



REVIEW

Cell-Selective mRNA Delivery for Precision Liver Therapy

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ABSTRACT: After nearly a decade of development, liver-directed mRNA therapies have entered early clinical studies, whereas delivery to non-parenchymal cells remains largely preclinical. Therapeutic efficacy depends on delivery to the intended cells, cytosolic release of intact mRNA, and production of active proteins. This review examines lipid nanoparticle, polymer, peptide, and extracellular vesicle platforms in the context of liver architecture and disease. We compare their applications in hepatocytes, Kupffer cells and recruited macrophages, hepatic stellate cells, and liver sinusoidal endothelial cells, and discuss emerging biliary, tumor, and immune cell targets. The protein corona, sinusoidal barrier, and receptor distribution determine which cells particles can access; endosomal escape and translational regulation influence productive expression after uptake. Fibrosis and inflammation alter both stages. Delivery requirements also differ among target cells. Hepatocyte therapies emphasize functional restoration and dosing intervals, macrophage delivery requires more efficient expression after uptake, and stellate cell delivery is constrained by fibrotic barriers and activation state. Sinusoidal endothelial cells serve as both therapeutic targets and a gateway to the liver parenchyma. We compare the mechanisms and scope of these strategies, interpreting therapeutic outcomes in relation to payload type and the sites of protein production and action. For chronic liver disease, functional potency in the target cells, performance under repeated dosing, and manufacturing consistency will jointly shape clinical translation.

KEYWORDS: mRNA; liver; lipid nanoparticles; cell-selective delivery; hepatic stellate cells; Kupffer cells; liver sinusoidal endothelial cells

1 Introduction

Messenger RNA (mRNA) is translated in the cytosol without entering the nucleus and, as an expression template, does not itself alter the genome [1,2]. By designing the mRNA sequence and carrier separately, the same delivery platform can express metabolic enzymes, secreted proteins, immunomodulatory factors, or gene editors for different therapeutic purposes [1,3–5]. Advances in vaccines and other nucleic acid medicines have provided a foundation for large-scale manufacturing and clinical use [1,3,6]. Chronic liver disease often requires systemic administration and repeated dosing, with requirements that differ from those of intramuscular vaccination [6,7]. Formulations must protect mRNA in the blood, deliver it to the relevant liver cells, and enable cytosolic release within acceptable limits of inflammation. For long-term protein replacement, delivery must remain effective across subsequent doses [1,7–9].

Systemic nucleic acid delivery to the liver has made relatively rapid clinical progress. In 2021, lipid nanoparticles (LNPs) carrying Cas9 mRNA and guide RNA reduced circulating transthyretin (TTR) in patients with TTR amyloidosis [2,10]. *In vivo* editing has since expanded to KLKB1, a target associated with hereditary angioedema, and PCSK9 base editing has entered clinical development [11,12]. Abundant blood flow, the sinusoidal microcirculation, and endogenous lipoprotein uptake pathways facilitate particle entry into the liver [1,8,13]. Once there, particles distribute among different cell types. Organ accumulation and the cellular expression required for therapy are therefore related but represent distinct stages of delivery [4,14]. Changes in circulating protein concentrations can indicate overall pharmacodynamic effects. Determining the contributions of hepatocytes, Kupffer cells, liver sinusoidal endothelial cells (LSECs), and hepatic stellate cells (HSCs) to expression requires cell-resolved measurements [4,10,15].

The spatial arrangement of liver cells helps explain particle distribution [16,17]. Kupffer cells directly contact sinusoidal blood, and LSECs form the interface between the circulation and the parenchyma. Hepatocytes lie beyond this interface, HSCs occupy the space of Disse, and cholangiocytes form the biliary network [13,18–20]. Lobular zonation and disease-associated states also alter the functions of cells within a given population [16,21–23]. Changes in receptor expression, sinusoidal permeability, extracellular matrix, and immune cell recruitment affect the likelihood that particles will reach these cells [13,17,19,21]. Fibrosis, for example, increases both the therapeutic need to target activated HSCs and the tissue barriers that restrict access to them.

We first examine how materials influence particle–cell interactions and cytosolic mRNA release, compare liver-directed delivery platforms, and then consider formulation choices for the therapeutic tasks of each cell type. The hepatocyte section focuses on functional restoration, expression duration, and repeated dosing. The macrophage, HSC, and LSEC sections address productive expression, access to diseased tissue, and the sinusoidal interface, respectively. Applications involving biliary, tumor, and immune cells illustrate how direct transfection and indirect therapeutic effects require different designs.

2 Delivery Platforms for Liver-Directed mRNA Therapy

Liver-directed nucleic acid delivery uses a range of material platforms, including LNPs, synthetic polymers, peptide and protein particles, condensates, DNA nanostructures, and extracellular vesicles (EVs) (Fig. 1). LNPs have the most established clinical and manufacturing foundations. Other platforms offer additional ways to control particle assembly, payload release, and cell recognition [24].

Recent reviews of targeted mRNA nanomedicines, liver-directed therapies, and engineered delivery systems provide broader context for these platforms [25–27]. Delivery routes remain important when comparing formulations: triplet mRNA delivered using MXene hydrogel microneedles has been studied for diabetic wound healing in animals [28]. This local, extrahepatic evidence illustrates a delivery design and does not establish hepatic cell selectivity after systemic administration.

2.1 Lipid Nanoparticles

After LNPs enter the blood, cells encounter a particle surface coated with adsorbed plasma proteins. Apolipoprotein E (ApoE) can promote uptake through the low-density lipoprotein receptor (LDLR) family on hepatocytes, with particle size and polyethylene glycol (PEG) coverage influencing this process. Even particles with similar lipid chemistries can acquire different protein coronas and undergo uptake by different liver cell populations. Some corona components increase uptake while also making the payload more susceptible to degradation. Differences between uptake and expression therefore help explain the cellular tropism of these formulations [14,29,30].

