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REVIEW

Key Clinical Frontiers of mRNA Loaded Lipid Nanoparticles in Cancer Vaccines

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Abstract: Cancer vaccines are promising, but clinical translation is constrained by inefficient antigen delivery and suboptimal immune activation. Lipid nanoparticles (LNPs)-validated for potency and safety in COVID-19 mRNA vaccines-offer a versatile, scalable, and immunogenic platform. Key barriers persist: precise targeting of tumors or lymphoid tissues, efficient intracellular mRNA release, and the immunosuppressive tumor microenvironment. This review synthesizes design principles for mRNA-loaded LNPs, emphasizing lipid chemistry, organ-selective biodistribution, and nano-engineering strategies that strengthen antigen presentation and T-cell priming. We also examine combination approaches with checkpoint blockade, chemotherapy-induced immunogenic cell death, and molecular adjuvants. Clinically, signals of efficacy are emerging-most notably the KEYNOTE-942 study, in which mRNA-4157 combined with pembrolizumab showed a sustained improvement in recurrence-free survival at 5 years compared with pembrolizumab alone-highlighting both the potential and the remaining questions for this modality. Finally, we outline manufacturing and regulatory considerations and map future directions-including thermostable formulations, self-amplifying RNA, and AI-guided lipid discovery-to address translational bottlenecks and expand global access to LNP-based cancer vaccines.

Keywords: lipid nanoparticles, mRNA cancer vaccines, organ-selective delivery, immunotherapy, nanomedicine

Introduction

Over recent years, messenger RNA (mRNA) vaccines formulated in lipid nanoparticles (LNPs) have progressed from an experimental niche to a public-health mainstay.[1–3] Following emergency authorizations of BNT162b2 and mRNA-1273 in late 2020,[4–6] more than 13 billion COVID-19 doses have been administered globally, establishing an unmatched real-world record for safety and manufacturability.[7–9] This deployment validated three defining attributes of the mRNA–LNP platform: (i) rapid, cell-free synthesis that compresses antigen-design timelines from months to days;[10–12] (ii) potent yet transient protein expression that mitigates genomic-integration risk;[13,14] and (iii) an ionizable-lipid carrier that shields polyanionic RNA, enables endosomal escape,[15,16] and is compatible with multi-billion-dose cGMP production.

The same agility is now being directed at one of oncology's most stubborn challenges patient-specific tumour heterogeneity.[17,18] mRNA can be algorithmically tailored to each individual's neoantigen repertoire, and LNPs deliver these blueprints to antigen-presenting cells (APCs), effectively turning the patient into an on-site bioreactor.[19,20] Clinical momentum is mounting. In 2024, the randomized phase-2 KEYNOTE-942 trial reported a 2.5-year recurrence-free survival of 74.8% for mRNA-4157 plus pembrolizumab versus 55.6% for pembrolizumab alone (hazard ratio ≈ 0.51) in resected stage III/IV melanoma.[21–24] Soon after, a Nature report on autogene cevumeran-an LNP-formatted poly-neoantigen vaccine for pancreatic ductal adenocarcinoma-showed that ~50% of recipients mounted durable CD8+ T-cell responses correlating with prolonged disease-free survival (median 13.4 months among responders).[25–28] As of June 2024, >70 active interventional trials are evaluating mRNA-based cancer vaccines, the majority employing LNP delivery.

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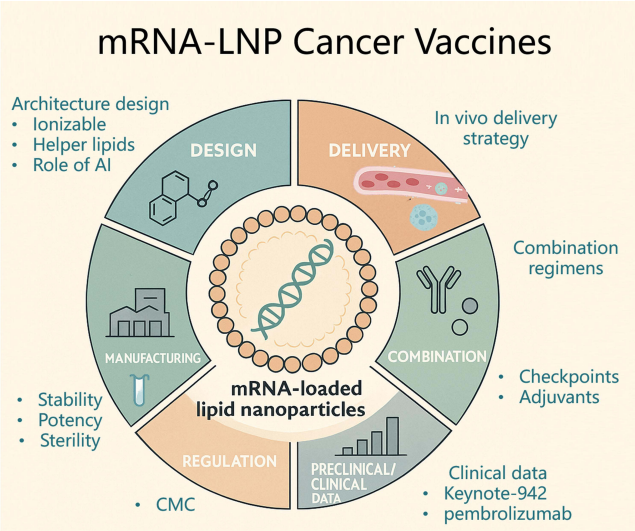
Graphical Abstract



While nucleoside chemistry and sequence engineering dictate transcript stability and translational yield, in vivo expression ultimately depends on the physicochemical orchestration of the LNP.[29,30] Ionizable lipids such as ALC-0315 and SM-102 become protonated primarily within the acidic endosome,[31,32] enabling tight RNA complexation during formulation yet minimizing systemic toxicity at physiological pH. Helper phospholipids and cholesterol stabilize non-bilayer (inverted-hexagonal) phases that facilitate endosomal destabilization and escape,[33,34] whereas PEG-lipids tune colloidal stability and circulation half-life. Iterative optimization of this four-component lattice has yielded third-generation ionizable lipids with enhanced biodegradability and lymph-node tropism-attributes expected to be pivotal for therapeutic cancer vaccination, where efficient dendritic-cell engagement is essential.[35,36]

Translating the infectious-disease success of mRNA-LNPs to solid tumours introduces discrete biological and logistical challenges. First, the immunosuppressive tumour microenvironment excludes effector T cells and up-regulates inhibitory checkpoints, motivating rational combinations with PD-1/PD-L1 or CTLA-4 blockade.[37,38] Second, therapeutic vaccines must prime robust, polyclonal CD4+ and CD8+ responses capable of infiltrating heterogeneous lesions, whereas prophylactic vaccines can rely more heavily on systemic antibody immunity.[39] Third, products demand an end-to-end manufacturing cycle of $\leq$ 6 weeks-from tumour sequencing and neoantigen prediction to mRNA synthesis and sterile LNP encapsulation.[40] Finally, regulatory frameworks adapted during the pandemic must be reconciled with a batch-to-patient paradigm, raising issues around potency assays, release testing, and comparability.[41] Personalized cancer vaccines encode a patient's private set of tumor neoantigens and deliver them as an mRNA payload in lipid nanoparticles (LNPs) to professional antigen-presenting cells. Upstream, contemporary neoantigen discovery couples matched tumor–normal sequencing and HLA typing with state-of-the-art prediction frameworks-pan-allelic peptide MHC binders (NetMHCpan and related deep models), peptide processing/transport predictors (MHCflurry, NetChop/NetCTLpan), and learning-based T-cell immunogenicity classifiers (HLAthena, PRIME/DeepImmuno)-increasingly calibrated with immunopeptidomics (eluted-ligand mass spectrometry), clonality filters, and uncertainty quantification.[42] These advances reduce false positives, compress design-to-dose timelines, and yield shorter, higher-quality epitope sets, which in turn facilitate efficient mRNA design and cGMP production. Downstream, the success of personalization is inseparable from LNP engineering: ionizable-lipid structure–activity relationships, helper-lipid ratios, PEG-lipid kinetics, and microfluidic mixing govern organ and APC tropism, encapsulation efficiency, and endosomal

escape, while route of administration (i.m./s.c./i.v./intranodal) and intrinsic/added adjuvanticity shape cross-presentation and T-cell priming.[43]

Against this backdrop, this review offers a critical appraisal of mRNA-loaded lipid nanoparticles as enabling vectors for cancer vaccination. We synthesize current design principles for mRNA–LNP vaccines, emphasizing the structure–activity relationships of ionizable lipids and process parameters relevant to scalable, cGMP-compliant manufacture. We then delineate major bottlenecks across the delivery cascade-from systemic pharmacokinetics and tissue distribution to cellular uptake, endosomal escape, and cytosolic trafficking-and survey emerging nanotechnologies intended to address these constraints. Representative preclinical and clinical findings reported through mid-2025, including KEYNOTE-942 and studies of autogene cevumeran, are summarized to illustrate both the promise and the current limitations of the modality. Finally, we consider practical issues of manufacturing, regulatory evaluation, and equitable access, and outline future directions such as self-amplifying RNA formats and computational/AI-guided lipid design. Collectively, these insights aim to equip investigators, clinicians, and translational stakeholders with an integrated framework for navigating the evolving interface among mRNA engineering, nanomedicine, and precision oncology.

