
mRNA Delivery Systems Recent Advances in Lipid Nanoparticles, Nanocarriers, Targeting Strategies, and Therapeutic Applications

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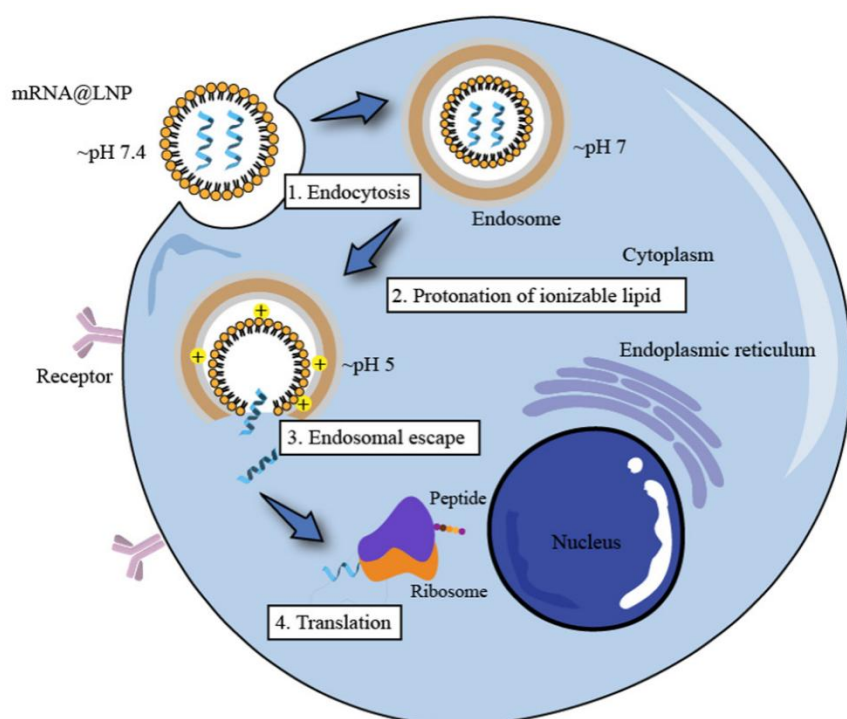
Abstract

Messenger RNA (mRNA) has emerged as a promising therapeutic platform because it enables transient and programmable protein expression without permanent genomic modification. However, its clinical application is strongly dependent on efficient delivery systems capable of protecting mRNA from degradation, facilitating cellular uptake, promoting endosomal escape and enabling cytoplasmic release. This review examines recent advances in mRNA delivery systems between 2015 and 2025, with particular emphasis on lipid nanoparticles (LNPs), emerging nanocarriers and targeted delivery strategies. The literature demonstrates that ionisable lipid-based LNPs have become the most clinically advanced platform owing to their high encapsulation efficiency, favourable delivery performance and scalable manufacturing potential. Nevertheless, conventional LNPs remain associated with limitations including preferential hepatic accumulation, endosomal entrapment, inflammatory responses, stability concerns and challenges in achieving extrahepatic delivery. Advances in ionisable lipid chemistry, selective organ targeting, ligand-mediated targeting, polymeric nanoparticles, lipid-polymer hybrid systems, peptide-based carriers and extracellular vesicles are providing opportunities to address these limitations. The therapeutic scope of mRNA delivery has also expanded beyond vaccination towards cancer immunotherapy, protein replacement, gene editing, regenerative medicine and genetic disorders. Overall, current evidence indicates a transition from conventional mRNA formulations towards more precise, biodegradable, tissue-selective and application-specific nanocarriers. Continued integration of RNA engineering, nanomaterial chemistry, targeting biology and scalable manufacturing will be essential for improving safety, therapeutic efficacy and clinical translation of next-generation mRNA medicines.

Keywords: mRNA delivery, lipid nanoparticles, nanocarriers, ionisable lipids, targeted delivery, endosomal escape, mRNA therapeutics

Introduction

Messenger RNA (mRNA) has emerged as a highly versatile therapeutic modality because it enables transient, programmable and potentially cell-specific production of functional proteins without requiring permanent genomic modification. Unlike conventional protein therapeutics, mRNA-based approaches allow the intracellular machinery of the recipient cell to synthesise the desired protein directly, creating opportunities for vaccination, protein replacement, cancer immunotherapy, regenerative medicine and gene-editing applications. However, the clinical translation of mRNA is strongly dependent on the development of delivery systems capable of protecting the nucleic acid from extracellular degradation, facilitating cellular uptake, promoting endosomal escape and releasing intact mRNA into the cytoplasm. These requirements have stimulated substantial progress in nanotechnology-based delivery platforms over the past decade (Rohner et al., 2022).