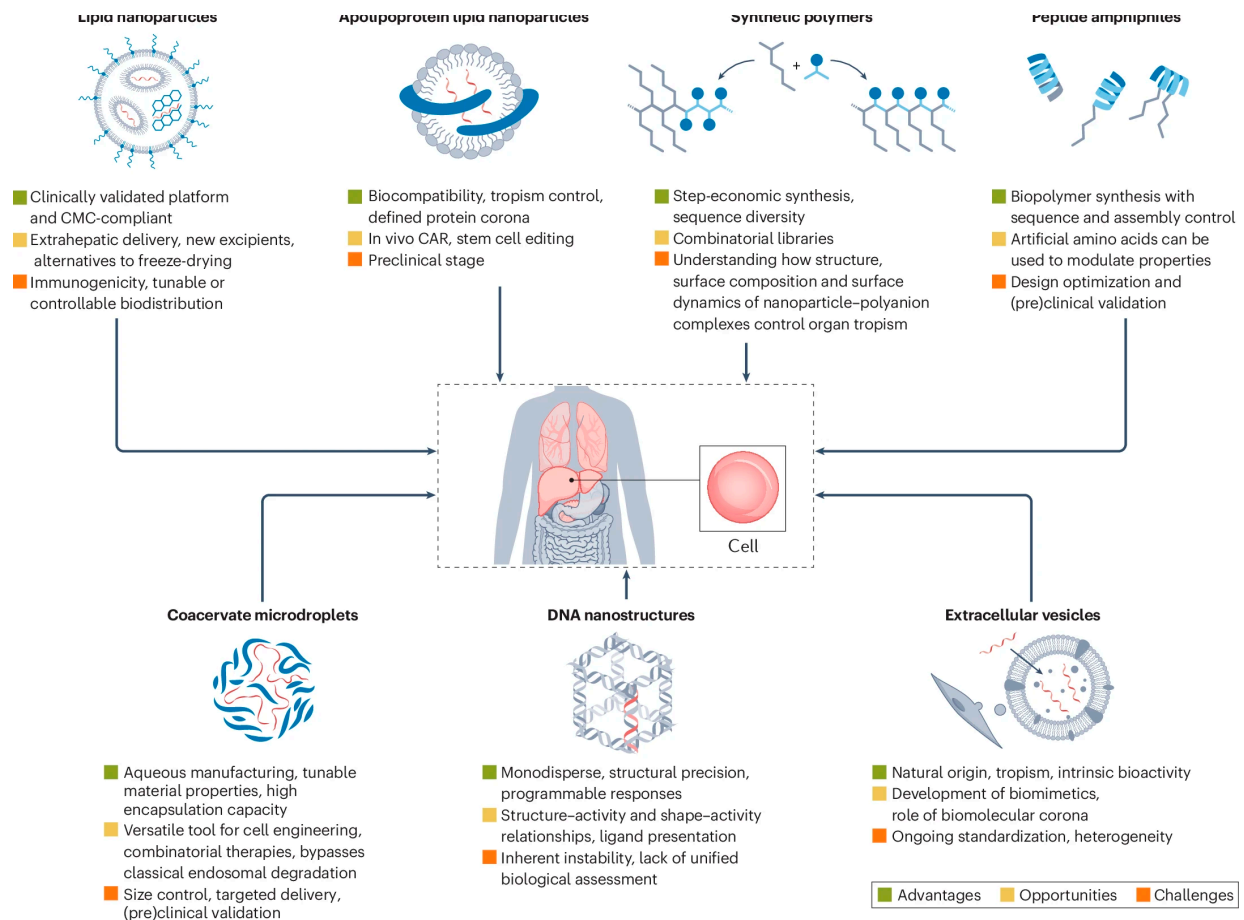


Figure 1: Materials for nucleic acid delivery. Lipid nanoparticles, apolipoprotein lipid nanoparticles, synthetic polymers, peptide amphiphiles, coacervate microdroplets, DNA nanostructures, and extracellular vesicles are compared in terms of their strengths, development opportunities, and remaining challenges. CAR, chimeric antigen receptor; CMC, chemistry, manufacturing and controls. Adapted with permission from [24]. Copyright Springer Nature, 2025.

Changing lipid composition can alter the tissue distribution of expression without adding a targeting ligand. Selective organ targeting (SORT) incorporates supplementary lipids to modify the apparent pKa and surface interactions of particles, shifting expression among the liver, lung, and spleen. Ionizable phospholipids and siloxane-containing lipids extend the range of formulation adjustments; these findings primarily describe changes in distribution between organs [31–34]. Within the liver, formulations using oxysterols or conformationally constrained phospholipids, as well as anionic LNPs, have biased delivery toward hepatic endothelial or immune cells. Biodegradable ester-core lipids also alter the relationship between particle accumulation and productive translation. These strategies use material properties to adjust cell contact and delivery, although their performance also depends on plasma composition and cellular state [35–38].

After cellular uptake, mRNA must escape the endosome and enter the cytosol before it can be translated. Membrane fusion models and single-particle imaging show that lipid exchange, membrane disruption, and cytosolic RNA entry do not always occur together. Dispersion of the particle's lipid signal does not directly demonstrate RNA release [39–41]. Observations differ as to which membrane changes accompany productive release. One study linked small pores repairable by the endosomal sorting complex required for transport (ESCRT) to productive expression and lower inflammation. Another observed productive release

alongside galectin-positive membrane damage but found no productive release in the ESCRT-associated events it examined. Differences in formulations, cell models, and imaging scales may help explain these divergent observations [42,43]. Relating membrane changes to cytosolic RNA and protein expression can clarify how individual formulations release their payloads.

PEG affects both circulatory stability and cell contact. It stabilizes LNPs but also shields their surfaces, influencing cellular recognition. The anchoring structure of PEG–lipids determines PEG shedding, which in turn affects protein adsorption, hepatocyte uptake, and particle retention in Kupffer cells. Faster PEG shedding should therefore not be the sole objective when adjusting intrahepatic cell distribution. Repeated dosing also requires consideration of antibody recognition of polymer surfaces. Brush polymer–lipids offer an alternative surface architecture that can reduce anti-PEG antibody binding [44–46]. In ligand-bearing formulations, ligand density and PEG shedding together influence ligand exposure on the particle surface and binding to cellular receptors [44–46].

2.2 Polymers and Lipid–Polymer Hybrid Nanoparticles

Polymer carriers allow the backbone, side chains, and end groups to be modified separately to control RNA condensation, material degradation, and membrane interactions. In oligopeptide-terminated poly(β -amino ester) (PBAE) systems, retinol modification and end-group composition influence protein adsorption and liver transfection. New PBAE libraries have expanded the tunable range of expression levels and duration, although some evidence comes from local administration or vaccine studies [47,48]. Their relevance to intrahepatic delivery after systemic administration must be assessed in relation to the blood environment and tissue barriers. Lipid–polymer hybrid particles combine degradable polymers with lipids capable of membrane interactions. Phospholipid or alkyl modification and the polymer-to-RNA ratio can alter organ-level expression, and these formulations need not follow the conventional four-component LNP architecture [49–51]. Cell sorting or *in situ* protein detection can establish how different cell types contribute to overall expression. Incorporating polymer structures also provides additional variables for controlling hybrid particle assembly and release.