What Do We Understand About mRNA-Loaded Lipid Nanoparticles Vaccines?

Architecture and Design Framework

Ionizable lipids (ILs) are generally engineered with a modular "head–linker–tail" architecture comprising an ionizable amine headgroup, a conformationally flexible linker, and one or more hydrophobic tails (Figure 1).[44] This layout decouples key design knobs-protonation behavior, membrane fusion propensity, hydrophobic packing, and degradability-so that each can be tuned without unduly perturbing the others. In practice, the headgroup dictates endosomal protonation and electrostatic complexation with polyanionic RNA; the linker modulates molecular mobility, hydrolytic or enzymatic lability, and overall packing; and the tails control bilayer insertion, non-bilayer phase formation, and interactions with helper lipids. Together, these features determine particle assembly, endosomal escape, and in vivo tolerability, providing a rational scaffold for structure–activity exploration in mRNA–LNP design.

Figure 1 illustrates the Silicon sCAlable Lipid nAnoparticle geneRation (SCALAR) platform, a microfluidics-based system developed for the controlled synthesis of mRNA-loaded LNPs. The device integrates replicated mixer arrays on a silicon chip to deliver rapid and reproducible formulation under well-defined hydrodynamic conditions (Figure 1A). Two inlet streams-an aqueous phase carrying the mRNA payload and an ethanolic lipid phase containing the ionizable lipid, cholesterol, helper phospholipid, and PEG-lipid-converge within microscale junctions that promote intense convective mixing. By tightly regulating nucleation and growth in a confined flow regime, the platform enables uniform nanoparticle self-assembly with consistent hydrodynamic diameter, low polydispersity, and high encapsulation efficiency-critical attributes for pharmacokinetic predictability and cGMP release.

Throughput scalability is achieved by parallel replication of the mixing units (Figure 1B). The SCALAR 1× configuration (1 mm chip) supports low-volume screening and early formulation development, yielding ~0.07 L h^{-1} of LNP suspension. The SCALAR 10× variant (5 mm) enables intermediate output suitable for in vivo preclinical studies at ~0.72 L h^{-1}. For clinical or industrial contexts, the SCALAR 256× chip (10 mm) reaches ~17 L h^{-1}, corresponding to ~8.5 g RNA h^{-1} processed, while preserving particle attributes established at smaller scales. Because scale-up relies on numbering-up rather than fluidic geometry changes, transitions from laboratory prototyping to clinical-grade manufacturing can proceed without major reformulation or process re-validation. This modular scaling strategy addresses a longstanding bottleneck in mRNA vaccines and therapeutics, where batch size, turnaround time, and lot-to-lot comparability are decisive. More broadly, SCALAR exemplifies how microfluidic design can be purpose-built for both precision and manufacturability in RNA nanomedicine workflows, coupling fine control of assembly kinetics with the practical demands of robust, high-throughput production.

This modularity enables systematic interrogation of structure–activity relationships, aiming to balance pKa,[45] membrane-fusion propensity,[46] and biodegradability.[47] Although empirical screening has yielded notable gains, recent efforts increasingly adopt rational, combinatorial design strategies that allow coordinated tuning of multiple

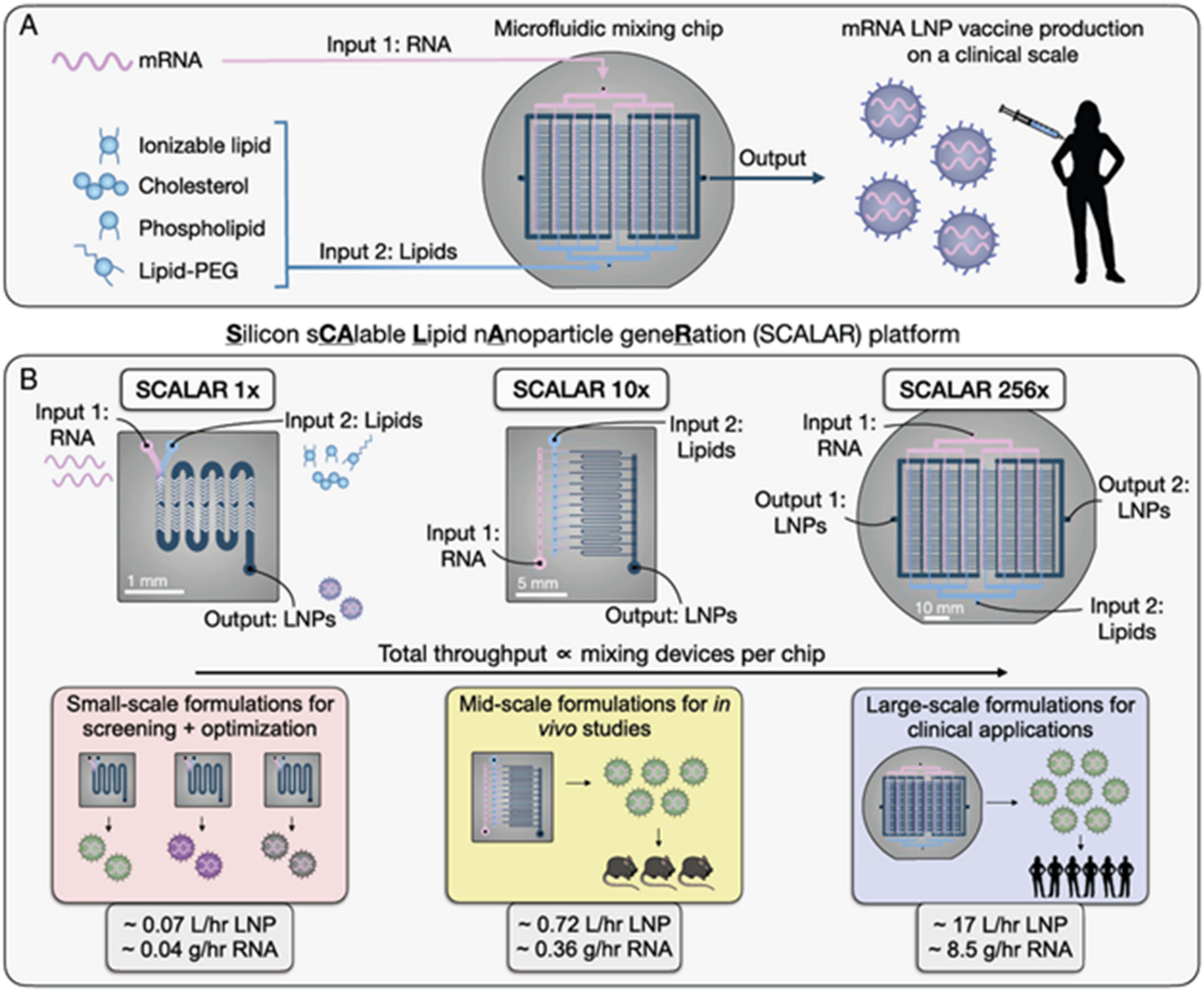


Figure 1 Design and scalability of the SCALAR microfluidic platform for mRNA–lipid nanoparticle formulation. (**A**) Diagram illustrating the basic configuration of the SCALAR system, which enables controlled mixing of mRNA and lipid components via a parallelized microfluidic chip for LNP synthesis. Input channels for RNA and lipid mixtures converge within silicon-based mixer arrays to produce uniform LNPs suitable for clinical-scale applications. (**B**) Comparison of three throughput levels within the SCALAR platform-SCALAR 1×, 10×, and 256×-differing in chip size and number of integrated mixing units. These configurations support a broad range of formulation needs, from low-volume screening (~0.07 L/hr LNP) and preclinical studies (~0.72 L/hr), to high-volume manufacturing (~17 L/hr), depending on the required output and application scale. Reproduced with permission from ref.[44] Copyright 2023 PNAS.

