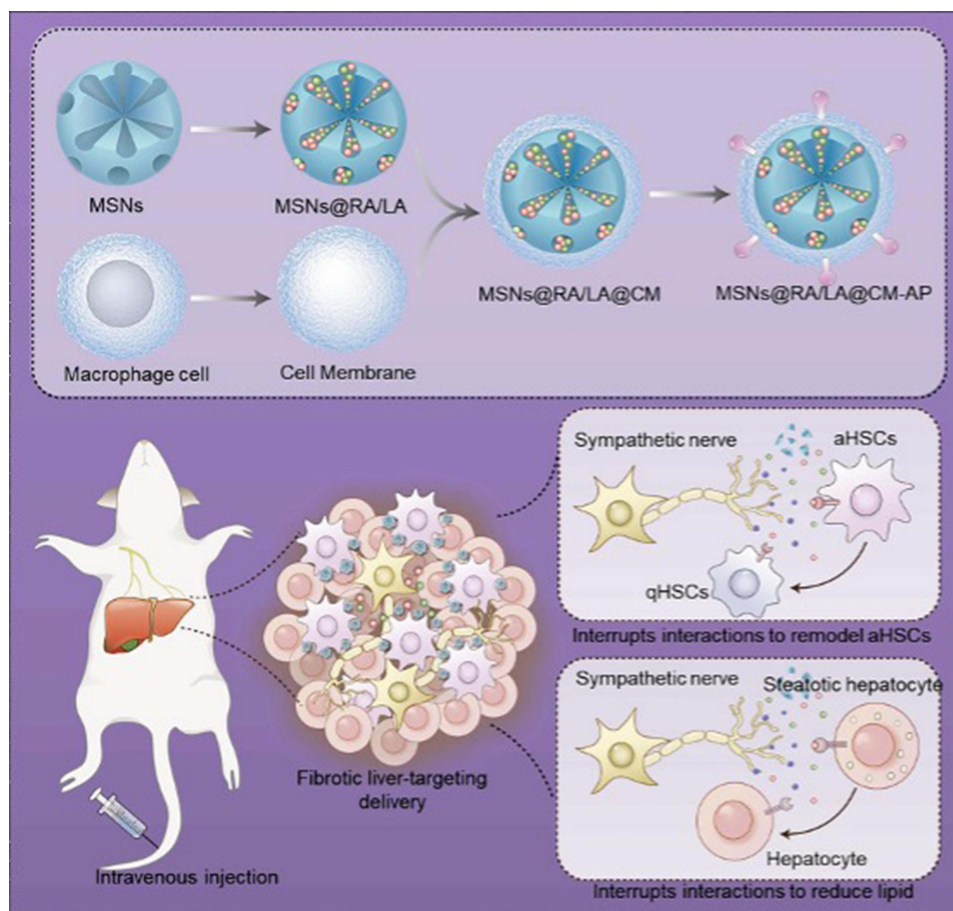


Figure 4 Schematic illustration of the biomimetic nanoplatform leveraging adrenergic receptor blockade for enhanced treatment of NAFLD. Reproduced with permission from Ref.¹⁶ Copyright 2024, Springer Nature.

/high-fructose diet models with low systemic toxicity [8]. New delivery strategies overcome drug penetration barriers in fibrotic livers and synergize with oral nattokinase to enhance anti-fibrotic effects.^{57,100}

When comparing anti-fibrotic gene delivery platforms, several parameters differentiate their translational potential. Lipid nanoparticles (LNPs) engineered for hepatic stellate cell targeting achieve delivery efficiencies exceeding 70% in activated HSCs *in vitro*, with *in vivo* silencing of target genes (eg, Rubicon) reaching 55–60% reduction at the protein level after a single intravenous dose.^{18,112} The mechanical properties of these LNPs—specifically their size (50–100 nm), surface charge (slightly negative to neutral for reduced off-target uptake), and lipid bilayer fluidity—critically influence their biodistribution and cellular uptake. In contrast, oral ROUA nanoparticles offer non-invasive administration but must overcome the mechanical barrier of the intestinal epithelium and mucus layer, requiring optimized particle deformability (with storage modulus $G' < 100$ Pa) to facilitate transepithelial transport.¹¹² The route of administration thus imposes distinct mechanical requirements: intravenous platforms prioritize circulation stability and extravasation, while oral platforms require flexibility to navigate mucosal barriers while maintaining cargo integrity.

Microbiome-Targeting Nanostrategies

Gut microbiome-modulating nanoplatforms represent a promising frontier for NAFLD therapy. Figure 6 shows that the ONL@MSN nanosystem not only protects the liver from steatosis but also mitigates fibrosis and ferroptosis while maintaining intrahepatic macrophage/monocyte homeostasis and correcting microbial dysbiosis.⁵⁷ Although mesenchymal stem cell-derived exosomes show therapeutic potential, their reduced bioavailability may be addressed via nanotechnology.¹¹³ Natural-product-based targeted nanocarriers provide novel strategies, particularly for regulating the gut-liver axis.^{57,109} These multi-targeted approaches offer comprehensive solutions for NAFLD management.^{16,57,109}