Charge-altering releasable transporters (CARTs) are designed around RNA dissociation, using programmed changes in charge to weaken material–RNA binding. Applications in the spleen, lung, and T cells support this release mechanism, with current evidence concentrated in these systems [52,53]. Whereas LNP release depends on lipid–membrane interactions, CARTs primarily promote RNA dissociation through charge changes.

2.3 Extracellular Vesicles and Biomimetic Carriers

EVs mediate nucleic acid and protein exchange among liver cells and can use existing intercellular communication pathways to deliver payloads. In experimental fibrosis, *lefty1* mRNA carried by HSC-derived EVs was associated with reduced HSC activation and matrix deposition. EVs also carry preformed proteins, however, and preparations contain non-vesicular components. The contributions of these components must therefore be excluded when interpreting the effects of mRNA. Vesicle uptake, RNA transfer, and new protein synthesis in recipient cells represent distinct stages of delivery [54,55].

Other biomimetic strategies use endogenous components with more defined compositions. PEG10 particles recognize RNA packaging sequences and use fusion proteins for cell entry; Arc-containing EVs and improved PEG10 systems have expanded payload capacity. These findings mainly come from the nervous system, cultured cells, or extrahepatic tumor models [56–58]. Assigning RNA packaging and cell entry to separate components allows each process to be optimized independently. Intein-based loading strategies

and GENRISE primarily enrich protein payloads, while engineered virus-like particles can deliver editor proteins or ribonucleoproteins [59–61]. These platforms allow comparison with mRNA carriers in terms of payload exposure and duration of action. Because the payload types differ, their performance cannot establish the transport efficiency of *in vitro*-transcribed mRNA. Distinguishing payload types helps match the choice of payload to the expression time course required for therapy.

EV potency is also closely linked to the source cells and production process. Culture and purification conditions alter membrane proteins, co-packaged RNA, and immunological activity, making batch-to-batch functional differences difficult to interpret from particle counts alone. MISEV2023 recommends reporting isolation methods, non-vesicular contaminants, payload composition, and functional controls to support comparisons between EV preparations [55].

2.4 Peptide and Protein Carriers

Peptides can combine RNA binding, receptor recognition, and membrane-active structures within a single material. Redox-responsive condensates and PEGylated assemblies control mRNA condensation and release, and peptoid particles have supported antibody expression *in vivo*. Evidence for condensates remains predominantly *in vitro*. Systemic applications must account for blood stability, payload dissociation, and hemolysis [62–64]. In these designs, peptides contribute directly to the organization of RNA within particles and to its release, rather than serving only as surface ligands. Peptides can also co-assemble with ionizable lipids for tissue-selective delivery of prime editor mRNA and prime editing guide RNA (pegRNA). Other peptides adjust organ tropism by changing protein corona composition [65,66]. Peptide-driven changes in distribution may therefore arise from receptor recognition, particle assembly, or protein adsorption, and the mechanism must be distinguished for each design.

Anti-Fc nanobodies can orient antibodies on the LNP surface to support immune cell targeting [67]. Applying this strategy to liver delivery requires consideration of particle interception by the same receptors on circulating cells and the effects of receptor-mediated intracellular trafficking on mRNA release. The value of higher binding affinity should therefore be assessed in relation to where particles arrive and how they traffic after uptake.

2.5 Tissue Context and Functional Screening of Intrahepatic Cellular Tropism

Here, hepatic accumulation denotes particle or payload localization in the liver, whereas cellular uptake denotes entry into a particular cell. Productive delivery requires cytosolic release of intact mRNA and subsequent protein expression. Cell selectivity describes how this productive expression is distributed among target and non-target cell populations; organ accumulation or uptake alone does not establish it.

The spatial arrangement of liver cells imposes a sequence on particle delivery. Particles first encounter sinusoidal phagocytes and endothelial cells, then cross the endothelial barrier to reach hepatocytes or HSCs (Fig. 2). In fibrosis, sinusoidal capillarization and matrix expansion restrict further passage, while recruited inflammatory cells provide additional sites of particle uptake. Spatial analyses of human liver have also identified fibrosis-associated hepatocyte states accompanied by disruption of normal zonation [8,22]. Disease stage thus affects both the state of the target cells and the routes by which particles reach them.

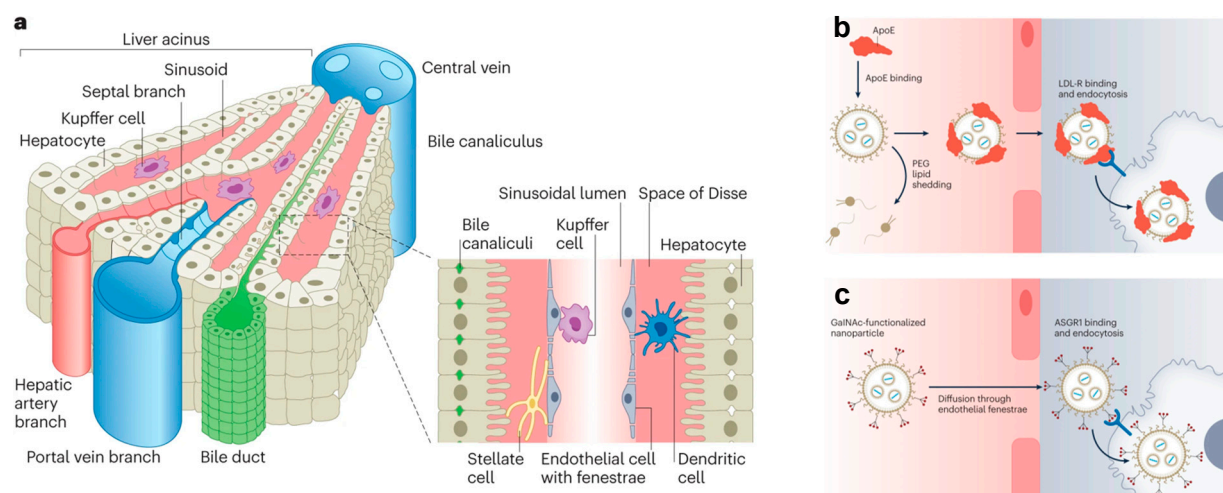


Figure 2: Liver microanatomy and hepatocyte uptake of lipid nanoparticles. (a) Liver acinar and sinusoidal anatomy, showing hepatocytes, Kupffer cells, liver sinusoidal endothelial cells, and hepatic stellate cells. (b) ApoE adsorption and PEG-lipid shedding support LDL receptor-mediated uptake by hepatocytes. (c) GalNAc-functionalized nanoparticles cross endothelial fenestrae and bind ASGR1 on hepatocytes. Adapted with permission from [8]. Copyright Springer Nature, 2023. The liver anatomy schematic in panel (a) was originally published by Adams and Eksteen (2006; doi:10.1038/nri1784), as credited in the source article.