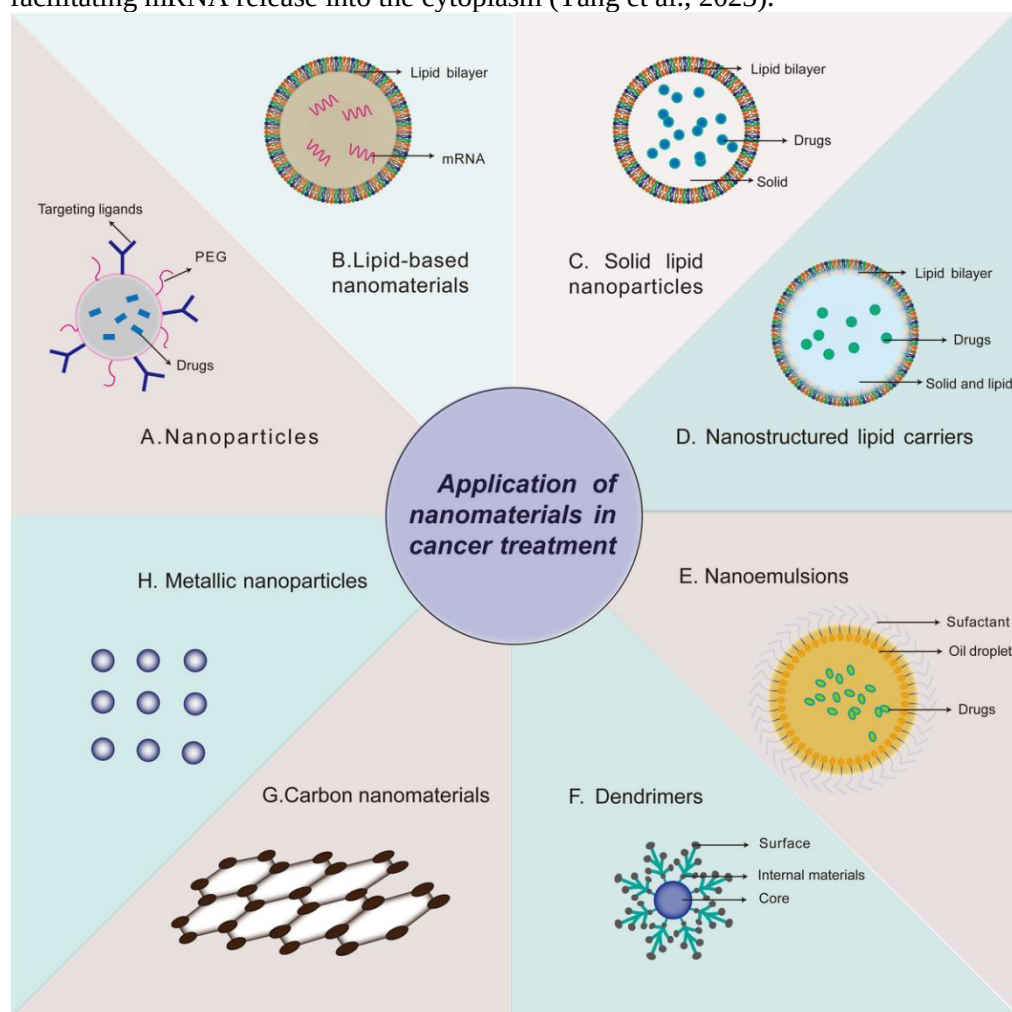
Among the available delivery technologies, lipid nanoparticles (LNPs) have become the most clinically advanced and extensively investigated systems for mRNA delivery. Their success is associated with the ability to efficiently encapsulate negatively charged mRNA, protect it from ribonuclease-mediated degradation and facilitate intracellular delivery. Contemporary LNPs generally comprise ionisable lipids, helper phospholipids, cholesterol and polyethylene glycol (PEG)-conjugated lipids, with each component influencing particle stability, biodistribution, cellular uptake and endosomal escape (Hou et al., 2021). The clinical success of LNP-formulated mRNA vaccines against COVID-19 demonstrated the feasibility of translating these systems from experimental nanomedicine into large-scale human applications, substantially accelerating research into broader mRNA therapeutics (Chaudhary et al., 2021).

Despite these advances, systemic mRNA delivery remains constrained by biological barriers, tissue-specific biodistribution, inefficient delivery to extrahepatic organs, inflammatory responses, potential toxicity and difficulties associated with manufacturing and storage. Consequently, current research increasingly focuses on engineering nanocarriers with improved physicochemical characteristics and developing passive, endogenous and active targeting strategies capable of directing mRNA towards particular tissues and cell populations (Paunovska et al., 2022; Wang et al., 2025). Beyond conventional LNPs, polymeric nanoparticles, lipid-polymer hybrid systems, liposomes, extracellular vesicles and other nanocarriers are being investigated to overcome limitations associated with conventional formulations.

Recent developments have consequently expanded the therapeutic landscape of mRNA delivery from infectious-disease vaccination towards cancer, genetic disorders, cardiovascular conditions, protein-replacement therapies and genome editing. Targeted mRNA nanomedicines are particularly important because improved tissue selectivity may enhance therapeutic efficacy while reducing off-target exposure (Kon et al., 2023). This review therefore examines recent advances in mRNA delivery systems, with particular emphasis on LNP design, alternative nanocarriers, targeting strategies, biological barriers and emerging therapeutic applications, while considering the principal challenges that continue to influence their clinical translation (Vasileva et al., 2024).

mRNA Delivery Systems and Nanocarrier Technologies

Messenger RNA delivery has progressed from experimental transfection approaches towards sophisticated nanomedicine platforms designed to protect mRNA, facilitate cellular uptake and enable cytoplasmic translation. Among these systems, lipid nanoparticles (LNPs) have become the dominant non-viral platform because of their high encapsulation efficiency, favourable scalability and ability to combine protection with intracellular release. Conventional LNPs generally contain an ionisable lipid, phospholipid, cholesterol and PEGylated lipid, with the relative composition determining particle stability, biodistribution, cellular uptake and endosomal escape (Hou et al., 2021). Ionisable lipids are particularly important because they remain comparatively neutral under physiological conditions but become protonated within acidic endosomes, promoting interactions with endosomal membranes and facilitating mRNA release into the cytoplasm (Tang et al., 2023).



The development of ionisable lipid chemistry has consequently become a major area of mRNA delivery research. Structural modification of lipid head groups, linkers and hydrophobic tails can influence pKa, membrane interaction, biodegradability and protein expression. Optimisation of these characteristics has contributed to the performance of clinically validated formulations and has also enabled exploration of novel LNP compositions for therapeutic applications beyond vaccination (Kulkarni et al., 2019). At the same time, alternative nanocarriers, including polymeric nanoparticles, peptide-based systems, lipid-polymer hybrids, extracellular vesicles and biomimetic vesicles, are being investigated to address limitations associated with conventional LNPs, particularly their tendency towards hepatic accumulation (Wang et al., 2024).

The effectiveness of an mRNA carrier is not determined solely by encapsulation or particle size. Delivery

involves a sequential biological process encompassing tissue distribution, cellular internalisation, endosomal escape and cytosolic release. Inefficiency at any stage can substantially reduce protein expression, making rational carrier design essential (Riley et al., 2024). Recent research has therefore moved towards integrating material chemistry with biological mechanisms, including high-throughput formulation screening, microfluidic manufacturing and computational optimisation. Such developments are expanding the potential of mRNA nanocarriers from vaccine delivery towards protein replacement, gene editing, cancer immunotherapy and treatment of inherited disorders.

Table 1. Major nanocarrier platforms investigated for mRNA delivery

Nanocarrier system	Principal characteristics	Major advantages	Key limitations	Representative applications
Lipid nanoparticles	Ionisable lipid, cholesterol, phospholipid and PEG-lipid	High mRNA encapsulation and efficient intracellular delivery	Hepatic accumulation, inflammatory responses	Vaccines, gene editing, cancer therapy
Polymeric nanoparticles	Biodegradable or cationic polymers	Structural versatility and controlled release	Potential toxicity and variable transfection efficiency	Protein replacement and gene therapy
Lipid–polymer hybrids	Combination of lipid and polymer components	Improved stability and tunable surface properties	More complex manufacturing	Targeted mRNA delivery
Peptide-based carriers	Cell-penetrating or membrane-active peptides	Potentially efficient cellular internalisation	Stability and immunogenicity concerns	Gene editing and therapeutic protein expression
Extracellular vesicles	Naturally derived membrane vesicles	Biological compatibility and intrinsic targeting potential	Loading and manufacturing challenges	Personalised and tissue-targeted delivery

Targeting Strategies, Biological Barriers and Optimisation of mRNA Delivery

Although LNPs have demonstrated substantial clinical success, their therapeutic potential is constrained by biological barriers and relatively non-selective biodistribution following systemic administration. After entering the circulation, nanoparticles interact with plasma proteins, immune cells and biological membranes, while their physicochemical characteristics influence organ accumulation and cellular uptake. Conventional LNPs exhibit a pronounced tendency towards hepatic delivery, which is advantageous for some metabolic and genetic disorders but limits applications requiring mRNA expression in the lungs, brain, heart, lymphatic tissues, tumours or other extrahepatic organs (Vasileva et al., 2024). Consequently, targeted delivery has become a central objective in contemporary mRNA nanomedicine.