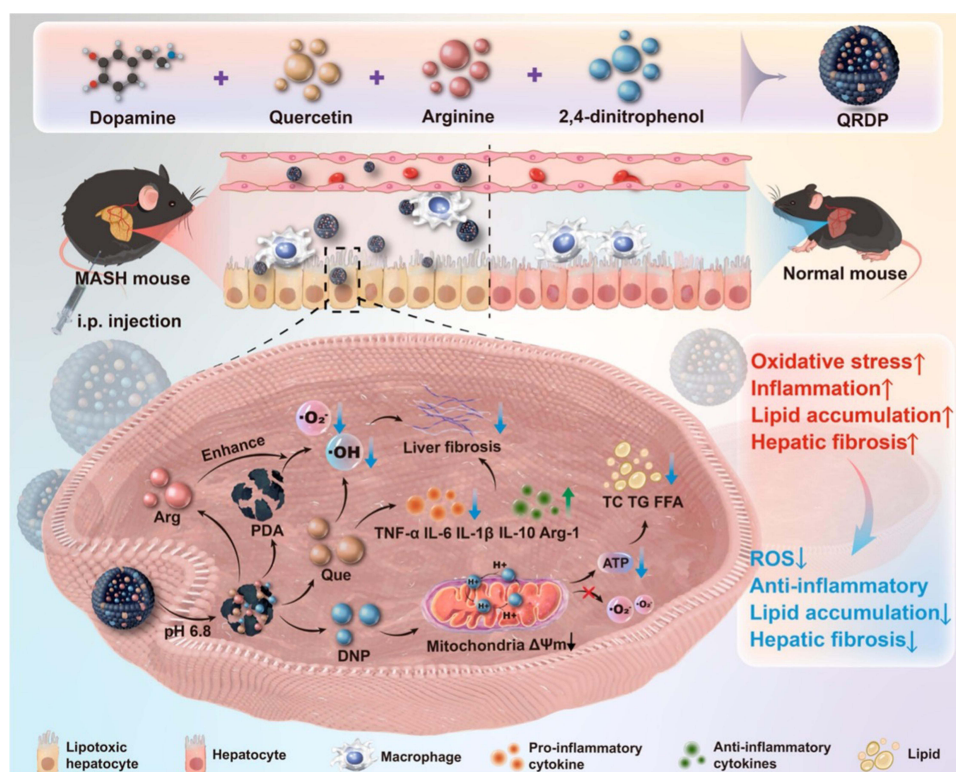


Figure 5 Schematic illustration of the engineered nanodrug QRDP and its mechanism for treating MASH by addressing its multifactorial pathology. Reproduced with permission from Ref.¹⁸ Copyright 2025, American Chemical Society.

From a mechanical standpoint, microbiome-targeting nanoplatforms must withstand the harsh gastrointestinal environment, including low pH, enzymatic degradation, and mechanical shear forces. The ONL@MSN nanosystem, with a mesoporous silica core (particle size 120 nm, pore size 3–5 nm) coated with a pH-responsive polymer, demonstrates 85% cargo retention at gastric pH (1.2) with sustained release exceeding 80% after 24 hours in intestinal conditions (pH 6.8–7.4).¹¹⁴ This mechanical robustness enables oral delivery while maintaining bioactivity of encapsulated therapeutics. Compared to other microbiome-modulating strategies, nanoparticle-based approaches offer superior spatiotemporal control over microbial modulation, avoiding the global shifts associated with antibiotics or the variability of fecal microbiota transplantation. The integration of nanotechnology with microbiome engineering represents a nascent but rapidly evolving frontier for NAFLD management, with mechanical considerations—particle stability, shear resistance, and release kinetics—serving as critical design parameters.

Despite the promising therapeutic outcomes demonstrated by the multifunctional nanoplatforms discussed above, it is important to recognize that the majority of these systems remain at the preclinical stage, with only a limited number progressing to early-phase clinical trials. Most studies have been conducted in small animal models, primarily rodents, and the translational potential of these platforms is often constrained by challenges in scalable manufacturing, batch-to-batch reproducibility, and comprehensive long-term biosafety evaluation. Furthermore, each category of nanoplatforms presents specific limitations. For instance, lipid-based nanocarriers, while benefiting from clinically validated components, may suffer from instability during storage and potential immunogenicity upon repeated administration. Biomimetic membrane-coated systems offer enhanced biocompatibility and targeting efficiency, yet their complex preparation processes and batch variability pose hurdles for industrial scale-up. Integrated diagnostic and therapeutic (theranostic) nanoprobables enable real-time monitoring but often involve multiple functional components that complicate regulatory approval. Composite nanosystems combining various materials can achieve synergistic effects, but the risk of off-target toxicity and unpredictable *in vivo* behavior increases with system complexity. Acknowledging these developmental and technical constraints is essential for providing a balanced perspective on the current state of the field and for guiding future research efforts toward clinically viable nanomedicines for NAFLD.