Functional screening shifts the focus from particle distribution to intracellular expression. Available approaches include Cre reporter systems, mRNAs encoding peptide barcodes, and multiplexed assays that combine translation readouts with spatial distributions across the liver lobule. Cre signals amplify and integrate successful delivery events, making them useful for identifying cells that have undergone productive delivery. They do not directly measure therapeutic protein concentrations. Barcode assays must likewise distinguish residual RNA from translated products [4,15,68,69]. For sustained protein replacement, expression levels and their decay must also be recorded to relate formulation performance to the required dosing interval.

Machine learning can predict lipid potency or jointly optimize potency and cell selectivity, but the endpoints learned by a model depend on its training data. Whole-liver luminescence measures overall expression without resolving expression in HSCs or inflammatory responses in Kupffer cells. Heterogeneity in RNA loading and particle morphology can also confound comparisons between material structure and function [70–72]. Material screening for intrahepatic cells should therefore link formulation characterization as model inputs to cellular function as outputs. Host conditions also influence screening outcomes. Species differences and metabolic states alter particle uptake and expression, and amino acid supplementation studies suggest that host metabolism should be considered when interpreting delivery results. These animal studies identify conditions that affect delivery but do not establish supplementation regimens for patients [73,74]. The same formulation encounters different cellular and tissue states in healthy, inflamed, and fibrotic environments; comparisons of material performance should account for these differences.

2.6 mRNA Design and Expression Control

Carrier composition influences the cellular distribution of mRNA, whereas mRNA design controls protein yield and expression duration after cell entry. LinearDesign combines structural stability with codon optimization. Chemical and topological cap designs and strategies to maintain the poly(A) tail are

used to improve translation or transcript stability. Capped transRNAs regulate translation of a target RNA through exogenous RNA, providing an adjustable input for expression [75–78].

Sequence design must account for translational fidelity as well as expression levels. mRNAs containing N¹-methylpseudouridine can undergo frameshifting at slippery sequences, and synonymous sequence redesign can reduce this effect. Current findings support examining susceptible sequences and their translation products, but do not establish clinically relevant harm from frameshifted products [79]. RNA sensors connect expression control to transcripts already present within a cell. Systems based on adenosine deaminase acting on RNA (ADAR) can recognize endogenous transcripts and couple recognition to protein translation [80]. In the liver, this approach could further restrict expression initiation according to intracellular transcripts after the carrier has accumulated. The usable selectivity window depends on disease marker stability, basal leakage, and the expression level required for the therapeutic protein.

3 Hepatocyte-Targeted mRNA Delivery

Hepatocytes are among the first cellular targets of liver-directed mRNA delivery to be investigated clinically. Sinusoidal fenestrae provide access to hepatocytes, and lipoprotein uptake receptors can mediate particle internalization. Delivery strategies range from exploiting endogenous uptake pathways to incorporating receptor-binding ligands. As protein replacement and gene editing enter clinical studies, design increasingly considers the functions to restore, the required expression duration, and sustained activity with repeated dosing.

Early LNP formulations mainly relied on adjustments to particle size and PEG content to exploit the ApoE-LDLR pathway for hepatocyte entry [14]. When LDLR function is impaired, increasing uptake through this pathway alone remains insufficient to meet delivery requirements. N-acetylgalactosamine (GalNAc) functionalization enables LNPs to enter hepatocytes through the asialoglycoprotein receptor (ASGPR). In LDLR-deficient nonhuman primates, these particles delivered base editor mRNA and guide RNA, edited ANGPTL3, and produced a sustained reduction in circulating levels of the corresponding protein [81]. GalNAc thus provides an alternative entry pathway for hepatocytes with impaired receptor function. Choosing between ApoE-LDLR and GalNAc-ASGPR should account for receptor function in the recipient, rather than rely solely on average expression in healthy liver [14,81].

Protein replacement aims to restore missing function; expression level is only one component of this objective. In a mouse model of progressive familial intrahepatic cholestasis type 3, ABCB4 mRNA improved phenotypes associated with biliary phospholipid transport. Ornithine transcarbamylase (OTC) mRNA restored urea cycle function in mouse models. Preclinical studies of G6PC and PAH mRNA also support metabolic correction in glycogen storage disease and phenylketonuria, respectively. For these enzymes and transporters, appropriate intracellular localization, retained protein activity, and improvement in metabolic abnormalities are more relevant to therapeutic goals than total protein abundance [82–85].

In diseases requiring long-term control, functional recovery also depends on subsequent doses. Research on full-length ATP7B mRNA for Wilson disease combined transporter replacement with repeated dosing. A formulation containing hydroxyl-terminated PEG increased relative expression in hepatocytes and reduced copper accumulation during long-term treatment in mice. Species differences in antibody responses and lipid metabolism affect interpretation of repeated-dosing results when translating this approach to human treatment [86]. mRNA-3927, a candidate therapy for propionic acidemia, encodes the two subunits of propionyl-CoA carboxylase and has provided early clinical data on repeated treatment. In the first-in-human study, 16 participants received 346 intravenous administrations. The results suggested a lower risk of subsequent metabolic decompensation events among participants with previous metabolic

decompensation. This small, open-label study provided evidence of repeated-dosing feasibility and preliminary efficacy signals, but its ability to support long-term comparative efficacy assessments remains limited. Pharmacokinetic and pharmacodynamic modeling can link the decay of functional protein levels to metabolic control and help determine dosing intervals [7,87].

Transient expression in hepatocytes can also support injury repair. In mice, hepatocyte growth factor (HGF) and epidermal growth factor (EGF) mRNA promoted liver repair or the expansion of transplanted hepatocytes. HNF4A mRNA restored hepatocyte functional programs and reduced fibrosis, with the associated research linking hepatocyte recovery to indirect changes in inflammation and HSC activation [88–90]. OTC mRNA reduced ammonia-related injury in fibrosis models, and transient OSK mRNA expression promoted partial reprogramming and repair in mice. Assessing OSK-mediated repair also requires considering the potential for aberrant dedifferentiation and sustained proliferation [91,92]. TCPTP mRNA altered metabolic and immune responses in preclinical models of metabolic dysfunction-associated steatohepatitis (MASH) and MASH-associated liver cancer. Because expression occurred mainly in hepatocytes, the immune effects are better interpreted as indirect modulation of the immune environment by hepatocytes [93].