Targeting can be achieved through modification of lipid composition, particle physicochemical properties, surface ligands or administration routes. Altering the chemical structure of ionisable lipids can modify biodistribution without necessarily requiring an external targeting ligand. Selective organ targeting approaches have demonstrated that relatively small changes in lipid structure can redirect nanoparticles towards tissues such as the spleen, lungs and other extrahepatic sites (Cheng et al., 2020). Ligand-mediated targeting represents another strategy, in which antibodies, peptides, aptamers or receptor-specific molecules are incorporated onto nanoparticle surfaces to facilitate recognition of particular cellular populations. Such approaches are particularly relevant to cancer therapy, where selective delivery to tumour cells or immune-cell populations may improve therapeutic activity while reducing systemic exposure (Miao et al., 2023).

Endosomal escape remains another critical bottleneck. Following cellular uptake, a large proportion of

nanoparticles may remain trapped within endosomal compartments rather than releasing mRNA into the cytosol. Ionisable lipids can facilitate membrane destabilisation under acidic conditions, but improving escape efficiency while maintaining acceptable tolerability remains an important formulation challenge (Patel et al., 2024). Recent rational-design approaches therefore consider the entire delivery cascade, integrating organ targeting, cellular uptake, endosomal escape and cytosolic release rather than optimising individual formulation parameters independently (Riley et al., 2024). These advances are also encouraging the development of extrahepatic delivery platforms and multifunctional nanoparticles capable of combining targeting, controlled release and intracellular trafficking.

Table 2. Principal strategies for improving targeted mRNA delivery

Targeting/optimisation strategy	Mechanism	Intended outcome
Ionisable lipid engineering	Modification of lipid pKa and molecular structure	Improved endosomal escape and tissue distribution
Lipid composition optimisation	Adjustment of lipid ratios and chemical structures	Controlled biodistribution and enhanced expression
Ligand-mediated targeting	Attachment of receptor-specific ligands	Selective cellular uptake
Size and surface engineering	Modification of particle size, charge and surface characteristics	Improved circulation and tissue penetration
Selective organ targeting	Rational lipid or formulation design	Delivery beyond the liver
Administration-route optimisation	Intravenous, intramuscular, intratumoural or local administration	Improved anatomical targeting
High-throughput screening	Parallel evaluation of diverse nanoparticle formulations	Identification of high-performing carriers
Microfluidic formulation	Controlled and reproducible nanoparticle assembly	Improved batch consistency and scalability
Stimuli-responsive delivery	Response to pH, enzymes or other biological signals	Site-specific intracellular release
Biomimetic delivery	Use of extracellular vesicles or biological membrane components	Improved biocompatibility and targeting potential

Need Of the Study

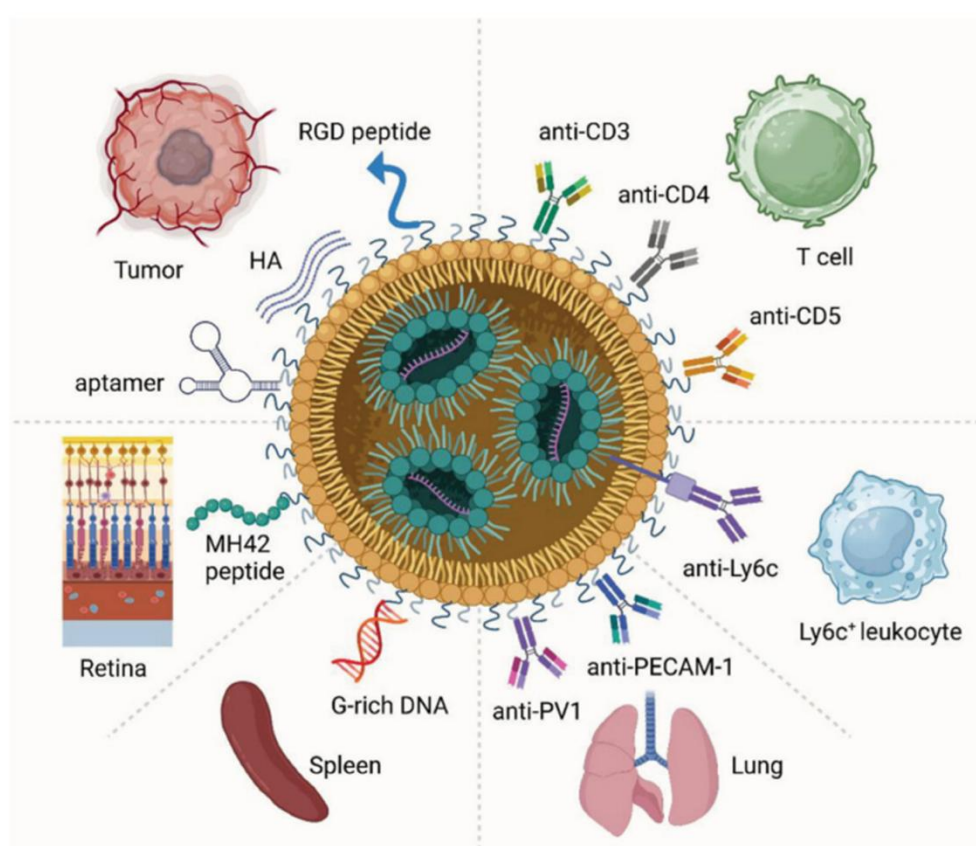
The rapid development of mRNA therapeutics has created a strong need for delivery systems that can overcome the intrinsic biological and physicochemical limitations of naked mRNA. Although mRNA offers transient protein expression without permanent genomic modification, its large molecular size, negative charge and susceptibility to enzymatic degradation substantially restrict cellular uptake and intracellular activity. The clinical success of lipid nanoparticles (LNPs) has demonstrated the feasibility of mRNA delivery, particularly for vaccines, while simultaneously highlighting important limitations concerning tissue distribution, extrahepatic delivery, endosomal escape, immunogenicity and formulation stability (Hou et al., 2021). These limitations have generated increasing interest in developing more sophisticated nanocarriers and targeting approaches capable of delivering mRNA selectively to desired tissues and cell populations.