physicochemical parameters. A frequently cited functional window for the head-group pKa of ionizable lipids is ~6.2–6.6.[48,49] Within this range, protonation under endosomal acidity promotes membrane destabilization and escape, while near-neutral charge at physiological pH mitigates systemic toxicity.[50,51] Cross-comparisons among established lipids-MC3, ALC-0315, and SM-102-indicate that deviations from this window often correlate with diminished in vivo transfection and higher off-target effects.[52] Tail geometry and saturation further determine phase behavior essential for endosomal release.[53,54] Multibranched, unsaturated tails-as in SM-102 and ALC-0315-favor formation of inverted-hexagonal phases under acidic conditions, enhancing bilayer disruption and cytosolic delivery. By contrast, saturated or overly short tails suppress fusogenic transitions and compromise intracellular transport.

A major design tension in next-generation ionizable lipids lies in balancing biodegradability with transfection efficiency. Biodegradable lipids-typically incorporating ester, carbonate, acetal, or disulfide linkages-enable rapid hydrolysis and clearance after delivery, thereby mitigating hepatic accumulation and systemic toxicity observed with more persistent cationic materials. However, excessive degradability can compromise nanoparticle integrity before endosomal escape, leading to premature payload leakage or reduced cytosolic delivery. For example, lipids containing short-chain

ester linkers or multiple labile bonds exhibit favorable pharmacokinetics but often yield lower protein expression due to truncated endosomal residence and limited membrane fusion capacity. Conversely, more stable ionizable backbones enhance mRNA translation by sustaining protonation and endosomal buffering but risk prolonged retention in hepatocytes and Kupffer cells, raising concerns about chronic exposure and immunotoxicity.

Personalized Antigen Coding Strategy

Personalized antigen coding begins with a curated neoantigen set and then engineers a transcript that maximizes productive epitope release and presentation while remaining manufacturable as an mRNA–LNP drug product. In practice, most groups encode polyepitope "string-of-beads" constructs rather than full-length proteins, using rational spacers and flanking motifs to steer proteasomal cleavage and limit junctional neoepitopes; recent experiments show that spacer chemistry and placement (like alanine-rich linkers) can markedly increase MHC-I presentation of intended peptides and should be co-optimized with epitope order and length constraints. Trafficking fusions are used to bias the presentation pathway: N-terminal ubiquitin (or degron) tags accelerate cytosolic degradation to favor MHC-I cross-presentation, whereas signals such as LAMP1 route antigens to endo-lysosomal compartments to enhance MHC-II loading and CD4+ help-both strategies have been validated preclinically and are increasingly adapted to mRNA vaccines. Because epitope selection upstream is imperfect, contemporary pipelines pair coding design with improved prediction frameworks trained on immunopeptidomics (like ImmuneApp and other AI models), which better prioritize binders and reduce low-yield inserts; this allows tighter payloads that fit within favorable mRNA lengths for high encapsulation efficiency and translation in APCs. Where polyepitope density risks translational crowding, teams split payloads across two or more transcripts (co-formulated in the same LNP) or combine antigen mRNAs with separate "immuno-programming" mRNAs (TriMix/TetraMix) that mature dendritic cells and potentiate T-cell priming without elongating the antigen ORF. Finally, coding design should include guardrails for safety and quality: avoid glycosylation motifs that could mask epitopes, screen for off-target homology to the human proteome, minimize creation of strong neo-junctional peptides, and confirm that UTR/codon choices sustain expression in target APCs while meeting CMC limits on transcript length and GC content. Together, these strategies link algorithmic neoantigen discovery with translationally robust coding architectures that are compatible with LNP delivery and cGMP manufacturing, thereby improving the likelihood that individualized mRNA–LNP vaccines achieve sufficient epitope density in draining lymph nodes to drive durable CD8+/CD4+ responses.

Biodegradability and Safety

Next-generation ILs frequently embed biodegradable linkages-esters, carbonates, or acrylates-to accelerate metabolic clearance and limit hepatic accumulation.[47,55,56] These motifs improve tolerability in preclinical models, but over-rapid cleavage shortens intracellular residence time and diminishes transfection, indicating that degradation kinetics must be matched to indication, route, and dosing schedule.[57]

(1) Organ targeting and lipid-composition effects. Adjusting the molar ratios of IL, helper phospholipid, cholesterol, and PEG-lipid, as well as tuning head-group polarity, can shift biodistribution profiles.[58,59] Certain ILs with modified polar head groups exhibit extrahepatic enrichment (eg, lung, spleen, lymph nodes), a property that is particularly desirable for cancer vaccines that benefit from lymphoid targeting and dendritic-cell engagement.

(2) PEG-lipids and kinetic stability. PEGylated lipids improve colloidal stability, mitigate opsonization and protein-corona formation, and thereby extend circulation half-life.[35,60] Yet, excessive PEG surface density can impede cellular uptake and membrane fusion. Emerging evidence points to the desorption kinetics of PEG-lipids from the particle surface as a critical determinant of dendritic-cell transfection efficiency.[61] Thus, formulations must balance stealth and stability against endosomal access and uptake, selecting PEG chain length, anchor hydrophobicity, and mol% to achieve optimal performance.

How AI Plays a Role Advanced Vaccine Development?

Computational tools, including generative deep learning and high-throughput screening platforms,[62,63] are being increasingly used to accelerate ionizable lipid discovery. For example, platforms like AGILE and other graph-based design

models can generate hundreds of synthetically accessible IL candidates,[64,65] some of which have demonstrated favorable in vitro performance. Nevertheless, predictive accuracy and in vivo translation remain active areas of investigation.

Despite accelerating discovery, high-throughput screening-from in-vitro panels and organoids to in-vivo DNA-barcoded libraries-still exhibits limited predictive accuracy for clinical translation. First, context dependence causes performance ranks to invert across cell types, tissues, routes, and payload classes; here, AI/ML domain-adaptation models and multi-task learners help quantify when a hit identified in murine spleen or in a reporter assay is unlikely to generalize to human lymph-node APCs or antigen mRNA. Second, pooling artifacts (barcode–cargo interactions, variant competition) bias readouts; AI-based causal inference and deconvolution can flag nonphysical correlations and correct for library-composition effects. Third, most high-throughput screening endpoints are surrogates (uptake, biodistribution) that weakly correlate with functional antigen presentation; AI-guided assay design and representation learning on multi-omic/PAT signals (endosomal pH dynamics, translational kinetics) can prioritize variants with higher likelihood of eliciting T-cell priming. Fourth, scale-up nonidealities (mixer geometry, N/P drift, PEG-lipid desorption) degrade external validity; physics-informed ML "digital twins" linking process parameters to CQAs enable in-silico stress tests that down-select variants resilient to manufacturing changes. Fifth, species and microenvironment gaps undermine portability; AI-assisted cross-species translators and Bayesian hierarchical models can align distributions between murine and human datasets and propagate uncertainty to decision thresholds. Finally, the field lacks standardized references and calibrated uncertainty; embedding probabilistic AI with explicit epistemic/aleatoric intervals, plus active-learning loops that propose the most informative confirmatory experiments (single-variant validation in primary human APCs, functional antigen-presentation assays), helps convert high-throughput screening "hits" into reproducible in-vivo efficacy. Repeated use of AI-assisted tools-to diagnose bias, to predict out-of-domain failure, and to steer confirmatory experiments-provides a pragmatic path to bridge high-throughput screening results with translational performance in mRNA–LNP cancer vaccines.