Gene editing separates the duration of expression from the duration of action: editor mRNA is transient, whereas the resulting DNA changes can persist. Preclinical studies achieved Angptl3 editing in mice and sustained reductions in blood lipids through PCSK9 base editing in nonhuman primates. Formulation, editor immunogenicity, and dose all affect editing efficiency and the effects of repeat dosing [5,94,95]. Clinical studies of TTR editing have extended to cardiomyopathy and polyneuropathy. Sustained protein reductions after a single dose, together with longitudinal follow-up, support liver-directed editing in humans. KLKB1 and PCSK9 programs have also advanced this approach, but disease endpoints and follow-up durations differ across programs. The magnitude of protein reduction therefore captures only part of each program's therapeutic outcomes [11,12,96,97].

Personalized editing is beginning to address rarer metabolic defects. In 2025, early follow-up after individualized base editing in an infant with CPS1 deficiency showed improved tolerance of dietary protein. Another study co-delivered prime editor mRNA and pegRNA in a mouse model of citrullinemia, correcting the pathogenic variant and restoring urea cycle function. The former is a single-patient report; the latter is an animal experiment. Because editing outcomes can persist, safety monitoring cannot end when the mRNA disappears. Long-term follow-up must also consider off-target events, structural variants, and irreversible pharmacodynamic effects [98,99].

Hepatocytes in the human liver also vary in zonation and functional state. Human liver atlases indicate species differences in hepatocyte zonation and its remodeling during regeneration after portal vein embolization. Multizonal organoids and adult hepatocyte organoids are suitable for comparing delivery and expression across functional states. Models that retain the sinusoidal barrier are also needed to determine whether particles can reach these hepatocytes [16,23,100,101].

4 Kupffer Cells and Liver Macrophages

Kupffer cells clear circulating substances and contribute to hepatic immune and metabolic regulation (Fig. 3). Their ready exposure to particles and capacity for phagocytosis do not necessarily lead to protein expression from the delivered mRNA. Defining the target population also affects delivery strategy. Spatial studies distinguish the microenvironments occupied by resident Kupffer cells and lipid-associated macrophages, while CD36-associated subsets in mouse resident cells reveal heterogeneity within this population. F4/80 positivity alone cannot distinguish these target populations with different therapeutic implications [17,18,102]. During disease, both resident and recruited macrophages can acquire lipid-associated

states and participate in repair through TREM2-associated clearance activities. Prior exposures also influence cell state: infection can cause persistent epigenetic changes, and maternal obesity can alter Kupffer cell programs in offspring [103–105]. Target selection should account for macrophage lineage, disease stage, current state, and exposure history.

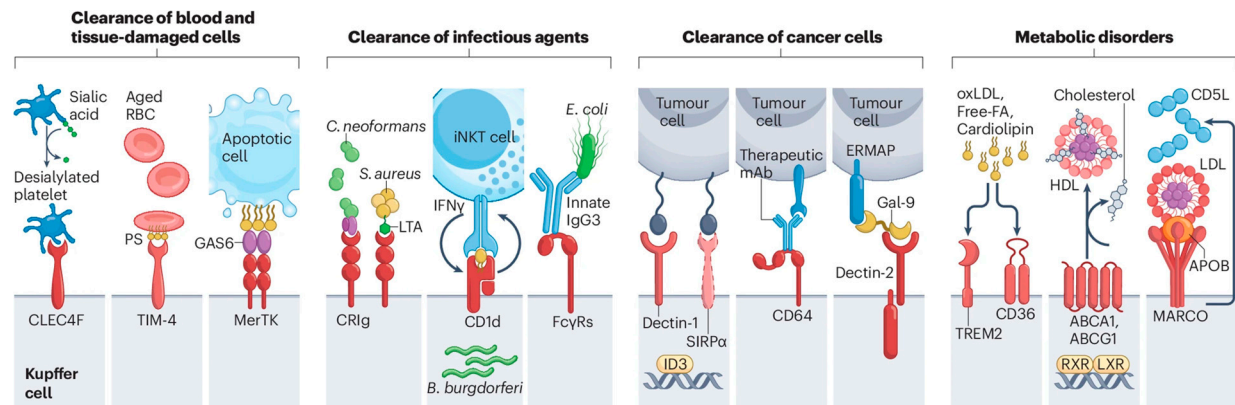


Figure 3: Receptors and pathways involved in Kupffer cell clearance and lipid handling. The schematic shows Kupffer cell recognition of damaged blood cells, apoptotic cells, infectious agents, and cancer cells, together with receptors and transporters involved in lipid uptake and cholesterol efflux. Adapted with permission from [18]. Copyright Springer Nature, 2026.

Converting phagocytosis into productive expression is an intracellular challenge for macrophage delivery. Phagocytosis by Kupffer cells favors particle accumulation but also routes payload toward degradation. Oxysterols, conformationally constrained phospholipids, and anionic LNPs have increased expression in liver immune cells; piperazine-derived lipids have also broadened *in vivo* immune cell delivery. Newly synthesized protein or editing activity reflects productive delivery, whereas particle fluorescence primarily records uptake [35–37,106]. Mannose–cholesterol LNPs link receptor recognition to PEG shedding and can target CD206-positive Kupffer cells and LSECs. Recruited macrophages can also express CD206, so targeting extends across lineages to distinct cell states that share this receptor [107].

The differing roles of macrophages in injury and repair call for different payload choices. In metabolic liver disease, Notch-RBPJ signaling promotes inflammatory differentiation. Human atlases of metabolic dysfunction-associated steatotic liver disease (MASLD) suggest that some lipid-associated macrophages can support hepatocytes through HGF. Broad suppression of the entire macrophage population would also impair its clearance and repair functions. The cell selectivity required to modulate inflammatory states differs from that needed to use reparative states to support hepatocytes [21,108].

Phagocytic and immunoregulatory pathway studies can guide payload selection for macrophage programming. In cancer research, ERMAP-galectin-9-dectin-2 interactions support phagocytosis of tumor cells, and ID3 regulates phagocytic receptors and antitumor immunity. VSIG4-CD5 signaling modulates T cell responses and can promote immune escape by poorly immunogenic metastases. These are pathway studies that provide a mechanistic basis for selecting candidate payloads [109–111]. In hepatitis B virus models, CD4⁺ T cells activate Kupffer cells through CD40-CD40L interactions. Kupffer cells then restore local CD8⁺ T cell activity through signals including IL-12 and IL-27. Designing mRNA interventions around this mechanism requires attention to both enhancing antiviral responses and limiting hepatocyte injury [112].