A systematic understanding of recent advances is therefore necessary because research has expanded rapidly across ionisable lipids, polymeric nanoparticles, lipid-polymer hybrid systems, extracellular vesicles and biomimetic carriers. Advances in selective organ targeting and ligand-mediated delivery have further demonstrated the possibility of overcoming the predominantly hepatic distribution associated with many LNP formulations (Cheng et al., 2020). Moreover, mRNA delivery is increasingly being explored beyond vaccination, including cancer immunotherapy, protein replacement, regenerative medicine and gene-editing applications. However, differences in carrier composition, targeting mechanisms, biological barriers and therapeutic objectives make direct comparison difficult. This review

is therefore needed to consolidate contemporary evidence on mRNA delivery technologies and critically examine how carrier design, targeting strategies and biological interactions influence therapeutic performance. Focusing on literature published between 2015 and 2025 provides an appropriate basis for evaluating the technological transition from experimental mRNA formulations towards clinically relevant and increasingly targeted delivery platforms.

Scope of the research

This review focuses on recent developments in mRNA delivery systems published between 2015 and 2025, with particular emphasis on nanotechnology-based approaches for improving the stability, cellular uptake, intracellular trafficking and therapeutic expression of mRNA. The scope primarily encompasses lipid nanoparticles (LNPs), including ionisable lipid-based formulations, while also considering polymeric nanoparticles, lipid-polymer hybrid systems, peptide-based carriers, extracellular vesicles and other emerging nanocarrier platforms. Particular attention is given to how carrier composition, physicochemical properties and formulation parameters influence mRNA encapsulation, biodistribution, endosomal escape and cytoplasmic release (Kulkarni et al., 2019).



The review further examines targeting strategies developed to overcome the predominantly hepatic distribution of many systemic LNP formulations. These include lipid structure optimisation, selective organ targeting, ligand-mediated targeting, surface modification and administration-route optimisation. The biological barriers encountered during mRNA delivery, including extracellular degradation, immune recognition, cellular internalisation and endosomal entrapment, are also considered in relation to delivery efficiency and therapeutic performance (Paunovska et al., 2022).

In terms of therapeutic applications, the review covers mRNA vaccines, cancer immunotherapy, protein replacement, gene editing, regenerative medicine and treatment of inherited and metabolic disorders. Particular consideration is given to the translation of mRNA nanomedicines from preclinical research into clinical applications, including formulation scalability, safety, stability and manufacturing challenges. The review does not focus extensively on mRNA sequence engineering or transcription

technologies except where these directly influence delivery performance. Overall, the scope is designed to provide an integrated assessment of how advances in nanocarrier engineering and targeting technologies are expanding the therapeutic potential of mRNA-based medicines.

Literature Review

Hou et al. (2021) described lipid nanoparticles (LNPs) as the most clinically advanced non-viral platform for mRNA delivery, reflecting the convergence of advances in nucleic-acid engineering, lipid chemistry and nanomedicine. The therapeutic potential of mRNA originates from its ability to provide transient intracellular instructions for protein synthesis without requiring permanent alteration of genomic DNA. However, naked mRNA is highly susceptible to extracellular ribonucleases, possesses a relatively large molecular size and carries a negative charge, which collectively restrict passive cellular entry. Consequently, effective delivery requires a carrier capable of protecting mRNA during biological transport, promoting cellular internalisation and facilitating release into the cytoplasm. LNPs address several of these requirements through a combination of ionisable lipids, helper phospholipids, cholesterol and PEGylated lipids. The rapid clinical translation of LNP–mRNA vaccines demonstrated that these systems can achieve reproducible biological activity in humans and established a foundation for broader therapeutic applications.

Karikó et al. (2015) demonstrated the importance of nucleoside modification in controlling the innate immune recognition of therapeutic mRNA. Incorporation of modified nucleosides, particularly N1-methylpseudouridine, can reduce activation of innate immune sensors while improving translational capacity. This development is particularly important because excessive recognition of exogenous RNA by Toll-like receptors and other intracellular RNA-sensing pathways can suppress translation and generate undesirable inflammatory responses. The progress of mRNA delivery has therefore depended not only on nanocarrier development but also on simultaneous optimisation of the RNA cargo itself. Sequence engineering, modified nucleosides, optimisation of untranslated regions and improved purification methods have progressively increased the stability and functional expression of therapeutic mRNA. The interaction between RNA design and delivery technology is consequently central to the performance of contemporary mRNA therapeutics.

Cullis and Hope (2017) established the broader technological significance of lipid nanoparticles for nucleic-acid delivery, particularly through the development of ionisable lipid systems capable of combining efficient nucleic-acid encapsulation with improved physiological tolerability. Ionisable lipids remain relatively neutral at physiological pH but become protonated in acidic environments such as the endosome. This pH-dependent behaviour enables efficient association with negatively charged mRNA during formulation while limiting persistent positive charge following administration. Once internalised, protonation within the acidic endosomal compartment promotes interactions between the nanoparticle and endosomal membranes, contributing to membrane destabilisation and cytoplasmic release. This mechanism distinguishes ionisable lipid systems from permanently cationic carriers, which may exhibit stronger nonspecific interactions and greater toxicity. The development of biodegradable and structurally optimised ionisable lipids has therefore become one of the principal directions in contemporary mRNA delivery research.

Kulkarni et al. (2019) further demonstrated that the molecular architecture of ionisable lipids substantially influences the efficiency of RNA delivery. Systematic optimisation of lipid head groups, linker structures and hydrophobic domains has enabled the development of materials with improved delivery activity and biological tolerability. The lipid's apparent pKa is particularly influential because it affects both mRNA encapsulation during formulation and membrane interactions following cellular uptake. Structural diversity among ionisable lipids has also demonstrated that relatively small chemical modifications can produce considerable differences in tissue distribution and protein expression. These observations have shifted LNP development from empirical formulation towards more rational structure–activity optimisation. High-throughput synthesis and screening of lipid libraries have consequently become important approaches for identifying candidate materials with improved potency, biodegradability and organ-selective behaviour.