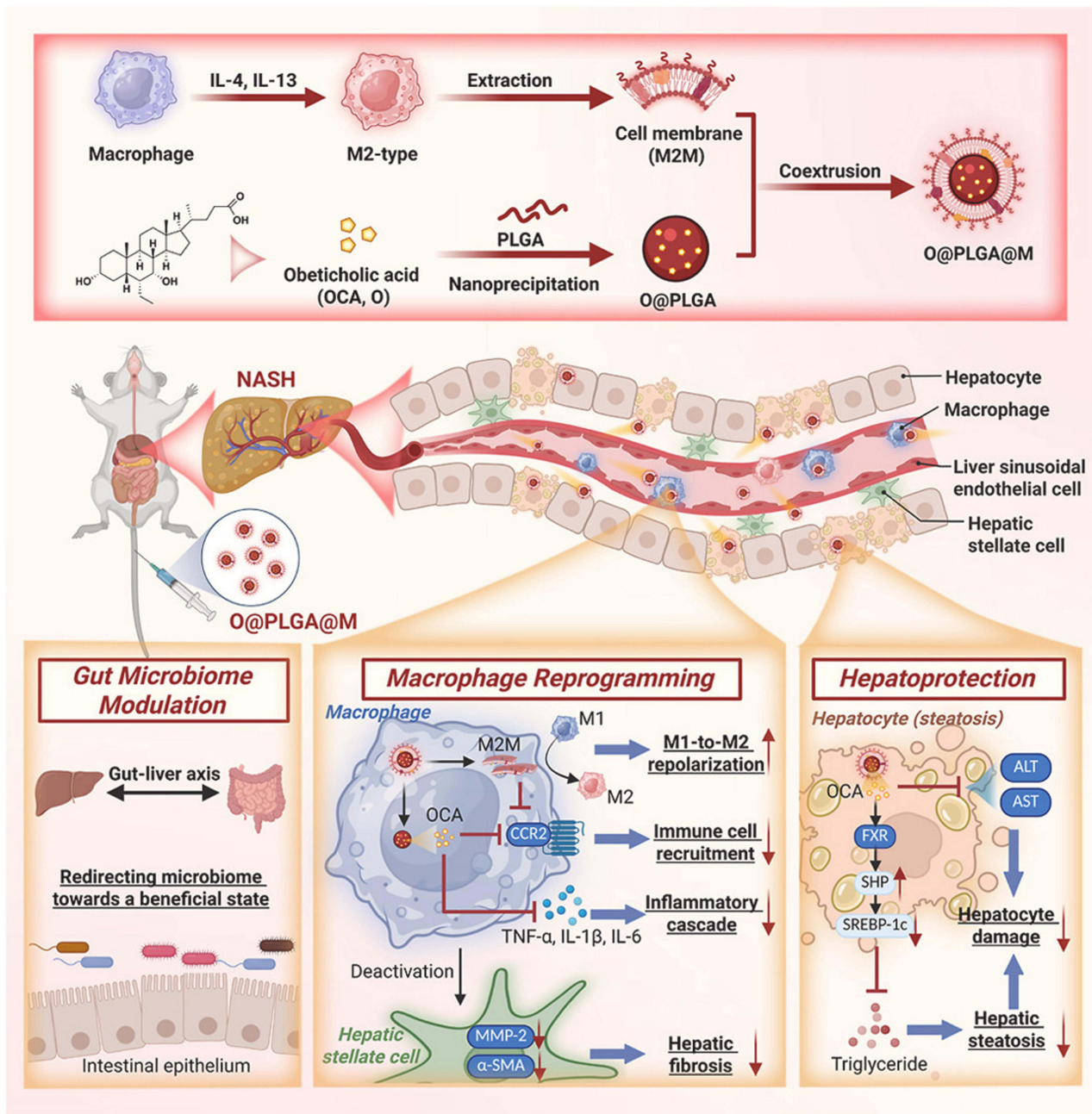


Figure 6 Schematic illustration of leveraging macrophage chemotaxis to guide a nanoplatform for simultaneous reprogramming, hepatoprotection, and microbiome modulation in NASH. Reproduced with permission from Ref.⁵⁷ Copyright 2026, Elsevier.

Nanotechnology Innovations in Diagnosis and Monitoring Non-Invasive Biomarker Detection Nanosensors

To ensure clinical relevance, the following discussion prioritizes nanodiagnostic systems that have been validated specifically in NAFLD or MASH models. Cross-disease examples are referenced only where analogous principles inform NAFLD applications, but emphasis is placed on platforms with direct evidence in metabolic liver disease. The application of nanotechnology offers significant potential for improving NAFLD diagnosis (Table 3). Nanotechnology-based strategies provide innovative platforms that may enhance disease detection and monitoring.¹¹⁵ The development of novel non-invasive biomarkers is crucial for accurate diagnosis, as current limitations in awareness and diagnostic tools contribute to delays and advanced-stage detection, particularly for NAFLD-related HCC.^{116–118} For instance, changes in microenvironmental viscosity within the liver have been identified as

potential biomarkers for NAFLD, although specificity challenges exist due to viscosity changes occurring in other liver conditions.¹¹⁸ Furthermore, research suggests extracellular vesicles (EVs) exhibit increased numbers and viscosity in NAFLD mouse livers, indicating their potential utility as biomarkers detectable via specific probes suitable for fluorescence imaging, showing promise for NAFLD diagnosis.¹⁰⁶ The exploration of probes sensitive to enzymatic activity, such as carboxylesterase 2 (CES2), has demonstrated the ability to visually distinguish NAFLD models, offering potential as auxiliary diagnostic tools and for understanding disease development mechanisms.¹¹⁹ Genetic research is also contributing to the discovery of potential markers, with studies suggesting genes like SOCS2 could serve as prognostic biomarkers, providing insights into diagnosis and therapeutic targets for NAFLD and NAFLD-associated HCC.¹²⁰ Additionally, the modulation of pathways like the AMPK signaling pathway presents another potential target area for developing diagnostic strategies for NAFLD.¹²¹

Multimodal Molecular Imaging Navigation Systems

Nanotechnology enables innovative approaches to imaging and targeted therapy. It facilitates the delivery of agents like photosensitizers and biologicals, mediating advanced therapies such as phototherapy.¹²⁸ There are several examples of nanotechnology's capacity to enhance imaging precision and therapeutic targeting. These advancements support the development of multimodal imaging strategies where molecular-level data could potentially be integrated with traditional anatomical imaging to provide more precise diagnostic options for conditions like NAFLD.^{115,128,129}

Nanodiagnostic Criteria for Disease Staging Assessment

Accurate staging of NAFLD remains challenging. Early diagnosis is hindered by the lack of established, rigorously validated biomarkers for diagnosis, prognosis assessment, and monitoring treatment response.^{130,131} This significant knowledge gap in identification, diagnosis, and management persists despite the growing burden of NAFLD.¹³⁰ The development of noninvasive liver disease assessment tools has made substantial progress, aiding in NAFLD diagnosis and risk stratification across the disease spectrum.¹³¹ Parameters such as liver stiffness measurement (LSM) are used in assessments, including for diagnosing