What Enables Scalable, cGMP-Compliant Manufacturing?

Microfluidic Mixing and Scale-Up Potential

Rapid solvent-shift co-mixing of ethanolic lipids with aqueous RNA in microfluidic geometries-T-junctions and chaotic-advection (eg, herringbone) mixers-drives nucleation-limited self-assembly of ~100 nm LNPs with low polydispersity and high batch reproducibility.[66,67] Tight control of the flow-rate ratio, total flow rate, and solvent composition preserves critical quality attributes across runs. Modular, chip-based systems achieve industrially relevant throughputs by parallelization/numbering-up of mixer units, reaching 17 L h^{-1} while maintaining < 5% variation in particle size and polydispersity across scales.[44,68] These closed, scalable platforms provide a traceable route from research-scale prototyping to cGMP clinical production without major reformulation, thereby supporting robust comparability and technology transfer.

Low-Volume Prototyping and Preclinical Flexibility

Disposable, 3D-printed microfluidic mixers support flow rates of 1–10 mL min^{-1}, enabling rapid, iterative formulation screening with minimal material consumption.[43,69] Their plug-and-play format, compatibility with closed, single-use assemblies, and straightforward reconfiguration of channel geometries make them well suited to early-stage candidate selection, DoE studies (varying FRR/TFR, buffer, and lipid ratios), and small-animal dosing in preclinical settings.

Purification and Integrated Continuous Manufacturing

Tangential-flow filtration remains the standard for solvent exchange and removal of unencapsulated RNA, efficiently reducing residual ethanol and small-molecule impurities while concentrating product.[70,71] In-line process analytical technologies-including dynamic light scattering, turbidity/optical backscatter, and UV–vis spectrophotometry-are being deployed to provide real-time readouts of particle size, polydispersity, and encapsulation, enabling feedback control and deviation capture.[72]

Emerging continuous platforms (eg, DIANT[73]) aim to integrate nanoparticle formation, solvent exchange, and sterile fill–finish within closed isolator systems, reducing hold times and contamination risk. To meet regulatory expectations, these systems must demonstrate robustness to scale-up stressors-notably shear sensitivity of LNPs, thermal burden during solvent removal, and control of solvent residuals and bioburden-while preserving critical quality attributes and aseptic assurance.

Critical Quality Attributes (CQAs) and Release Testing

Industry practice has converged on a core CQA panel for mRNA–LNPs:[74,75] particle size, PDI, RNA encapsulation percentage, zeta potential, residual solvent, dsRNA content, endotoxin, and sterility. Additional program-specific CQAs may include osmolality, pH, nuclease impurities, and lipid identity/ratio. While real-time PAT provides trend monitoring and supports continued process verification, batch release remains anchored in offline characterization (DLS/EM, RiboGreen or dye-exclusion assays, GC for solvents, LC–MS for lipid composition) coupled with accelerated and long-term stability studies. Together, these controls establish comparability across scales and lots and underpin cGMP compliance.

Raw Materials and Supply Chain Challenges

Although medical-grade phospholipids and modified nucleotides are increasingly accessible, ionizable lipids remain concentrated under proprietary control and constrained by manufacturing capacity. Market analyzes project an ~19% compound annual growth rate (CAGR) for LNP production,[76] highlighting the need for sustained process intensification, diversified sourcing, and long-term supply agreements to secure reliable and cost-effective inputs. Risk-mitigation strategies include second-source qualification of critical lipids, adoption of modular/continuous unit operations to smooth demand surges, and implementation of traceable raw-material specs aligned with pharmacopeial standards.

Design and manufacture of mRNA–LNP cancer vaccines demand concurrent optimization at the molecular (lipid chemistry, RNA format, excipient ratios) and process (mixing, purification, fill–finish) levels.[77,78] Substantial progress has been made in elucidating structure–function relationships for ionizable lipids and in scaling platform technologies from lab to cGMP production.[79,80] Nevertheless, key variables remain under active refinement. Priority areas include: (i) tissue targeting beyond the liver and toward lymphoid organs; (ii) enhancement of in vivo translation efficiency while maintaining safety; and (iii) regulatory alignment for patient-specific products, encompassing comparability, potency assays, and real-time release paradigms. Addressing these gaps will require interdisciplinary collaboration across lipid chemistry, RNA engineering, bioprocessing, analytics, and regulatory science.

Deploying Nanotechnologies to Elevate in vivo Delivery

Productive expression in tumours or lymphoid tissues requires that LNPs negotiate a multistep cascade-from systemic pharmacokinetics to endosomal release. Following intravenous or intramuscular administration, particles are rapidly coated by a protein corona that governs opsonization, hepatic uptake via scavenger receptors, and-in a subset of formulations-complement activation–related pseudoallergy (CARPA). Contemporary clinical lipids bias delivery toward hepatocytes, rendering extrahepatic exposure limited and frequently stochastic. After cellular entry, typically <2% of the encoded mRNA reaches the cytosol; most cargo is routed to lysosomes or recycled to the plasma membrane, making endosomal escape a dominant bottleneck. In parallel, ionizable lipids and residual dsRNA can engage innate sensors (TLR4, TLR7/8, NLRP3), elevating reactogenicity at higher vaccine doses and further constraining tolerability. Collectively, these layered barriers compress the therapeutic window for systemically administered cancer vaccines.[33] Several complementary nanotechnological strategies have been proposed to mitigate these constraints. Selective-organ-targeting (SORT) LNPs incorporate a fifth "SORT" small-molecule lipid to re-direct biodistribution toward lung or spleen while maintaining formulation stoichiometry, and have recently been produced at clinical scale on the same microfluidic platforms used for conventional vaccines.[81]

A recent study[81] described a structure-guided strategy to engineer ionizable lipids with enhanced organ selectivity for mRNA delivery, particularly to lung and liver. Departing from conventional amine-headgroup cationic lipids, the authors constructed a degradable core–amine–tail library in which poly(ester) backbones (nAcx) were conjugated to variable