Hou et al. (2021) emphasised that the four-component architecture of conventional LNPs provides

complementary functions during mRNA delivery. Ionisable lipids facilitate mRNA complexation and endosomal escape, while helper phospholipids contribute to membrane structure and particle stability. Cholesterol influences nanoparticle morphology, packing and membrane interactions, whereas PEG-lipids regulate particle size, colloidal stability and interactions with biological components. However, PEGylation also involves a formulation trade-off because excessive PEG density can reduce cellular uptake and endosomal escape, whereas insufficient PEG may promote aggregation and alter pharmacokinetics. Consequently, the molar ratios and chemical identity of individual components must be carefully controlled. Modern LNP formulation therefore involves optimisation of multiple interdependent parameters rather than selection of a single optimal lipid.

Chaudhary et al. (2021) highlighted the importance of LNPs in the clinical development of mRNA vaccines, particularly following the rapid implementation of mRNA-based vaccination against SARS-CoV-2. The clinical success of these vaccines provided compelling evidence that mRNA can be manufactured, encapsulated and administered at a population scale while retaining sufficient biological activity. LNP-mediated delivery enabled the mRNA to reach antigen-presenting cells and other relevant cells following administration, where transient production of viral antigen stimulated adaptive immune responses. This achievement also validated several principles of mRNA nanomedicine, including the importance of efficient encapsulation, intracellular release and controlled innate immune activation. Nevertheless, vaccine delivery represents only one application of the technology, and the requirements for therapeutic mRNA delivery to non-hepatic tissues or specific cellular populations are considerably more demanding.

Yang et al. (2022) reviewed the expanding use of LNPs in cancer therapy, infectious diseases, protein replacement and gene editing, demonstrating that the therapeutic scope of mRNA delivery extends considerably beyond vaccination. In cancer immunotherapy, mRNA can encode tumour antigens, cytokines, immune-modulatory proteins or components designed to modify immune cells. LNPs can protect these transcripts and facilitate their intracellular expression, making them attractive platforms for both therapeutic vaccination and direct immune modulation. In gene-editing applications, mRNA can encode programmable nucleases or other editing components, allowing transient production of genome-editing proteins while avoiding prolonged expression from DNA-based vectors. This transient expression is particularly attractive for reducing the duration of nuclease activity and potentially limiting unwanted genomic alterations. Similar principles support protein-replacement strategies in which mRNA temporarily supplies proteins that are deficient because of inherited or acquired disorders.

Zhang et al. (2023) demonstrated that lipid-based delivery systems encompass a broader technological family than conventional LNPs. Liposomes, lipid-like nanoparticles, solid lipid nanoparticles, lipid-polymer hybrid nanoparticles, nanoemulsions, exosomes and lipoprotein-associated systems have all been investigated for RNA delivery. These platforms differ in structure, loading mechanisms, stability and biological interactions. Liposomes can provide a relatively flexible lipid bilayer architecture, whereas lipid-polymer hybrids combine the biological compatibility of lipid components with the structural and functional versatility of polymers. Extracellular vesicles provide a biologically derived alternative with potentially favourable biocompatibility and endogenous targeting characteristics. However, challenges related to loading efficiency, production consistency, purification and large-scale manufacturing continue to limit some alternative systems. Consequently, although LNPs currently dominate clinical translation, alternative nanocarriers remain important for overcoming delivery barriers that conventional LNPs cannot adequately address.

Rybakova et al. (2021) examined the role of formulation parameters in determining the biological performance of mRNA-LNP systems and highlighted the importance of particle size, surface properties, lipid composition and mRNA-to-lipid ratio. Nanoparticle characteristics influence circulation, protein adsorption, cellular uptake and intracellular trafficking. Particle formation is frequently performed using rapid mixing or microfluidic approaches, which allow controlled interaction between the aqueous mRNA phase and lipid-containing organic phase. Microfluidic production has contributed to improved reproducibility and scalability by providing controlled mixing conditions and relatively uniform particle characteristics. Nevertheless, scaling laboratory formulations to industrial manufacturing introduces

additional considerations involving raw-material quality, process control, encapsulation consistency, sterile processing, storage and stability. Thus, formulation optimisation must consider both biological performance and manufacturability.

Paunovska et al. (2022) demonstrated that the biological fate of RNA nanoparticles is strongly influenced by their physicochemical composition and interactions with the host environment. Following systemic administration, nanoparticles encounter serum proteins that can modify their biological identity and influence tissue distribution. Many conventional LNPs preferentially accumulate in the liver, where they can efficiently deliver nucleic acids to hepatocytes. Although hepatic delivery is advantageous for several metabolic and genetic disorders, it restricts applications requiring expression in tissues such as the lungs, heart, brain or skeletal muscle. The development of tissue-selective nanoparticles has therefore become a major objective in mRNA nanomedicine. Importantly, tissue targeting cannot be attributed exclusively to surface ligands; lipid composition, particle morphology, protein adsorption and route of administration can all contribute to biodistribution.

Cheng et al. (2020) provided important evidence that rational lipid design can alter the tissue distribution of RNA-loaded nanoparticles, supporting the concept of selective organ targeting. Their work demonstrated that changes in lipid structure can redirect nanoparticles towards organs beyond the liver, providing an alternative to conventional ligand-mediated targeting. This approach is particularly significant because many systemic nanoparticles exhibit predictable hepatic accumulation as a consequence of their interaction with serum proteins and the mononuclear phagocyte system. Selective organ targeting therefore represents a potentially scalable strategy in which the chemical structure of the carrier itself determines biodistribution. Such developments are important for mRNA therapeutics requiring expression in extrahepatic tissues and illustrate how nanocarrier chemistry can be used to influence biological fate.

Kon et al. (2023) focused specifically on the potential of mRNA-LNP systems for cancer treatment and highlighted the increasing interest in targeted oncology applications. Cancer therapy presents distinctive delivery challenges because tumour tissue is heterogeneous and is characterised by abnormal vasculature, variable extracellular matrix composition and immunosuppressive microenvironments. LNPs can potentially be engineered to deliver mRNA encoding tumour antigens, immune-stimulatory cytokines or other therapeutic proteins. Surface modification with targeting ligands may further improve interaction with selected tumour or immune-cell populations. However, the translation of targeting concepts from animal models to humans remains challenging because receptor expression, tumour architecture and nanoparticle transport can differ substantially between experimental models and patients. Consequently, effective cancer mRNA delivery requires consideration of both nanoparticle design and the complex biological characteristics of individual tumours.

Patel et al. (2024) identified endosomal escape as one of the principal intracellular barriers limiting the efficiency of mRNA nanocarriers. Cellular uptake alone does not guarantee productive delivery because internalised nanoparticles may remain within endosomal compartments and subsequently undergo degradation. Ionisable lipids are particularly important in this context because protonation under acidic endosomal conditions can promote membrane destabilisation. Nevertheless, only a fraction of internalised mRNA may ultimately reach the cytoplasm, meaning that improvements in endosomal escape can substantially influence functional potency. Current research therefore investigates lipids and auxiliary materials capable of increasing membrane disruption while maintaining acceptable toxicity. The challenge is to achieve sufficient endosomal membrane interaction for productive mRNA release without producing extensive cellular membrane damage or inflammatory responses.