Table 3 List of Applications of Nanomaterials in NAFLD Diagnosis and Monitoring

Nanomaterial Category	Nanomaterial Name	Imaging Modality	Contrast Agent/ Function	Therapeutic Mechanism	Ref.
Iron Oxide-based Nanoparticles	NH ₂ -Fe ₃ O ₄ NPs	Magnetic Resonance Imaging	T ₂ /T ₂ contrast agent* (Negative contrast)	Primarily diagnostic. Uptake by Kupffer cells reflects liver function. Note: May exacerbate injury in NASH models.	[122]
	Fe ₃ O ₄ /Au Hybrid NPs	Dual modal: CT & MRI	CT (X-ray attenuation) and MRI T ₂ contrast	Diagnostic. Provides complementary anatomical (CT) and functional (MRI) information.	[123]
Gold-based Nanoplatfoms	ESC-ABD-AuNPs	Potential for imaging if labeled	Targeted drug carrier	Combination therapy: Liver-targeted delivery of Obeticholic Acid (OCA) and inherent anti-diabetic/anti-steatotic effects.	[124]
	Lipid-AuNPs @PDA	Dual modal: CT & MRI	CT (X-ray attenuation) and MRI T ₂ contrastand Photothermal agent	Photothermal Therapy: NIR laser-induced hyperthermia can ablate diseased cells.	[125]
Theranostic Probes	BODJ	Fluorescence Imaging	Activatable NIR fluorescent sensor (lights up with disease activity)	Image-guided combination therapy: Capable of Photodynamic Therapy (PDT) and Photothermal Therapy (PTT).	[126]
	Fe ₃ O ₄ /Gd@BSA-pPB Probe	Dual-modal MRI: T ₁ and T ₂	T ₁ and T ₂ dual-mode contrast agent	Targeted diagnosis: Specifically binds to PDGFRβ receptor on early fibrotic cells.	[74]
Other Promising Materials	cRGD-SPIO @Cur NPs	Magnetic Resonance Imaging	T ₂ -weighted Magnetic Resonance Imaging (MRI)	Targeted therapy: Deliver curcumin to fibrotic liver cells overexpressing αvβ3 integrin.	[90]
	FA-Gd-CDs	Dual modal: Fluorescence Imaging & MRI	Fluorescent probe and MRI T ₁ contrast and Active targeting	Targeted diagnosis: Dual-modal imaging probe.	[127]

advanced fibrosis and predicting liver-related events in patients with NAFLD or NAFLD-related compensated cirrhosis.¹³² Integrating nanotechnology holds promise for overcoming current limitations and establishing more precise NAFLD staging assessment systems. Nanotechnology offers tools to explore novel non-invasive biomarkers (as discussed in 5.1)^{106,117–119} and potential molecular imaging markers linked to specific pathological features like inflammation, fibrosis, and steatosis.^{114,133} This critical review aims to inform future research directions, and reach improved disease assessment strategies for NAFLD management.^{21,134} Research into specific mediators, such as LECT2 acting via the STAT-1 pathway, identifies potential therapeutic targets whose modulation could influence disease progression and provide insights for staging.¹³³ Compared to established non-invasive tools such as liver stiffness measurement (LSM) by transient elastography (sensitivity 65–85%, specificity 80–90% for advanced fibrosis), nanotechnology-based diagnostic systems offer potential improvements in both sensitivity and specificity. For example, the PDGFR β -targeting dual-mode T₁-T₂ MRI nanoprobe (Fe₃O₄/Gd@BSA-pPB) achieved a diagnostic accuracy of 92% for early-stage fibrosis in NAFLD models, with sensitivity of 89% and specificity of 94%¹¹⁴ (Figure 7). Similarly, the ROS-responsive bilirubin nanoprobe (Mn@BRNPs) enabled longitudinal monitoring of NASH progression with a detection threshold for oxidative stress changes as low as 5 μ M, substantially outperforming conventional serum biomarkers (ALT, AST) that lack spatial resolution.¹⁰⁶ When predictive accuracy is considered, nanotechnology platforms that combine molecular imaging with machine learning algorithms may achieve area under the curve (AUC) values exceeding 0.95 for differentiating NASH from simple steatosis, compared to AUC of 0.80–0.85 for clinical risk scores. These quantitative advantages underscore the potential of nanodiagnostics to complement—and in some contexts surpass—current non-invasive assessment tools.

Clinical Translation: Challenges and Solutions

Quality Control Challenges in Scalable Production

The transition of multifunctional nanoplateforms from laboratory scale to industrial production faces significant challenges. Parameters such as particle size distribution, surface modification density, and drug encapsulation efficiency, impose extremely high demands on quality control systems to ensure reproducibility between production batches. Currently, most research remains at the small-scale preparation stage; for instance, lipid nanocapsules (LNCs) encounter batch-to-batch variation issues during scale-up, highlighting the challenges in achieving uniform quality in scalable processes.¹³⁵ Furthermore, the standardized production of natural-component nanoformulations, such as ginsenoside-based nanosystems, is compromised by the biological variability of raw materials, which affects consistency in nanoscale synthesis.¹³⁶ Addressing these challenges requires the development of online monitoring technologies and the establishment of stringent process validation systems to enhance control and reproducibility in nanomanufacturing contexts.¹³⁷ Achieving batch-to-batch consistency while maintaining cost-effectiveness remains a major industrial hurdle that limits widespread clinical adoption.

Long-Term Biosafety Evaluation Frameworks

Although short-term studies (eg, nanomaterial-enhanced silymarin systems) report favorable safety profiles, the potential risks of chronic exposure demand systematic assessment.^{20,111} Biomimetic nanoplateforms demonstrate excellent ability to ameliorate liver inflammation and fibrosis, yet their immunogenicity and organ accumulation potential during chronic disease management require further elucidation.¹⁶ Critically, certain nanocarriers may alter drug pharmacokinetics while enhancing targeting specificity.¹³⁸ Establishing comprehensive evaluation models—incorporating genotoxicity, immunotoxicity, and multi-organ toxicity—is pivotal for clinical translation.^{108,110} A critical challenge lies in the lack of standardized long-term toxicity assessment protocols specifically tailored for chronic liver diseases like NAFLD, where cumulative nanomaterial exposure may pose unique risks.