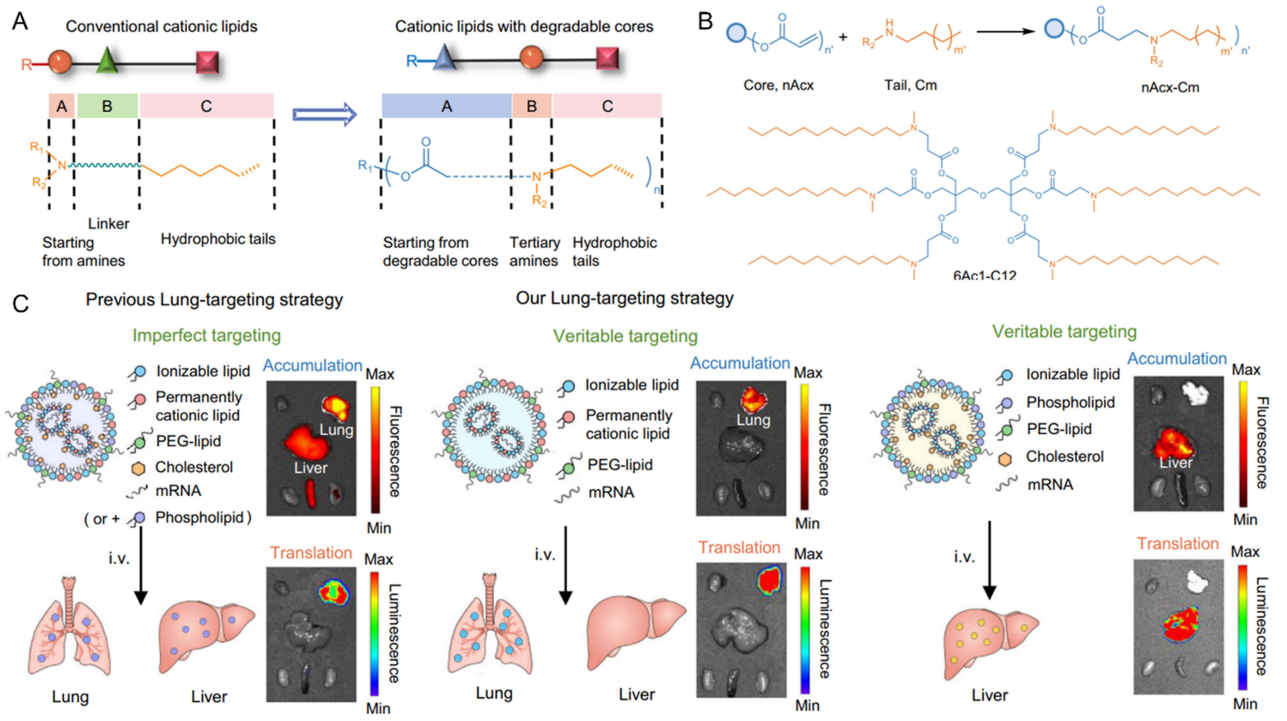


Figure 2 Structure-guided engineering of degradable ionizable lipids for organ-specific mRNA delivery. (**A**) Conceptual comparison between traditional cationic lipids synthesized from amine precursors and a redesigned class of degradable ester-based lipids assembled via modular core–linker–tail architectures. (**B**) Schematic of the Michael-type conjugation strategy used to couple poly(ester) cores (nAcx) with alkylated amine tails (Cm), yielding the nAcx-Cm lipid library. (**C**) In vivo fluorescence and luminescence imaging of mice administered different LNP formulations via tail-vein injection, illustrating organ-selective mRNA accumulation and translation. Representative lung-targeting and liver-targeting formulations achieved selective biodistribution by varying both lipid composition and structural topology. Reproduced with permission from ref.[81] Copyright 2024 Springer Nature.

hydrophobic amines (Cm) via Michael addition, yielding an nAcx–Cm platform with tunable biodegradability, phase behavior, and packing (Figure 2). In vivo screening in mice showed that selected nAcx–Cm combinations could redirect mRNA–LNP biodistribution from liver to lung, enabling organ-preferential expression. Fluorescence and bioluminescence imaging corroborated that lung-tropic formulations supported substantial mRNA translation in pulmonary tissue while minimizing off-target activity in hepatic regions. These findings highlight lipid-scaffold re-engineering as a practical lever to modulate LNP tropism and broaden the therapeutic scope of non-viral mRNA delivery.

High-throughput DNA barcoding now enables in vivo screening of hundreds of lipid variants within a single animal, revealing chemotypes that preferentially target lung, lymph node, or tumour tissue and compressing SAR discovery cycles from months to weeks.[82] For lymph-node–directed immunization, investigators have reported vitamin B5–derived ionizable lipids and sterol-rich helper lipids that bias particle trafficking toward antigen-presenting cells in draining nodes, thereby lowering effective doses and systemic reactogenicity.[79] At the cellular level, endosomal-escape enhancers-from photocleavable lipids to pH-activatable fusogenic peptides[83]-are being integrated into LNP shells; although most evidence remains preclinical, several candidates have increased cytosolic release by approximately one order of magnitude without compromising serum stability. In parallel, live-cell imaging and split-luciferase reporters are enabling quantitative visualization of intracellular trafficking, furnishing benchmarks that inform rational design and optimization.[84,85] While many of these strategies are still early in development, taken together they delineate a coherent path to surmount dominant delivery barriers and expand the therapeutic index of mRNA–LNP cancer vaccines.

The therapeutic efficacy of mRNA–lipid nanoparticle cancer vaccines is constrained by delivery bottlenecks spanning multiple physiological compartments (Table 1). After systemic administration, LNPs undergo rapid protein corona formation, opsonization, reticuloendothelial clearance, and hepatic sequestration, sharply limiting accumulation in target tissues such as tumours or lymph nodes.[86] Of the particles that are internalized, only a small fraction of the mRNA

Table 1 Key Delivery Challenges and Nanotechnological Strategies for mRNA-LNPs

Delivery Bottleneck	Key Observations	Representative Nanotechnological Strategies Under Investigation	References
Serum-phase interactions and rapid RES uptake	Protein-corona remodeling by apolipoproteins triggers opsonisation and Kupffer-cell clearance; corona formation can cut circulation $t_1/_2$ by >70% compared with freshly formulated particles.	(i) Zwitterionic and glyco-stealth lipids to replace or complement PEG (ii) Macrophage- or platelet-membrane cloaked LNPs that "pre-adsorb" an immunologically silent corona.	[50–52,89]
Liver-biased biodistribution limiting extra-hepatic exposure	Standard MC3/SM-102/ALC-0315 LNPs deliver ≈ 90% of the injected mRNA dose to hepatocytes after i.v. injection in rodents.	(i) **Selective-organ-targeting (SORT) LNPs**: addition of a fifth "SORT" lipid (eg, DOTAP or 18PA) shifts tropism to lung or spleen without reformulating the core four-component LNP. (ii) **High-throughput DNA bar-coding screens** that rank hundreds of chemotypes for innate organ tropism in a single mouse, accelerating SAR loops.	[71,90,91]
Inefficient lymph-node access for APC priming	Less than 1% of systemically dosed clinical LNPs reach draining lymph nodes in murine models.	(i) Vitamin-B5-derived ionizable lipids and sterol-rich helper lipids that bias trafficking to lymphoid tissues, increasing DC transfection >5-fold at the same dose.	[92]
Poor tumour accumulation and stromal penetration	Interstitial fluid pressure and dense extracellular matrix restrict LNP extravasation; head-to-head comparisons show liver: tumour ratios > 50:1 for conventional particles.	(ii) DNA-bar-coded screening identified LNP^HNSCC that preferentially deposits in head-and-neck tumours after i.v. dosing• PEG shells cleavable by tumour-up-regulated MMP-2/9 expose a cationic surface in situ, doubling intratumoral mRNA expression in orthotopic models.	[93–95]
Tumour-microenvironment barriers (hypoxia, dense ECM, immunosuppression)	Hypoxic tumour cores show 3- to 5-fold lower LNP uptake than peripheral regions; collagen-rich stroma correlates with diminished luciferase read-outs.	(i) ECM-degrading peptide amphiphiles that self-assemble with LNPs• Ultrasound-mediated cavitation or microbubble co-therapy to transiently lower interstitial pressure and enhance nanoparticle extravasation.	[96,97]
Cellular uptake and endosomal escape (< 2% cytosolic release)	Live-cell split-luciferase assays indicate that only a small fraction of internalised LNPs succeed in releasing mRNA into the cytosol.	(i) pH-activatable, photocleavable or cyclic-disulfide lipids that destabilise late endosomes, yielding up to 10-fold higher luciferase expression. (ii) Topology-optimised helper lipids that promote inverted-hexagonal phase formation during endosomal acidification.	[98–100]
Innate immune sensing and inflammasome activation	Certain ionizable lipids trigger NLRP3 activation; in vitro assays show >7-fold IL-1β release relative to vehicle at therapeutic doses.	(i) Rational substitution of tertiary amine head-groups with biodegradable esters to reduce lysosomal rupture• Co-encapsulation of MCC-950 or other NLRP3 inhibitors within the same LNP to dampen cytokine surge without impairing transfection.	[101,102]
mRNA stability and translational yield in the cytosol	Oxidative stress and residual RNases in tumours shorten functional mRNA half-life to <4 h.	Co-delivery of antioxidant lipids (eg, α-tocopherol analogues) that quench ROS• Self-amplifying RNA (saRNA) backbones that boost antigen expression 10- to 100-fold at the same nanogram dose.	[100]