Karmacharya et al. (2022) reported that lipid-based mRNA systems have considerable potential in cancer immunotherapy but also emphasised the continuing difficulties associated with extracellular degradation, endosomal entrapment and efficient tumour delivery. Surface functionalisation with antibodies, peptides or other targeting agents may improve cellular specificity, while changes in lipid composition can modify uptake and intracellular trafficking. Nevertheless, the addition of targeting ligands can increase formulation complexity and may influence stability, immunogenicity and manufacturing reproducibility. The therapeutic value of active targeting therefore depends on whether the targeting ligand produces a

meaningful improvement in functional intracellular delivery rather than merely increasing nanoparticle binding to a particular cell type. This distinction is important when evaluating targeted mRNA systems because cellular association and cytoplasmic protein expression are not necessarily equivalent outcomes. Riley et al. (2024) emphasised that successful mRNA delivery should be evaluated as a multistage process rather than through isolated measurements of encapsulation efficiency or cellular uptake. A therapeutically effective nanoparticle must survive administration, distribute to the desired tissue, interact with the appropriate cells, undergo internalisation, escape intracellular vesicles and release intact mRNA in the cytoplasm. Each stage can represent a separate bottleneck, and optimisation of one stage may adversely affect another. For example, increasing nanoparticle stability may improve circulation but potentially reduce intracellular release, while increasing membrane-disruptive activity may improve expression at the expense of tolerability. This systems-level perspective has encouraged researchers to combine material science, pharmacokinetics, intracellular trafficking studies and quantitative imaging to understand nanoparticle behaviour more comprehensively.

Yang et al. (2022) further indicated that the next generation of mRNA delivery systems is likely to depend on improved targeting, biodegradable materials and more precise control of intracellular release. The field is increasingly moving towards multifunctional carriers capable of integrating several functions within a single formulation. These may include tissue targeting, controlled release, enhanced endosomal escape and protection from immune recognition. Advances in microfluidic manufacturing and high-throughput screening are also accelerating the discovery of new lipid structures and formulation combinations. Such approaches may help address the current limitations of conventional LNPs while maintaining the scalability that has contributed to their clinical success.

Hariri et al. (2025) highlighted the continued evolution of LNP technology towards more sophisticated formulations with improved safety, stability, targeting and therapeutic performance. Recent developments increasingly focus on overcoming the limitations revealed through clinical experience, including storage requirements, immunogenicity, repeat-dose administration and tissue-selective delivery. The expansion of mRNA applications into therapeutic vaccination, oncology, gene editing and protein replacement requires delivery systems that are more adaptable than those developed primarily for infectious-disease vaccination. In this context, the future development of mRNA nanomedicine is likely to depend on coordinated optimisation of mRNA chemistry, lipid composition, nanoparticle architecture, targeting mechanisms and manufacturing processes. The literature from 2015–2025 consequently demonstrates a transition from proof-of-concept mRNA delivery towards increasingly rational, clinically oriented and application-specific nanocarrier engineering.

Author(s)	Year	Primary focus	Major contribution	Identified limitation/gap	Relevance to present review
Karikó et al.	2015	Modified mRNA	Established the importance of nucleoside modification for reducing innate immune activation and improving translation	RNA modification alone cannot overcome extracellular and intracellular delivery barriers	Provides the molecular foundation for therapeutic mRNA
Cullis & Hope	2017	Lipid nanoparticles	Established the importance of ionisable lipid technology for efficient nucleic-acid delivery	Conventional systems may show limited tissue selectivity	Supports the development of modern LNP platforms
Kulkarni et al.	2019	Ionisable lipid chemistry	Demonstrated that lipid molecular structure strongly	Optimal lipid structures remain	Supports rational LNP design

			affects RNA delivery performance	application-dependent	
Cheng et al.	2020	Selective organ targeting	Demonstrated that lipid structure can influence organ-specific RNA delivery	Extrahepatic targeting remains challenging	Provides evidence for chemical approaches to tissue targeting
Rybakova et al.	2021	LNP formulation	Highlighted the influence of particle characteristics and formulation parameters on mRNA delivery	Manufacturing and formulation optimisation remain complex	Supports formulation and process optimisation
Chaudhary et al.	2021	mRNA vaccines	Demonstrated the clinical relevance of LNP-mediated mRNA delivery through vaccine development	Vaccine-oriented delivery does not automatically translate to systemic therapeutic applications	Establishes clinical validation of the platform
Hou et al.	2021	mRNA-LNP technology	Reviewed LNP composition, mechanisms and therapeutic applications	Hepatic accumulation, stability and tolerability remain important concerns	Provides a comprehensive basis for LNP technology
Karmacharya et al.	2022	Cancer mRNA delivery	Examined lipid-based systems for cancer immunotherapy and targeted delivery	Tumour heterogeneity and inefficient tumour penetration limit translation	Supports oncology applications
Paunovska et al.	2022	Nanoparticle biodistribution	Demonstrated the importance of nanoparticle physicochemical properties in determining biological fate	Predictable delivery to non-hepatic tissues remains difficult	Supports analysis of biodistribution and targeting
Yang et al.	2022	Therapeutic mRNA delivery	Examined applications across vaccines, cancer, protein replacement and gene editing	Delivery efficiency and tissue specificity remain major barriers	Demonstrates the expanding therapeutic scope
Kon et al.	2023	Cancer-targeted LNPs	Highlighted targeted LNP approaches for tumour and	Translation from animal models to humans remains uncertain	Supports active targeting strategies

			immune-cell delivery		
Zhang et al.	2023	Alternative nanocarriers	Examined liposomes, hybrid nanoparticles, extracellular vesicles and related systems	Loading efficiency, reproducibility and scalability remain limitations	Enables comparison between LNPs and emerging carriers
Patel et al.	2024	Endosomal escape	Identified intracellular release as a critical bottleneck in functional mRNA delivery	Improving escape without increasing toxicity remains difficult	Supports mechanistic analysis of intracellular delivery
Riley et al.	2024	Delivery cascade	Emphasised the importance of evaluating tissue distribution, uptake, trafficking and cytosolic release collectively	Simultaneous optimisation of all delivery stages remains challenging	Provides an integrated framework for evaluating delivery systems
Hariri et al.	2025	Next-generation LNPs	Highlighted advances in safety, stability, targeting and therapeutic performance	Repeat dosing, manufacturing, stability and extrahepatic delivery remain unresolved	Establishes the current direction of mRNA nanomedicine

Methodology

This review-based research paper adopts a narrative literature review methodology to critically examine advances in mRNA delivery systems published between 2015 and 2025. Relevant peer-reviewed literature was identified primarily through Google Scholar and scholarly biomedical databases using combinations of keywords including “mRNA delivery systems”, “lipid nanoparticles”, “mRNA nanocarriers”, “targeted mRNA delivery”, “ionisable lipids”, “endosomal escape”, “selective organ targeting” and “therapeutic mRNA”. Studies were selected according to their relevance to the development, optimisation, targeting and therapeutic application of mRNA delivery technologies.