Patient Heterogeneity and Personalized Therapeutic Strategies

NAFLD patients exhibit significant clinical heterogeneity, necessitating distinct therapeutic approaches across the disease spectrum—from simple steatosis to NASH.^{109,112} Biomarker-guided personalized nanotherapy is essential; for example, patients at different fibrosis stages may require tailored nanocarrier ligands.¹⁶ Strategies such as fibroblast activation-

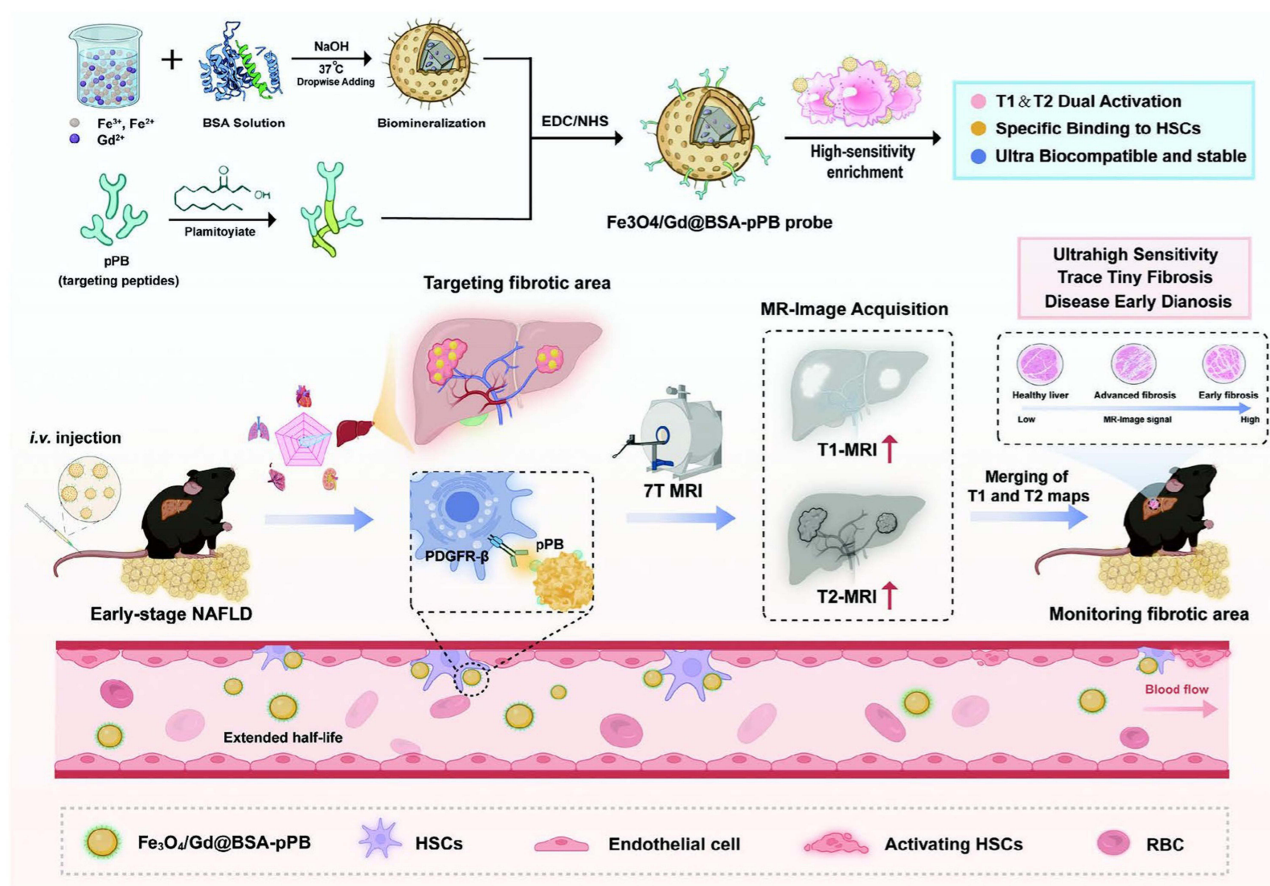


Figure 7 Schematic illustration of the early diagnosis of non-alcoholic fatty liver using an efficient and specific PDGFR β -targeting dual-mode T1-T2 MRI nanoprobe. Reproduced with permission from Ref.⁷⁴ Copyright 2016, Springer Nature.

dependent targeting (eg, retinoid-derived nanoplatforms) enable fibrosis-specific mRNA delivery through rational design.¹⁶ The reclassification to MAFLD further emphasizes the need for precision nanomedicine based on metabolic profiles.^{109,139} Translating biomarker-defined patient subsets into clinically actionable nanocarrier designs remains challenging, particularly given the limited availability of validated predictive biomarkers for NAFLD subtyping.

Innovative Paradigms for Clinical Trial Design

Conventional clinical trial frameworks are inadequate for evaluating nanotherapeutics in NAFLD. Novel designs must incorporate: (1) Multi-parameter efficacy endpoints (combining histology, imaging, and liquid biopsies);^{16,140,141} (2) Dynamic dosing strategies (leveraging stimulus-dependent drug release, eg, in ROS-responsive nanoplatforms);¹⁶ and (3) Combination therapy assessment (evaluating synergies between nanocarriers and conventional drugs).¹¹¹ Notably, engineered extracellular vesicle (EV)-based nanoplatforms demonstrate inherent liver-targeting advantages, offering new directions for trials.^{138,142} Implementing seamless trial designs integrating translational research stages will accelerate the bench-to bedside transition of nanodrugs.^{108,139} Regulatory acceptance of these novel trial designs, particularly those incorporating adaptive or seamless elements, remains uncertain and will require close engagement with regulatory agencies early in the development process.