typically reaches the cytosol owing to inefficient endosomal escape. Compounding these issues, immunostimulatory by-products- including ionizable-lipid degradation fragments and residual double-stranded RNA-can trigger innate sensors, especially at higher doses required for efficacy.[87,88] Collectively, these systemic and intracellular barriers depress on-target bioavailability and compress the therapeutic window, posing significant translational challenges.

To mitigate these limitations, recent work has focused on rational LNP design at the interface of materials science, chemical biology, and immunoengineering. As summarized in Table 1, strategies such as tumour-responsive PEG cleavage and high-throughput in vivo barcoding are being used to redirect biodistribution and enhance extrahepatic delivery. At the cellular level, novel lipid topologies and endosomal-disruptive chemistries are being optimized to raise cytosolic mRNA release without compromising tolerability.[95] In parallel, self-amplifying RNA templates and co-delivery of immunomodulatory payloads aim to prolong antigen expression and reduce dose burden.[103] Together, these convergent advances outline a coherent path to overcoming intrinsic delivery barriers and expanding the clinical utility of mRNA–LNP platforms in oncology.

A central determinant of the clinical efficacy of mRNA–LNP cancer vaccines is the biodistribution pattern of the nanocarrier. Conventional LNPs exhibit a strong hepatic tropism due to ApoE-mediated uptake by hepatocytes and Kupffer cells, which, while advantageous for liver-targeted protein replacement therapy, limits vaccine potency because only a small fraction of the mRNA reaches professional antigen-presenting cells. Organ-selective LNPs are engineered to redirect this biodistribution through rational modulation of ionizable-lipid structure–activity relationships (SARs), helper-lipid ratios, PEG-lipid content, and surface charge.

However, even optimally delivered mRNA vaccines rarely achieve durable tumor control alone due to immunosuppressive cues within the tumor microenvironment. Therefore, combination strategies are emerging as the most rational path forward. Checkpoint inhibitors (anti-PD-1/PD-L1, CTLA-4, LAG-3) relieve adaptive T-cell exhaustion and synergize with vaccine-induced priming, as demonstrated in the KEYNOTE-942 trial, where the mRNA-4157 vaccine plus pembrolizumab improved 2.5-year recurrence-free survival compared to pembrolizumab monotherapy. Chemotherapy or radiotherapy can induce immunogenic cell death, releasing damage-associated molecular patterns and tumor-associated antigens that broaden the antigenic repertoire recognized by vaccine-primed T cells. Moreover, pattern-recognition receptor agonists-such as TLR7/8, STING, and CD40 agonists-can be co-formulated or co-administered to enhance DC maturation, cytokine release (IL-12, type I IFNs), and cross-presentation efficiency. Recent studies also highlight the synergy between LNP-encoded immune modulators (such as mRNAs encoding CD40L, OX40L, IL-15 superagonists, or co-stimulatory ligands) and antigen mRNAs within the same formulation, termed "immune-programming cocktails". Such co-formulations leverage the modularity of the mRNA–LNP platform while preserving manufacturing uniformity. Future strategies may employ AI-guided LNP optimization to couple organ-targeting properties with payload design, ensuring that each antigen or adjuvant component reaches its optimal immunological niche.

Altogether, organ-selective LNP design and rational combination therapy represent synergistic axes of innovation: the former dictates *where* the vaccine signal originates, while the latter defines *how* it is integrated into systemic antitumor immunity. Their convergence promises to transform mRNA–LNP vaccines from experimental tools into clinically reliable, precision-engineered cancer therapeutics.

What Do Preclinical and Clinical Data Show?

A consistent observation across animal studies is that fine-tuning the lipid scaffold alters both magnitude and site of expression, yielding not only higher protein output but also a redistribution of where that protein is produced. In syngeneic mouse tumour models, substituting classical MC3-type lipids with degradable, vitamin B5–derived ionizable lipids redirected LNPs to draining lymph nodes and increased dendritic-cell transfection by >5-fold at an equivalent dose; the lead formulation (LNP-5097) elicited stronger neoantigen-specific CD8+ responses and delayed tumour growth without evidence of hepatic toxicity (Figure 3).[92] Complementary studies using cyclic disulfide–containing lipids demonstrated that reinforcing endosomal rupture raised cytosolic mRNA release by ~one order of magnitude in vivo, producing superior antigen expression and improved survival in PD-1–refractory murine melanoma.[99] In parallel, high-throughput DNA barcoding has accelerated discovery of organ-tropic chemotypes, identifying lipid families that favour lung, spleen, or tumour deposition after a single systemic injection and compressing traditional structure–activity

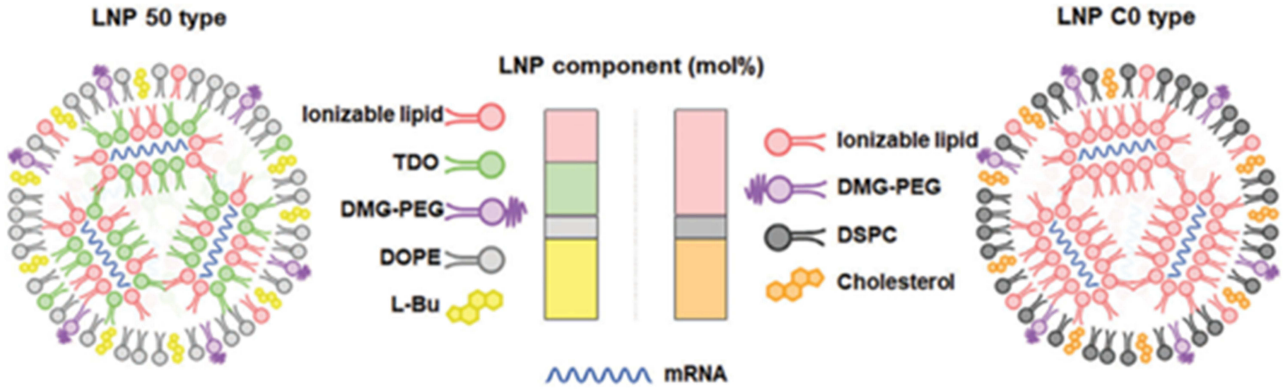


Figure 3 Comparative composition of two lipid nanoparticle (LNP) systems used for mRNA delivery in lymphoid-targeting studies. The LNP 50 type includes a vitamin B5–derived ionizable lipid, TDO, DOPE, DMG-PEG2000, and L-Bu in a 25:25:1.5:10:38.5 molar ratio, designed for lymphoid targeting. The LNP C0 type uses a conventional composition with ionizable lipid, cholesterol, DSPC, and DMG-PEG2000 at 50:1.5:10:38.5, serving as a liver-targeted control. Reproduced with permission from ref.[92] Copyright 2024 Wiley.

optimization from months to weeks.[104] Collectively, these findings provide proof of concept that rational lipid engineering, coupled with in vivo selection tools, can overcome entrenched delivery bottlenecks and lower the dose thresholds imposed by innate immune sensing.