The review included original research articles, systematic and narrative reviews, and clinically relevant studies published within the specified period. Particular emphasis was placed on research addressing LNP composition, ionisable lipid chemistry, alternative nanocarriers, biodistribution, cellular uptake, endosomal escape, tissue-specific targeting and therapeutic applications. Literature concerning mRNA vaccines, cancer immunotherapy, protein replacement and gene-editing applications was also incorporated where delivery technology represented a substantial component of the investigation.

The retrieved literature was critically analysed thematically rather than quantitatively pooled. Studies were compared according to delivery platform, targeting mechanism, therapeutic application, principal advantages, limitations and translational relevance. Greater emphasis was given to recent studies demonstrating technological advancement and clinically relevant outcomes. The analysis was subsequently organised around three major themes: mRNA delivery systems and nanocarrier technologies; targeting strategies and biological barriers; and therapeutic applications and translational challenges. This approach enabled comparison of established LNP platforms with emerging nanocarriers while identifying persistent research gaps related to extrahepatic delivery, safety, stability, endosomal escape, manufacturing and clinical translation.

Comparative Performance of LNPs and Emerging mRNA Nanocarriers

Hou et al. (2021) demonstrated that lipid nanoparticles have become the most extensively developed delivery platform for therapeutic mRNA because they combine efficient encapsulation, protection against enzymatic degradation and intracellular delivery. The present review indicates that the principal advantage of LNPs lies in the complementary function of their components, particularly ionisable lipids, cholesterol, phospholipids and PEGylated lipids. Ionisable lipids facilitate mRNA association during formulation and contribute to endosomal escape following cellular uptake, while the remaining components regulate particle structure, stability and pharmacokinetic behaviour. Kulkarni et al. (2019) showed that modifications to ionisable lipid architecture can substantially influence delivery potency, supporting the development of structure–activity relationships for next-generation LNPs.

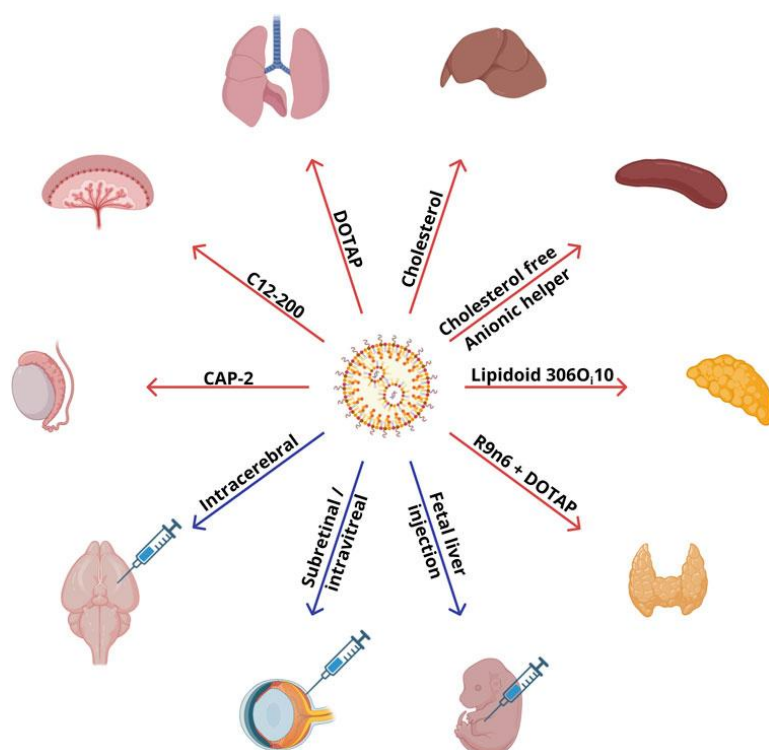
Rybakova et al. (2021) indicated that particle size, lipid composition, encapsulation efficiency and manufacturing conditions collectively influence mRNA expression. These findings suggest that formulation performance cannot be assessed using a single parameter. Alternative systems, including polymeric nanoparticles, lipid–polymer hybrids and extracellular vesicles, provide additional opportunities for improving stability, targeting and biological compatibility. However, Zhang et al. (2023) indicated that these emerging systems still face challenges concerning reproducible mRNA loading, scalable manufacture and consistency between batches. Consequently, LNPs retain a substantial translational advantage despite their limitations.

Chaudhary et al. (2021) demonstrated the clinical maturity of LNP technology through mRNA vaccine development, whereas Yang et al. (2022) showed that the platform is increasingly applicable to gene editing, cancer therapy and protein replacement. The comparative evidence therefore suggests that conventional LNPs currently provide the strongest combination of efficacy and manufacturing feasibility, while alternative nanocarriers may become increasingly valuable where tissue-specific delivery or specialised intracellular behaviour is required.

Delivery platform	Delivery efficiency	Targeting potential	Manufacturing maturity	Principal limitation
Conventional LNPs	High	Moderate	Very high	Predominantly hepatic distribution
Ionisable lipid LNPs	High	Moderate–high	High	Lipid-dependent toxicity and optimisation
Polymeric nanoparticles	Moderate–high	High	Moderate	Potential toxicity and formulation complexity
Lipid–polymer hybrids	High	High	Moderate	More complex manufacturing
Extracellular vesicles	Variable	Potentially high	Low–moderate	Loading and scalability
Peptide-based systems	Moderate	High	Moderate	Stability and immunogenicity concerns

Advances in Targeted mRNA Delivery and Overcoming Biological Barriers

Paunovska et al. (2022) demonstrated that nanoparticle composition strongly influences biodistribution and biological fate, highlighting a major limitation of conventional systemic mRNA delivery. Many LNP formulations exhibit substantial hepatic accumulation, which is therapeutically useful for liver-associated diseases but restricts applications involving the lungs, heart, brain, skeletal muscle and other extrahepatic tissues. Cheng et al. (2020) provided important evidence that selective organ targeting can be achieved through rational modification of lipid structures. This finding is particularly significant because it demonstrates that tissue distribution can potentially be manipulated through the carrier itself rather than relying exclusively on externally attached targeting ligands.