Antifibrotic chimeric antigen receptor (CAR) macrophages provide more direct examples of mRNA delivery. LNPs modified with anti-CD163 antibodies can deliver mRNA encoding a CAR that recognizes fibroblast activation protein (FAP). Another system co-delivered anti-FAP CAR mRNA and TRIM13 mRNA, promoting phagocytosis and inflammation resolution in mice with fibrosis [113,114]. The transfected macrophages express therapeutic proteins and act on activated HSCs. Thus, mRNA delivery and antifibrotic action involve different cell populations.

5 HSC-Targeted mRNA Delivery

HSCs store vitamin A and help maintain hepatic lobular homeostasis. Liver injury drives some HSCs into an activated, extracellular matrix-producing state. HSCs are functionally heterogeneous, with roles that vary by lobular zone, disease etiology, and disease stage (Fig. 4). For example, HSC-derived R-spondin 3 contributes to the regulation of hepatocyte zonation, liver size, and metabolism [19,115,116]. Antifibrotic delivery is therefore better directed toward pathologically activated HSCs, as broad HSC depletion would also weaken stromal signals that support liver function.

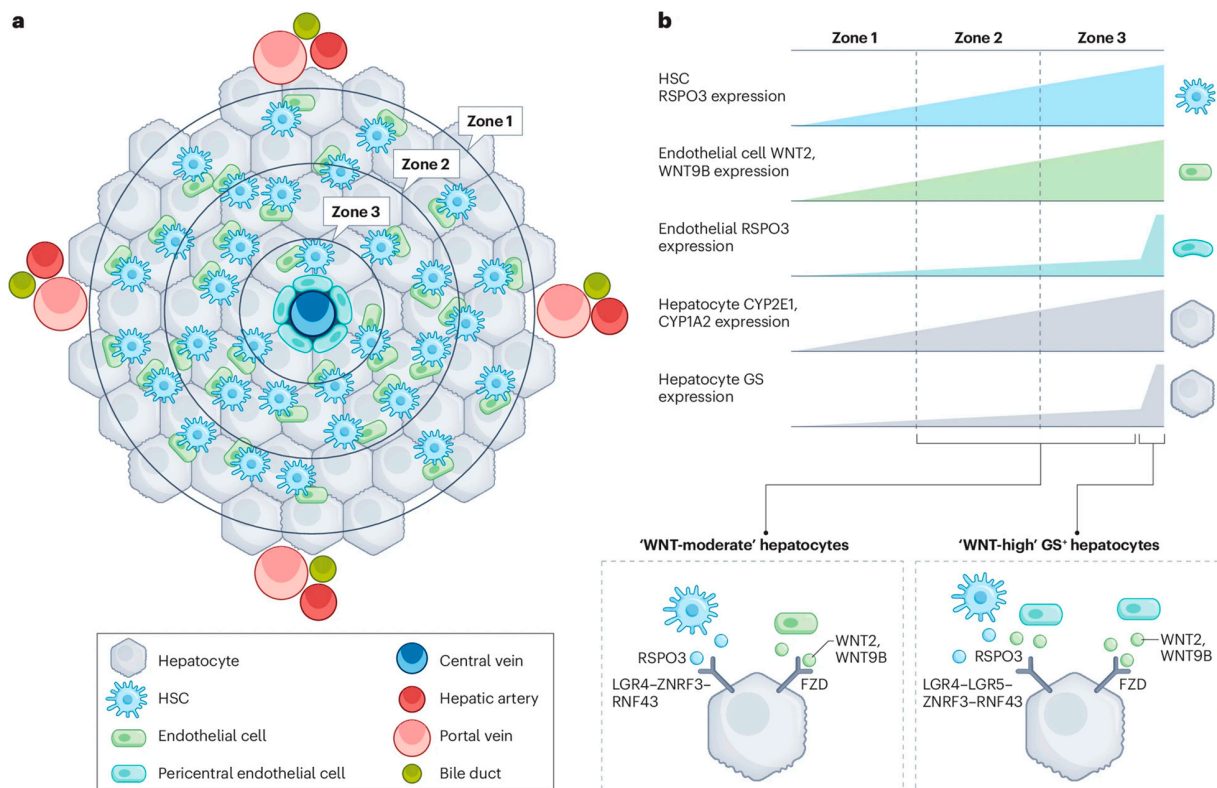


Figure 4: HSC-derived RSPO3 and endothelial WNT signals regulate hepatocyte zonation. **(a)** Distribution of HSCs, endothelial cells, and hepatocytes across lobular zones 1–3. **(b)** Zonal expression of RSPO3, WNT2, and WNT9B and the associated hepatocyte expression of CYP2E1, CYP1A2, and glutamine synthetase (GS). HSC-derived RSPO3 supports WNT activity in midlobular and pericentral hepatocytes, whereas endothelial RSPO3 supports high WNT activity in the most pericentral GS-positive hepatocytes. Adapted with permission from [19]. Copyright Springer Nature, 2025.

Restoring HSC quiescence offers another therapeutic approach. In advanced MASH models, reduced signaling through farnesoid X receptor (FXR) and G protein-coupled receptors is associated with impaired

communication among sinusoidal cells. Differentiation analyses also link ROR α to HSC metabolic differentiation and quiescence. Multimodal analyses of human HSCs have identified quiescent, activated, and inflammation-associated subsets. In MASH, activated subsets are enriched and show higher expression of extracellular matrix-related genes [117–119]. These findings suggest that mRNA payloads could also be designed to modulate cellular programs that maintain quiescence, alongside strategies to eliminate collagen-producing cells.

Activated HSCs, however, reside in fibrotic tissue that is less accessible. Particles must cross the sinusoidal endothelium, a route constrained by capillarization, basement membrane formation, and collagen deposition. Activation also changes receptor expression and endocytic pathways, altering how the same formulation enters cells in healthy and fibrotic livers. Pathways related to retinol binding, platelet-derived growth factor receptor β (PDGFR β), integrins, CD44, and sigma receptors are candidate targets. The relevant receptors are also expressed by other cells, and their distributions vary across species and disease stages. Beyond ligand binding, HSC delivery also depends on crossing tissue barriers and achieving expression after uptake.

The sigma receptor-binding lipid AA-T3A-C12 delivered heat shock protein 47 (HSP47) siRNA to activated HSCs, whereas evidence of luciferase expression from mRNA with this system came from *in vitro* experiments. siRNA-mediated silencing and mRNA-driven expression involve different payloads and intracellular processes; *in vivo* siRNA efficacy cannot be treated as direct evidence for therapeutic mRNA. In mice with carbon tetrachloride-induced fibrosis, AA-T3A-C12 enhanced HSP47 silencing and reduced collagen compared with MC3 LNPs [120]. For CL15A6, changes in composition, particle size, and apparent pKa biased reporter expression from mRNA toward activated HSCs after intravenous administration in mice. The study examined the roles of PDGFR β and clathrin-mediated endocytosis in uptake and assessed acute and chronic safety at doses up to 2 mg kg⁻¹ [121].