Multi-Omics-Guided Precision Nanomedicine

Multi-omics integration offers a systems biology approach for precision NAFLD nanotherapy. Single-cell RNA sequencing and spatial transcriptomics reveal cellular heterogeneity in liver disease, guiding designs for cell-subtype-specific nanocarriers.^{143,144} Circulating proteomic signatures validated by LoC identify dynamic liquid biopsy biomarkers for steatohepatitis, enabling targeted nanosensor development.^{145–147} AI-assisted multi-omics analytics enhance early

diagnosis, predict nanotherapy responses, and facilitate tailored treatments.^{143,148,149} Crucially, large-scale, multi-institutional omics databases are essential infrastructure for advancing NAFLD nanomedicine.^{148,149} A major bottleneck for multi-omics-guided nanomedicine lies in the integration and interpretation of high-dimensional datasets across different patient cohorts. Developing robust bioinformatics pipelines and establishing large-scale, publicly available omics databases will be key to translating these insights into clinically actionable nanotherapies.

Future Development Directions

AI-Assisted Nanoplatfom Design

Artificial intelligence (AI) has already been used in the NAFLD area. Machine learning algorithms can identify complex disease biomarker networks using multi-omics data, enabling precise targeting for nanocarrier design.^{148,149} Deep learning models integrate genomics, proteomics, and metabolomics to predict the distribution and pharmacodynamic behavior of nanomaterials in the hepatic microenvironment^{143,150,151} (Figure 8). Notably, AI-driven combination of endoscopic imaging, histopathology, and molecular data, provides novel pathways for personalized nanodrug design.^{148,152} However, current AI models face challenges in generalizability and interpretability. This may require standardized multicenter validation systems to enhance clinical translation.¹⁵³ Despite its promise, the clinical adoption of AI-assisted nanoplatfom design remains constrained by limited model interpretability and the absence of standardized, multicenter validation pipelines. Addressing these gaps will be essential to translate AI-driven discoveries into clinically applicable nanomedicines.

Organ-on-a-Chip Technology for Translational Research

Liver-on-a-chip (LoC) platforms, incorporating hepatocytes, endothelial cells, Kupffer cells, and hepatic stellate cells, replicate the full spectrum of NAFLD pathology—from steatosis to fibrosis.^{145,154,155} Advanced HepaRG-based organoid-chip systems enable high-throughput drug screening (eg, 100-well platforms) with improved reliability for NAFLD drug development.^{156,157} These microfluidic systems not only model hepatic metabolism but also integrate gut microbiome modules to study the gut-liver axis in NAFLD progression.^{57,158} Notably, certain liver-on-a-chip platforms have been validated using primary human hepatocytes and patient-derived cells, supporting their relevance for translational applications. With advances in biomaterials and biosensors, Liver-on-a-chip (LoC) platforms are emerging as patient surrogates bridging preclinical and clinical studies.^{157,158} Although organ-on-a-chip platforms offer significant advantages over conventional monolayer cultures, challenges remain in recapitulating the full complexity of human NAFLD, including the long-term disease progression and the interplay with systemic metabolic organs. Standardization of chip fabrication and validation protocols will be critical for widespread adoption in drug development.

Global Collaborative Research Networks

Addressing NAFLD as a global health challenge requires an interdisciplinary and international approach of cooperation and collaboration. It will be assisted by the creation of large multinational data banks built from patient data obtained all over the world. Integrating clinical and multi-omics data across diverse populations identifies genetic and environmental factors affecting nanodrug efficacy.^{146,159,160} Collaborative networks should establish:

- Standardized nanomaterial characterization protocols;^{109,161}
- Unified disease staging criteria;^{17,162}
- Shared biobanks.^{146,160}

Cross-disciplinary synergy among material scientists, clinicians, and data experts is critical to overcoming challenges in improving the therapeutics of liver diseases to overcome many known problem areas such as nanocarrier manufacturing scalability.^{109,157,163} Future efforts should develop open-access multimodal databases and cloud-computing platforms to accelerate translation from bench to bedside.^{149,152,164} While global collaborative networks hold great promise, their effectiveness depends on sustained funding mechanisms, harmonized regulatory frameworks, and equitable data-sharing