Kon et al. (2023) showed that active targeting approaches are particularly relevant to cancer applications, where antibodies, peptides and receptor-binding molecules may improve interactions with tumour or immune-cell populations. However, targeted delivery remains dependent on receptor availability, tumour heterogeneity and nanoparticle penetration. Increasing surface targeting does not necessarily result in greater cytoplasmic mRNA expression because nanoparticles must still undergo internalisation, intracellular trafficking and endosomal escape.

Patel et al. (2024) identified endosomal escape as a critical bottleneck following cellular uptake. This finding indicates that improving delivery requires optimisation of the entire intracellular pathway rather than simply increasing nanoparticle internalisation. Riley et al. (2024) similarly emphasised that tissue distribution, cellular uptake, endosomal escape and cytoplasmic release represent interconnected stages of the delivery process. Excessive membrane-disruptive activity may increase expression but can simultaneously compromise cellular viability and tolerability. Therefore, the most effective targeting strategy is not necessarily the one that produces the greatest cellular uptake, but the one that produces efficient functional mRNA expression at an acceptable safety level.

Biological barrier	Effect on mRNA delivery	Current strategy	Remaining challenge
Extracellular RNase degradation	mRNA degradation before cellular uptake	Nanoparticle encapsulation	Maintaining protection during circulation
Rapid clearance	Reduced exposure at target tissue	Surface and lipid optimisation	Prolonged and predictable circulation
Non-specific biodistribution	Reduced target-tissue delivery	Selective organ targeting	Reliable extrahepatic distribution
Cellular membrane	Limits mRNA entry	Nanoparticle-mediated uptake	Cell-specific internalisation
Endosomal entrapment	Prevents cytoplasmic release	Ionisable and membrane-active lipids	Efficient escape without toxicity
Immune recognition	Inflammation and reduced translation	Modified nucleosides and optimised formulations	Safe repeat administration
Tissue heterogeneity	Variable delivery efficiency	Ligand-mediated targeting	Consistent human translation

Therapeutic Applications, Clinical Translation and Future Development of mRNA Delivery Systems

Chaudhary et al. (2021) established mRNA-LNP vaccination as a major demonstration of clinical translation, showing that transient mRNA expression can generate therapeutically meaningful biological responses in humans. The success of this approach has subsequently encouraged investigation of mRNA delivery for applications extending beyond infectious diseases. Yang et al. (2022) identified cancer immunotherapy, protein replacement and gene editing among the principal emerging applications. In cancer, mRNA can encode tumour antigens, cytokines or immune-modulating proteins, while in gene editing it can provide transient expression of genome-editing machinery. This transient activity offers a potential safety advantage over persistent expression systems.

Karmacharya et al. (2022) reported considerable potential for lipid-based mRNA systems in cancer immunotherapy, although tumour penetration and cellular specificity remain significant challenges. The therapeutic requirements also vary considerably between diseases. Hepatocyte delivery may be sufficient for certain inherited metabolic disorders, whereas successful treatment of neurological or muscular diseases requires efficient extrahepatic and potentially tissue-specific transport. Consequently, a single universal mRNA carrier is unlikely to satisfy all therapeutic requirements.

Hariri et al. (2025) highlighted the continuing evolution of LNPs towards improved stability, safety, targeting and therapeutic versatility. The literature indicates that future development will increasingly depend on biodegradable ionisable lipids, organ-selective formulations, multifunctional carriers and improved manufacturing technologies. Repeat-dose administration represents another important consideration because many chronic diseases may require repeated mRNA treatment rather than a single administration. Long-term tolerability, immune responses, storage stability and manufacturing consistency therefore remain central translational considerations.

Overall, the results demonstrate a transition from first-generation mRNA delivery towards application-specific nanocarriers. LNPs currently provide the strongest clinical foundation, whereas emerging carriers and targeting strategies offer opportunities to overcome tissue-specific limitations. The future direction of the field is consequently likely to involve integration of RNA engineering, lipid chemistry, targeting biology and precision formulation rather than reliance on any single delivery technology.

Therapeutic application	mRNA function	Preferred delivery requirement	Current development status
Vaccination	Encodes antigen	Efficient immune-cell exposure	Clinically validated
Cancer immunotherapy	Encodes tumour antigens or immune modulators	Tumour/immune-cell targeting	Advanced preclinical and clinical development
Protein replacement	Encodes deficient therapeutic protein	Sustained tissue-specific expression	Active clinical development
Gene editing	Encodes editing proteins	Controlled intracellular delivery	Rapidly developing
Regenerative medicine	Encodes growth or repair factors	Localised tissue delivery	Mainly experimental
Genetic/metabolic disorders	Restores functional protein production	Organ-selective delivery	Increasing translational interest
Cardiovascular applications	Encodes therapeutic or regenerative proteins	Cardiac/vascular targeting	Predominantly preclinical
Neurological applications	Encodes therapeutic proteins	Blood-brain barrier penetration	Major unresolved challenge

Conclusion

The present review demonstrates that mRNA delivery has progressed substantially between 2015 and 2025, moving from experimental nucleic-acid delivery towards clinically relevant nanomedicine

platforms. Lipid nanoparticles have emerged as the most established delivery technology because of their efficient mRNA encapsulation, protection, cellular uptake and capacity to facilitate cytoplasmic release. The clinical success of LNP-based mRNA vaccines has provided strong validation of this platform and accelerated research into applications extending beyond infectious diseases. At the same time, the literature demonstrates that conventional LNPs remain limited by hepatic accumulation, endosomal entrapment, inflammatory responses, formulation stability and challenges associated with repeated administration.

Recent advances in ionisable lipid chemistry, selective organ targeting, ligand-mediated targeting and alternative nanocarriers are addressing several of these limitations. Polymeric nanoparticles, lipid-polymer hybrids, peptide-based carriers and extracellular vesicles provide additional opportunities for improving tissue specificity and intracellular delivery, although their clinical maturity remains below that of LNPs. The evidence further indicates that successful mRNA delivery depends on the coordinated optimisation of multiple stages, including biodistribution, cellular uptake, endosomal escape and cytoplasmic translation rather than on encapsulation efficiency alone.

Therapeutically, mRNA delivery is expanding into cancer immunotherapy, protein replacement, gene editing, regenerative medicine and genetic disorders. Future progress will depend on developing safer biodegradable materials, improving extrahepatic targeting, achieving reproducible large-scale manufacturing and addressing stability and repeat-dose requirements. Overall, mRNA nanomedicine is moving towards increasingly precise, tissue-specific and application-oriented delivery systems, positioning advanced nanocarriers as an important foundation for the next generation of mRNA therapeutics.

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