HSC-derived EVs provide another route for intercellular communication. The full sequence of intact mRNA transfer into recipient cells, cytosolic release, and *de novo* protein production has not yet been documented at single-cell resolution. Existing experiments nevertheless link vesicle transfer to antifibrotic effects: EVs carrying lefty1 mRNA attenuated TGF- β -driven HSC activation and matrix deposition [54].

FORT combines delivery to diseased tissue with local retention of therapeutic proteins. The formulation replaces part of the cholesterol with carboxylated retinoic acid. In mice treated with CCl₄ for six weeks, it produced approximately tenfold higher hepatic luciferase reporter expression than the original ALC-0315 formulation. A collagen-binding domain increased retention of secreted proteins in the lesion matrix, influencing their site of action rather than establishing HSC-specific expression. Delivery of mRNAs encoding fusions of a collagen-binding domain with relaxin or IL-10 increased protein retention within lesions and reduced fibrosis in male MASH animal models [122].

These strategies achieve selectivity at different levels. CL15A6 biases expression toward activated HSCs, HSC-derived EVs participate in intercellular signaling, and FORT increases expression in fibrotic regions while prolonging local protein retention. Comparisons of therapeutic effects should distinguish direct changes in HSC state from indirect antifibrotic effects mediated by hepatocytes or macrophages. For formulations that rely on receptors associated with activation, the range of action narrows as fibrosis resolves and receptor expression declines. Current evidence for CL15A6 comes mainly from reporter studies in mice; therapeutic payload performance and cross-species behavior remain unresolved translational questions. Comparing expression across HSC subsets and other fibroblasts at different disease stages could clarify how a formulation's range of action changes as fibrosis progresses or resolves.

6 LSEC-Targeted mRNA Delivery

LSECs are both targets for mRNA therapy and the interface that particles cross before reaching hepatocytes and HSCs. Fenestrae and the absence of a continuous basement membrane support sinusoidal exchange, while scavenger receptors mediate uptake and antigen presentation contributes to immune tolerance. Following injury, LSEC capillarization is accompanied by reduced endothelial nitric oxide synthase (eNOS)–nitric oxide (NO) signaling, promoting HSC activation, portal hypertension, and hepatocyte dysfunction [13]. Restoring protein function in LSECs therefore also alters the environment of downstream cells (Fig. 5).

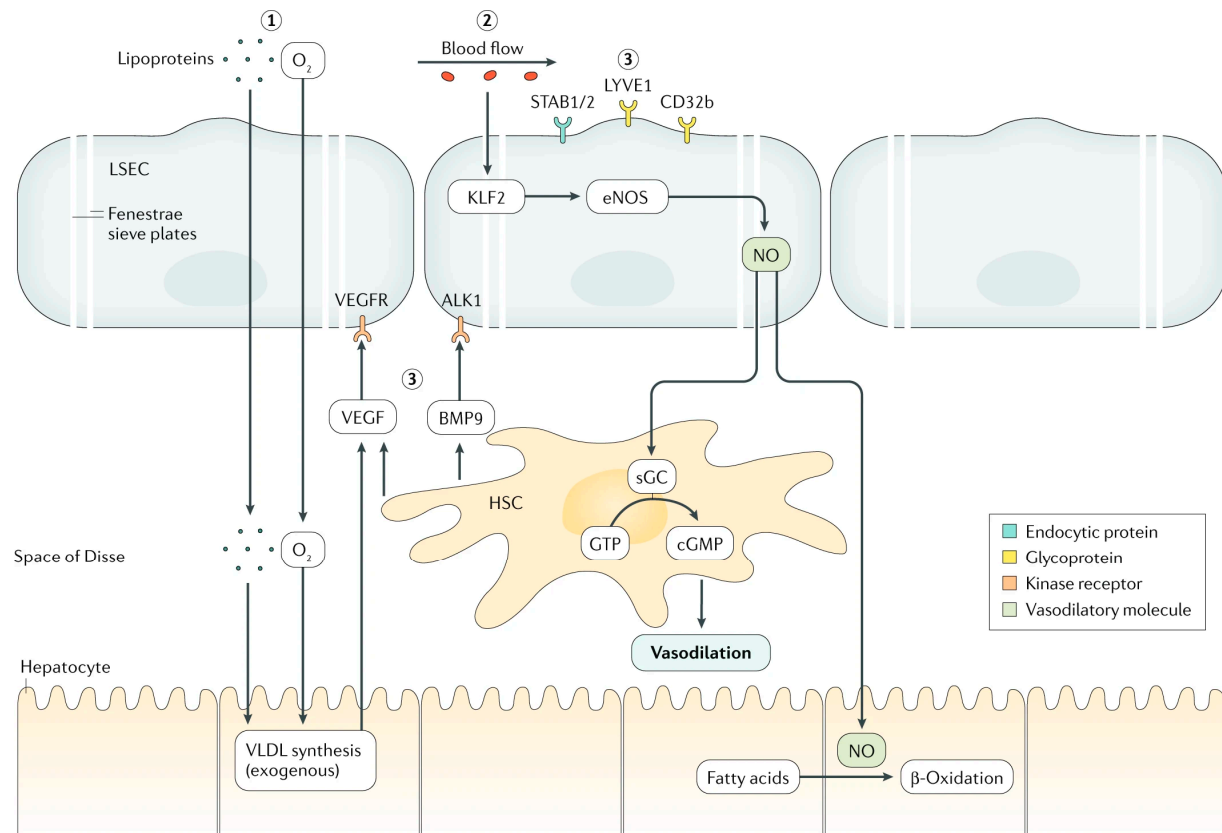


Figure 5: Sinusoidal structure and intercellular signaling in liver homeostasis. The schematic shows exchange through LSEC fenestrae, shear stress–KLF2–eNOS–NO signaling, NO-dependent signaling in HSCs and hepatocytes, and VEGF–VEGFR and BMP9–ALK1 interactions. Adapted with permission from [13]. Copyright Springer Nature, 2021.