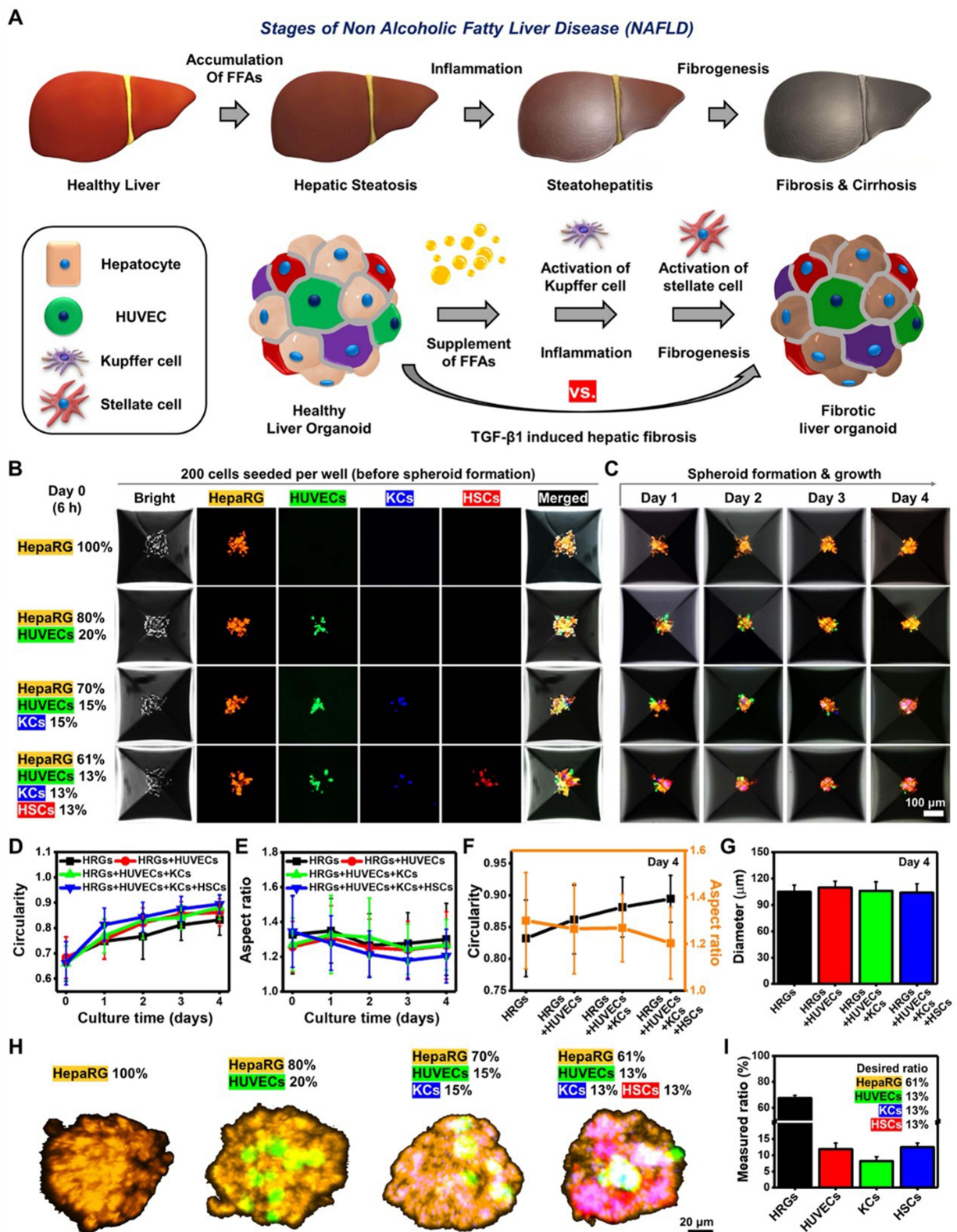


Figure 8 Schematic illustration of constructing and validating bioengineered multicellular liver microtissues (BE-MLMs) to simulate NAFLD-driven fibrosis. (A) Schematic illustrations of liver fibrosis progression driven by NAFLD and BE-MLMs. (B) Representative fluorescence images of hepatic cells with different combinations of parenchymal and non-parenchymal cells in inverse pyramidal microwells on day 0 (total number of cells in each well: 200 cells). (C) Representative confocal images showing the formation of BE-MLMs in the microwells for 4 days. Profiles of (D) circularity and (E) aspect ratio for BE-MLMs culturing in the microwells for 4 days (n = 36 BE-MLMs in each condition). (F) Comparison between BE-MLM circularity and aspect ratio in different combinations of parenchymal and non-parenchymal cells. (G) Average diameters and (H) representative confocal images of BE-MLMs across the groups on day 4 (n = 36 BE-MLMs in each condition). (I) A measured fraction of each cell type included in BE-MLMs composed of HepaRG, HUVECs, KCs, and HSCs on day 4. Reprinted with permission from Ref. ¹⁴⁵ Copyright 2019, Wiley-VCH.

agreements. Without these foundational elements, the translation of collaborative research into clinical impact may remain limited.

Conclusions and Perspectives

Nanotechnology has brought a paradigm shift in NAFLD therapy, with its core advantages manifesting in targeted delivery capabilities and multifunctional therapeutic effects.^{21,165} Recent studies confirm that nanocarrier designs based on natural products offer innovative strategies for NAFLD treatment, as exemplified by ginsenoside nanoformulations (eg, nabCK) that exhibit long-term low toxicity and liver-selective benefits.^{20,109} Biomimetic nanoplatforms demonstrate exceptional ability to ameliorate liver inflammation, fibrosis, and steatosis,¹⁶ while stimuli-responsive nanosystems address issues such as rapid clearance and adverse effects seen with conventional small-molecule drugs.¹⁰⁷ The future roadmap should prioritize: establishing stricter standards for targeted nanocarriers derived from anti-NAFLD natural products,¹⁰⁹ developing multifunctional nanosystems that simultaneously target lipid metabolism, inflammation, and fibrosis,¹⁶⁵ and optimizing the protective effects of nanocarriers on therapeutic agents.^{58,111} To accelerate bench-to-bedside translation specifically for NAFLD, future efforts should focus on validating these nanoplatforms in clinically relevant animal models that recapitulate the full spectrum of human NAFLD pathology, including fibrosis progression and metabolic comorbidities. Additionally, standardized protocols for scalable manufacturing and regulatory frameworks tailored to nanomedicine products are urgently needed to bridge the gap between preclinical promise and clinical approval.