A study[92] reports the development and evaluation of a novel class of lipid nanoparticles (LNPs) incorporating vitamin B5-derived ionizable lipids, designed to improve the safety and lymphoid tissue-targeting of mRNA vaccines (Figure 3). By synthesizing 17 structurally diverse ionizable lipids based on pantothenic acid (vitamin B5) backbones, the authors aimed to reduce systemic toxicity while maintaining high mRNA transfection efficiency and long-term stability. Among the candidates, the lead formulation-referred to as LNP 5097-demonstrated superior structural and physicochemical properties, with effective mRNA delivery to both spleen and lymph nodes in mouse models. The optimized LNP 50 formulation, which included TDO and n-butyl lithocholate (L-Bu), achieved enhanced lymphoid tissue accumulation compared to conventional liver-biased LNPs (LNP C0), and elicited a balanced Th1/Th2 immune response alongside potent neutralizing antibody production. Importantly, LNP 5097 was well tolerated in vivo, suggesting its promise for future applications in both infectious disease and cancer vaccine platforms requiring lymph node targeting.

This study is scientifically significant for mRNA vaccine delivery because it tackles a persistent limitation of standard LNPs-their strong hepatic bias that constrains efficient delivery to immune-relevant sites such as lymph nodes and spleen. By introducing vitamin B5–derived ionizable lipids, the authors present a rational, biocompatible scaffold that supports effective cytosolic release while improving lymphoid tropism. The central innovation is a combinatorial lipid-engineering strategy that couples structurally tunable, ester-containing backbones with immunologically active helper lipids (like L-Bu, TDO), yielding a class of LNPs optimized for immune activation rather than hepatic deposition. Advantages demonstrated include reduced systemic reactogenicity, favourable physicochemical stability, and enhanced targeting of antigen-presenting cells within secondary lymphoid organs-features well aligned with indications in which vaccine priming efficiency is critical. The identification of a lead formulation (LNP-5097) via structure–function screening adds translational weight, showing balanced Th1/Th2 responses and sustained expression with minimal off-target activity.

Several limitations temper these conclusions. Most targeting and immunogenicity data derive from murine models, leaving cross-species translation uncertain. Mechanistic underpinnings of organ tropism-such as protein-corona composition and receptor-mediated uptake-remain incompletely resolved. Moreover, while toxicity was reduced, comprehensive immunotoxicology and biodistribution at higher doses and in non-human primates will be essential to support clinical advancement. Notwithstanding these caveats, the work advances a credible path toward more precise and better-tolerated mRNA delivery systems for cancer and infectious-disease vaccination.

Translation to humans is progressing rapidly. The randomized Phase 2b KEYNOTE-942 trial demonstrated that adding the mRNA vaccine mRNA-4157 to pembrolizumab after resection of high-risk melanoma improved 2.5-year

Table 2 Clinical landscape - mRNA-LNP cancer Vaccines

Candidate/Study	Indication /Design	Efficacy/Safety	Reference
mRNA-4157 + Pembrolizumab KEYNOTE-942 P201	Adjuvant stage III/IV melanoma; randomized P2b	2.5-y RFS 74.8% vs 55.6%; HR 0.51; DMFS 62% risk-reduction; mostly G1-2 AEs	[21]
Autogene Cevumeran (BNT122) MSK P1	Resected PDAC; single-center; vaccine + atezolizumab + mFOLFIRINOX	Vaccinated responders (8/16) → CD8+ clones persisting ≥3 y; median RFS NR vs 13.4 mo; well-tolerated	[106,111]
RO7198457/BNT122-01	ctDNA+ resected stage II–III CRC; randomized P2	Early-stage; efficacy not yet reported; ctDNA-guided design	[26,112]
BNT111 + Cemiplimab Lipo-MERIT P2	Anti-PD-1-refractory unresectable stage III/IV melanoma	24-wk ORR 63.6%; CBR 78.8%; manageable safety	[112,113]
BNT113 + Pembrolizumab AHEAD-MERIT P2/3	First-line HPV16+ HNSCC; randomized 2-arm	Preliminary data show robust immunogenicity + antitumor activity; safety acceptable	[114,115]
GRANITE (GRT-C901) + ICIs	Metastatic MSS-CRC; adaptive P2	21% PFS risk-reduction overall; 38% in low-ctDNA subgroup; well-tolerated	[116,117]
CV8102 (intratumoral RNA) ± PD-1 NCT03291002	PD-1-refractory melanoma and other injectable tumors; dose-escalation /expansion P1	ORR 17% (5/30) in combo arm; 0% mono; good tolerability	[118,119]
mRNA-5671 (V941) (KRAS-mut solid tumors)	NSCLC/CRC/PDAC; open-label P1	Program officially discontinued; no further development plans	[120]

recurrence-free survival from 55.6% to 74.8% (hazard ratio ≈ 0.51);[105] three-year follow-up confirmed durable benefit with no new safety signals. In pancreatic ductal adenocarcinoma, autogene cevumeran elicited long-lived CD8+ T-cell clones that persisted for a median of 7.7 years in responders, correlating with prolonged disease-free survival in a Nature 2024 report.[106] A multi-centre phase 2 study (BNT122-01) is now enrolling 327 patients with ctDNA-positive stage II/III colorectal cancer to test the same lipid platform in a minimal-residual-disease setting, with primary completion expected. Beyond fully personalized products, semi-universal vaccines are also advancing: BNT111 combined with cemiplimab met its phase 2 primary endpoint in anti-PD-1-refractory melanoma,[107] showing clinically meaningful response rates, whereas GRANITE (GRT-C901) achieved a 21% reduction in progression risk as maintenance therapy for microsatellite-stable colorectal cancer,[108] with the greatest benefit seen in patients with low ctDNA burden.[109] Importantly, across these trials the safety profile has remained manageable, dominated by low-grade flu-like symptoms and injection-site reactions, suggesting that modern ionizable lipids can deliver high transcript loads without prohibitive reactogenicity.

The pre-clinical and clinical data converge on a central message: delivery science is now directly influencing clinical outcomes. Improvements in lipid chemistry that enhance lymph-node or tumour access are being mirrored by stronger T-cell immunity and early signs of disease control in patients, lending cautious optimism that the long-sought goal of effective, systemically administered mRNA cancer vaccines is within reach.

A growing number of clinical trials are evaluating mRNA–LNP cancer vaccines across tumour types and therapeutic settings, as summarized in Table 2. Candidate formulations span personalized and semi-universal strategies, tested as monotherapy or in combination with checkpoint blockade, with several programs advancing to randomized Phase 2 and Phase 3 studies-an indicator of rising regulatory and translational maturity. Indications include high-risk melanoma, resected pancreatic and colorectal cancers, and advanced microsatellite-stable tumours,[110] where conventional immunotherapy has limited activity. Milestones reported in 2024–2025 feature early efficacy signals in minimal-residual-disease contexts, objective responses in checkpoint-refractory disease, and organ-selective translation enabled by novel lipid chemistries. Safety profiles remain broadly favourable, with adverse events predominantly grade 1–2, though some programs (eg, V941) have been deprioritized due to strategic considerations or lack of signal. Collectively, these trends underscore how mRNA–LNP platforms are entering clinical spaces that require precise antigen delivery, durable T-cell engagement, and acceptable tolerability across diverse tumour indications.