The intrinsic clearance activity of LSECs can guide the design of delivery materials. Scavenger receptors take up anionic macromolecules, and anionic LNPs can bias expression toward the hepatic reticuloendothelial system [37]. Oxysterols and degradable ester-core lipids likewise increase expression in hepatic endothelial cells without additional ligands [35,38]. These formulations alter cell tropism through material composition, although their delivery performance remains influenced by plasma protein adsorption and species-specific receptor distributions. Adjusting particle size and PEG content can favor expression in hepatocytes, whereas adding mannose can redirect delivery toward LSECs [14]. In mice, mannose–cholesterol LNPs increased particle uptake and functional mRNA delivery in CD206-positive LSECs and Kupffer cells. Shortening the acyl chains of PEG–lipids can promote PEG shedding, making surface mannose more accessible to cells [107]. Because CD206 is also expressed by Kupffer cells, mannose targeting can

support delivery to both Kupffer cells and LSECs. Combinations of stabilin family members, LYVE1, or cell-state markers could be explored to refine targeting toward specific LSEC subsets.

The antigen-presenting function of LSECs has been used for mRNA-mediated immune modulation. LSEC-directed delivery of mRNA encoding T-cell epitopes from peanut allergens induced regulatory T cells and reduced allergic reactions in mice [123]. Candidate payloads for vascular repair include proteins that regulate eNOS–NO signaling, fenestrae, and BMP/WNT pathways, although direct evidence for therapeutic mRNA in this setting remains limited. LSECs also regulate coagulation, immune tolerance, and sinusoidal blood flow. The effects of payloads encoding continuously secreted proteins also extend to these physiological processes.

LSEC uptake can compete with delivery to hepatocytes and HSCs, but protein expression in LSECs still requires cytosolic release. Variation in scavenger receptor expression and fenestration among LSEC subsets may influence whether particles are retained in the endothelium or reach downstream cells.

7 Emerging Cellular Targets in the Liver

7.1 Biliary Epithelium and Cellular Plasticity

Cholangiocyte polarity and biliary anatomy impose delivery barriers that differ from those encountered by cells within the liver sinusoids. Human-derived organoids can reproduce biliary branching and support biliary repair in *ex vivo* perfused human livers, although cultured cells still differ from their counterparts *in situ* [20,124]. These models show the therapeutic value of cholangiocytes, but reaching this population after intravenous administration remains a separate delivery problem. Organoids assembled from hepatocytes, cholangiocytes, and portal tract mesenchymal cells can also model bile drainage and biliary fibrosis, allowing delivery barriers and epithelial responses to be examined within the same model [125].

VEGFA mRNA delivered in LNPs promoted the conversion of cholangiocyte-associated cells into hepatocytes and ameliorated steatosis and fibrosis in injured mouse livers [126,127]. Findings on epithelial plasticity in humans also support this concept, but do not yet constitute evidence of clinical efficacy. Because VEGFA acts after secretion, the protein-producing cells need not be the cells undergoing a change in fate. This strategy uses local signaling to alter epithelial cell responses.

7.2 Expression and Local Activity in Intrahepatic Tumors

Systemically administered LNPs carrying mRNA can transfect orthotopic liver tumors and some liver metastases, although tumor expression is lower than expression in normal liver tissue in some preclinical models [128]. Tumor vasculature, stroma, and the metabolic environment alter particle accessibility. For cytotoxic payloads, background expression in normal liver tissue directly affects the available therapeutic window. Secreted antitumor proteins can act without direct transfection of every tumor cell; their selectivity derives primarily from binding to target antigens. mRNAs encoding GPC3-targeted bispecific T-cell engagers or IFN- α –anti-GPC3 fusion proteins have produced antitumor effects in preclinical models [9,129]. Antigen recognition concentrates their activity at the lesion, allowing these proteins to act within tumors even when produced by cells outside the lesion.

The effects of antitumor payloads also depend on the preexisting immune environment of the liver. In models of nonalcoholic steatohepatitis, aberrant CD8⁺ T-cell activation is associated with liver injury. Metastasis-associated macrophages can eliminate activated T cells and reduce responses to immunotherapy [130,131].

7.3 Transient Programming of Immune Cells

mRNA can also modify immune cells, which then enter lesions and exert therapeutic effects. In 2022, T-cell-targeted LNPs generated antifibrotic CAR T cells *in vivo* and ameliorated cardiac injury in mice. A 2025 study extended *in vivo* programming to human-derived cell systems, mice, and nonhuman primates [132,133]. For liver applications, engineered cells must reach the affected liver tissue and recognize target antigens whose distribution may differ between pathogenic and repair-associated cells.

LNPs carrying PDL1 mRNA have generated tolerogenic antigen-presenting cells in extrahepatic models of autoimmunity [114,134]. Transient mRNA expression can reset immune-cell function, as illustrated by these studies and the hepatic CAR macrophage work discussed above, and can also supply soluble proteins. Programming tolerogenic antigen-presenting cells for liver disease remains a therapeutic concept extrapolated from extrahepatic models. For formulations carrying multiple mRNAs, the relationship among payloads must be defined at the design stage. Effects requiring coexpression in the same cell impose different co-delivery requirements from those mediated by secreted signals between cells.

8 Conclusions and Future Directions

Cell-selective mRNA delivery within the liver has developed along several therapeutic paths. Protein replacement and gene editing in hepatocytes have entered early clinical studies, whereas applications targeting macrophages, HSCs, and LSECs remain largely preclinical.

The relationship between the sites of protein production and action also shapes the selectivity required for therapies using exogenous mRNA. CAR macrophages can exert antifibrotic effects by recognizing activated HSCs, whereas secreted antitumor proteins can act within lesions through target-antigen recognition. In both cases, the cells expressing the therapeutic protein can differ from the targets of its effects. Formulations for chronic treatment must also be evaluated throughout the treatment course, extending beyond a single dose. Vaccine studies have documented formulation-associated inflammation and changes in anti-PEG antibodies. Because routes of administration and dosing conditions differ, these findings must be interpreted in the specific context of intravenous therapy. Hydroxyl-terminated PEG has the potential to reduce antibody binding and complement activation, providing a specific material approach to improving performance during subsequent dosing [135–138].

Manufacturing must preserve the formulation attributes linked to these functions. RNA purity, mixing, and storage conditions all alter delivery performance. Parallel microfluidic production and standardized LNP databases can help establish reproducible formulation development workflows [139–141]. For cell-selective formulations, scale-up should preserve both physicochemical properties, such as particle size and encapsulation efficiency, and target-cell potency, assessed by active protein or editing outcomes. Spatial expression profiles and functional readouts in human-derived disease models can further connect material screening with diseased tissue. Protein replacement requires assessing whether function is maintained throughout each dosing interval. Gene-editing follow-up should extend long enough to assess persistent genetic changes. Regeneration and immunomodulation require assessment of whether tissue benefits persist after transient expression has ended.

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