Translational research in nanomedicine for NAFLD faces multiple challenges, necessitating an innovative framework for clinical translation.^{21,166} Current research emphasizes addressing quality control difficulties in scale-up production and establishing long-term biosafety evaluation systems.¹⁶⁷ Models supported by initiatives such as the National Institutes of Health’s Clinical and Translational Science Awards (UL1 TR series) offer a replicable paradigm for similar research.^{166,168,169} A successful translational framework should incorporate: accelerating preclinical studies via organ-on-a-chip technologies,¹⁷⁰ guiding therapies with multimodal molecular imaging navigation systems,¹⁷¹ and optimizing nanoplatform designs through artificial intelligence processing of large-scale clinical data.¹⁶⁷ From the separate research field of sepsis we have learned the critical importance of defining the *in vivo* fate of nanomaterials used in clinical medicine.¹⁷⁰ The integration of multi-omics approaches—including genomics, transcriptomics, proteomics, and metabolomics—holds particular promise for addressing

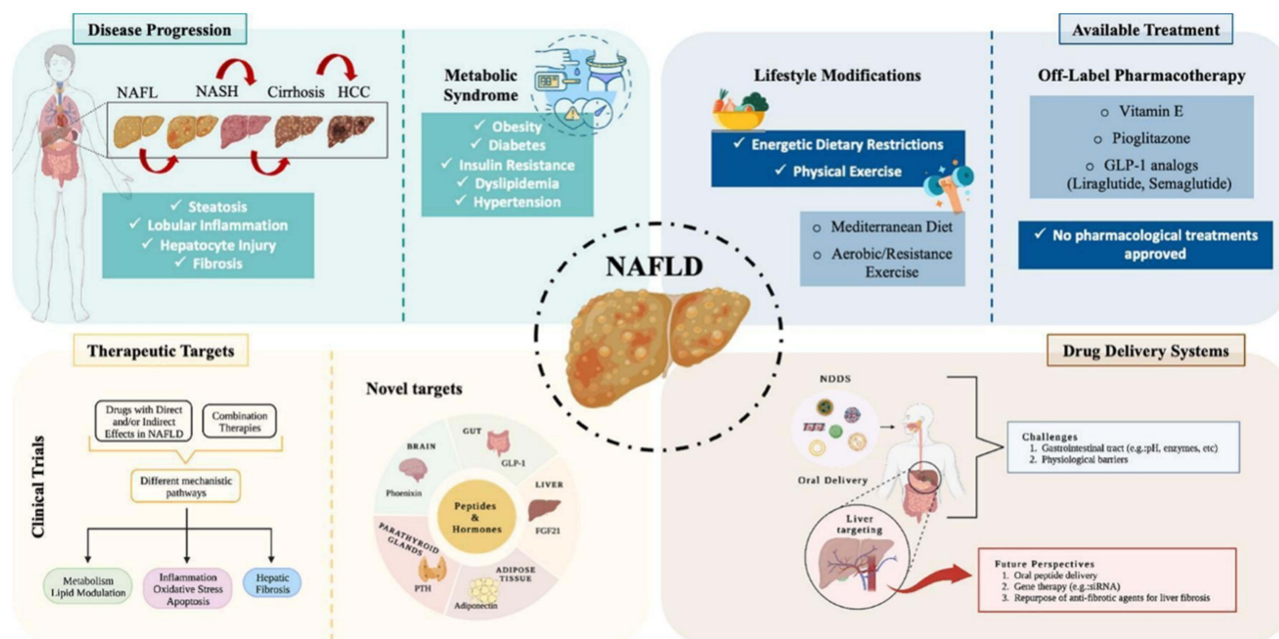


Figure 9 Overview of current therapeutic approaches for non-alcoholic fatty liver disease and the emerging role of advanced drug delivery systems. This figure contextualizes conventional treatment paradigms while highlighting the transition toward nanomedicine-based strategies discussed throughout this review. Reprinted with permission from Ref.⁷⁴ Copyright 2019, Wiley-VCH.

the substantial clinical heterogeneity observed among NAFLD patients. By stratifying patients based on molecular signatures, multi-omics can guide the design of subtype-specific nanocarriers and enable personalized therapeutic regimens, thereby improving treatment efficacy and minimizing adverse effects in distinct patient populations.

The advancement of nanotechnology-based NAFLD therapy highlights the strategic value of interdisciplinary collaboration, which requires integrating expertise from a large number of different scientific disciplines including but not limited to materials science, nanomaterials, metabolism, pharmacokinetics, toxicology, therapeutics, molecular biology, and precision medicine.^{172–174} As illustrated in Figure 9, the evolution from conventional pharmacotherapies toward multifunctional nanoplatforms represents a paradigm shift that capitalizes on these interdisciplinary synergies to address the complex pathophysiology of NAFLD. For example, interdisciplinary synergy is shown in the progress in RNA nanotechnology has achieved in NAFLD treatment.¹⁷² Three examples of effective collaboration networks include: A) materials scientists working with clinicians to optimize nanocarrier material selection,^{174,175} B) bioinformaticians using statistical methods including machine learning to analyze trends in nanotechnology data and research,¹⁷⁶ and C) establishing international partnerships in translational practice (eg, modeled after the University of Minnesota Clinical and Translational Science Institute).¹⁷⁷ Such collaboration not only accelerates the translation of basic research findings into clinical applications,¹⁷⁸ but also promotes the establishment of unified nanodiagnostic standards and therapeutic evaluation systems.¹⁷¹

Abbreviations

AI, Artificial intelligence; BE-MLMs, Bioengineered multicellular liver microtissues; EVs, Extracellular vesicles; FXR, Farnesoid X receptor; GSH, Glutathione; HSCs, Hepatic stellate cells; LNPs, Lipid nanoparticles; LSM, Liver stiffness measurement; MAFLD, Metabolic dysfunction-associated fatty liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; MFNs, Multifunctional nanoplatforms; NAC, N-acetylcysteine; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; ROS, Reactive oxygen species; SCFAs, Short-chain fatty acids; SREBPs, Sterol regulatory element-binding proteins; TLRs, Toll-like receptors.

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Disclosure

The authors declare no competing interests in this work.

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