Orchestrating Combination Regimens for Greater Efficacy

An expanding body of preclinical and clinical evidence supports combining mRNA–LNP cancer vaccines with complementary immunotherapies to address the multifactorial immune evasion typical of solid tumours. Among the most studied partners are immune checkpoint inhibitors (ICIs),[121] particularly antibodies against PD-1/PD-L1 and CTLA-4. Clinical data-exemplified by KEYNOTE-942, which paired a neoantigen mRNA vaccine with pembrolizumab-demonstrate meaningful gains in recurrence-free survival over ICI monotherapy. Mechanistically, vaccine-driven priming and expansion of antigen-specific T cells can overcome ICI resistance by increasing tumour-infiltrating lymphocytes and reprogramming the tumour microenvironment toward an inflamed, effector-permissive state.[122]

Subtherapeutic chemotherapy or radiotherapy can induce immunogenic cell death, releasing tumour-associated antigens and DAMPs that potentiate vaccine responses. For example, combining low-dose radiotherapy with neoantigen-based LNP vaccines increased T-cell infiltration and depleted immunosuppressive cell populations in murine melanoma models.[27] The synergy likely arises from improved antigen availability and enhanced cross-priming by dendritic cells.

Co-delivery of molecular adjuvants-notably small-molecule agonists of pattern-recognition receptors such as TLRs or the STING pathway[123]-has also emerged as a promising tactic. Preclinical studies show that encapsulating STING agonists or TLR7/8 ligands alongside tumour-specific mRNAs within LNPs promotes dendritic-cell maturation,[124] increases antigen-presentation efficiency, and strengthens T-cell priming, potentially lowering the required antigen dose and widening the therapeutic window.

Regulatory and CMC Considerations

As clinical development of mRNA–LNP cancer vaccines accelerates, rigorous attention to regulatory frameworks and chemistry, manufacturing, and controls is paramount. Critical quality attributes-including lipid identity and purity, residual solvents, encapsulation efficiency, particle-size distribution, surface charge, and RNA integrity-must be prospectively defined, phase-appropriate, and consistently met across lots.[125] Ensuring batch-to-batch consistency is particularly challenging for personalized products with compressed turnaround times. Stability management further complicates operations: stringent cold-chain logistics safeguard integrity but impose cost and access constraints, whereas lyophilization can relax storage requirements at the expense of added process complexity and potential reconstitution variability, with trade-offs that are magnified in resource-limited settings.[126,127]

Industrial manufacture of mRNA–LNP vaccines couples a well-controlled IVT/purification workflow for capped, sequence-validated mRNA with high-shear ethanol/aqueous mixing to drive rapid self-assembly of ionizable-lipid particles, followed by TFF-based concentration/buffer exchange and sterile filtration under cGMP. Recent engineering advances are pushing this train toward continuous unit operations: numbering-up microfluidic or turbulent mixers for encapsulation integrated with on-line purification and in-line process analytical technologies for particle size/encapsulation control, in line with ICH Q13 expectations for continuous manufacturing and lifecycle control of critical process parameters and critical quality attributes. In parallel, process optimization at the back end is addressing high-concentration TFF and 0.2-μm sterilizing filtration (a known bottleneck for ~80–100-nm LNPs), enabling clinically relevant doses and faster turnaround for oncology applications, including personalized batches. To expand cold-chain latitude, several groups report lyophilization or otherwise thermostable formulations (and lipid designs) that retain potency after weeks to months above 2–8 °C, with growing interest in continuous freeze-drying trains compatible with PAT. Finally, formulation levers with direct manufacturing implications-especially PEG-lipid identity/content and desorption kinetics that influence particle size, filterability, and release testing-are being quantified to guide QbD/DoE control strategies at scale.

Regulatory alignment under frameworks such as ICH Q6A and ICH Q12 demands robust, orthogonal analytics to characterize both the lipid shell and the RNA payload throughout the product lifecycle.[128,129] Advanced methods-including analytical ultracentrifugation, differential scanning calorimetry, and orthogonal chromatographic separations coupled to mass spectrometry-provide structural and compositional insight, support comparability during scale-up and site transfers, and enable data-driven control strategies. Nevertheless, achieving enduring regulatory clarity for batch-

specific, patient-tailored formulations remains an active dialogue with health authorities, necessitating clear potency paradigms, well-justified specification limits, and risk-based approaches to real-time release.

To fully unlock the translational potential of mRNA–LNP cancer vaccines, scientific innovation must be complemented by deliberate policy action. Establishing adaptive regulatory frameworks that accommodate individualized vaccine design, incentivizing public–private partnerships to expand flexible cGMP manufacturing capacity, and promoting equitable access through global technology-transfer hubs are essential steps. Such policy-driven initiatives can shorten development timelines, reduce cost barriers, and ensure that emerging mRNA–LNP platforms benefit patients across diverse healthcare systems, bridging the gap between laboratory success and real-world clinical impact.

The Future Prospective

Recent advances place lipid nanoparticle–mediated mRNA delivery at a transformative inflection, linking innovative lipid chemistry, sophisticated nano-engineering, and clinical translation. Although conventional LNP platforms have proven highly effective for prophylactic vaccination, their extension into therapeutic oncology demands unprecedented control over biodistribution, organ selectivity, and immune modulation. As reviewed, state-of-the-art lipid engineering-including vitamin B5–derived degradable lipids, SORT components, and endosome-disruptive chemistries-has begun to systematically overcome entrenched barriers, yielding enhanced lymphoid targeting, wider therapeutic windows, and encouraging early clinical signals. Nonetheless, substantial gaps persist, notably a mechanistic understanding of organ tropism, scalable workflows for personalized products, and assurance of long-term tolerability at therapeutic dose levels. Addressing these gaps will require sustained, multidisciplinary collaboration across nanomedicine, bioinformatics, immunology, and regulatory science. Even so, the rapid, iterative discovery cycle and early translational readouts underscore a favourable trajectory toward robust, mRNA therapeutics in oncology and beyond.

Looking forward, a central technological frontier is the development of thermostable LNP formulations amenable to ambient storage, which could markedly reduce the logistical burden of ultra-low-temperature cold chains. Approaches under evaluation include lyophilized “dry-cake” presentations with optimized reconstitution profiles and pro-lipid precursors activated on hydration-strategies with the potential to expand access in resource-constrained settings by simplifying distribution and lowering total cost of care. In parallel, next-generation ionizable lipids tailored for extra-hepatic delivery-particularly to lymph nodes-continue to gain momentum. Emerging ester-based, vitamin-derived, and peptide-modified scaffolds exhibit organ-selective biodistribution and improve vaccine performance by directly engaging antigen-presenting cells. Concurrently, self-amplifying RNA platforms that harness alphaviral replicase to boost intracellular transcript copy number may enhance potency at substantially lower input doses, thereby diminishing systemic reactogenicity while sustaining antigen expression.

Artificial-intelligence–driven design is poised to accelerate LNP discovery by enabling virtual screening and predictive modelling of structure–activity landscapes, compressing timelines and cost to identify lead chemotypes. Combined with multiplexed antigen architectures-poly-epitope cassettes and tandem antigens-these computational pipelines could yield formulations with improved breadth, durability, and manufacturability.

Finally, ethical and implementation considerations remain paramount. Fully individualized vaccines raise pressing questions of equitable access and affordability, particularly in low- and middle-income regions. Progress will depend on coordinated policy and infrastructure solutions, including regional manufacturing hubs, pooled procurement mechanisms, and the deployment of thermostable presentations that simplify transport and storage. Taken together, the evolving combination regimens, regulatory paradigms, and next-generation technologies outlined here provide a clear roadmap for continued progress, positioning mRNA–LNP immunotherapies as potentially transformative interventions for patients with cancer worldwide.

Data Sharing Statement

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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