

Lipid Nanoparticles as versatile tool for (intradermal) vaccine delivery

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Introduction

Lipid nanoparticles (LNPs) have quickly evolved from a niche formulation tool to a central technology for delivering genetic medicines. Their rise is closely linked to the success of messenger RNA (mRNA) vaccines, particularly during the COVID-19 pandemic. LNPs act as nanoscale delivery vehicles for transporting therapeutic molecules into target cells. They protect fragile molecules like mRNA or silencing RNA (siRNA) from degradation in the body. In addition, they guide the entry of these molecules into cells, where they can help the body fight diseases or correct genetic defects, regulate abnormal protein production, or stimulate tissue repair. This protective and targeted delivery makes LNPs a flexible, scalable, and safe platform for prophylactic vaccines and treatments [1].

Structural and Functional Flexibility of LNPs

Structurally, LNPs are small, round particles made up of four main lipid components: ionizable lipids, phospholipids, cholesterol, and polyethylene glycol-lipids (PEG-lipids). Each component plays a distinct but important role [Fig. 1] [1].

Ionizable lipids are the main functional components of LNPs. They stay neutral in the bloodstream, which helps reduce side effects, but become positively charged in the acidic environment of the endosome, allowing them to interact with RNA and support its release into the cell [2].

Phospholipids such as DSPC help stabilize the structure and support interaction with cell membranes. Cholesterol improves the flexibility and stability of the particle. PEG-lipids form a protective layer around the LNP to keep it from clumping and help it stay longer in the bloodstream [1]. What makes LNPs so adaptable is that these lipid components can be mixed in different ratios or chemically tweaked to fine-tune things like size, surface charge, and which organs they target. For example, small changes in lipid structure or coating can shift delivery from the liver to the lungs or spleen. Recent findings also highlight how modulating ionizable and helper lipid composition can enhance delivery efficiency and tissue specificity [3].

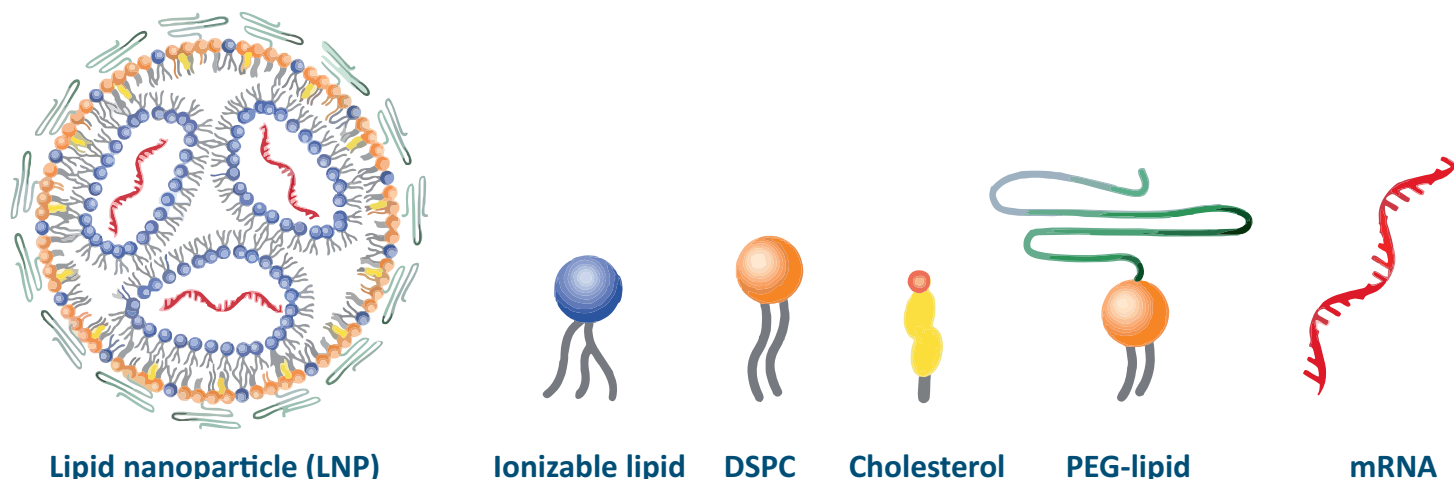
The Evolution of LNP Applications

The development of LNPs as delivery vehicles has been shaped by scientific discovery, regulatory opportunity, and global urgency. The first major milestone came with the FDA approval of Patisiran (Onpattro®) in 2018, an siRNA therapy for hereditary transthyretin-mediated amyloidosis. Patisiran marked the first time a nucleic acid therapeutic delivered via LNPs, was brought to market. This approval signaled the maturation of LNPs as a clinically viable technology and sparked growing interest in its applications for gene silencing and correction [4].

Soon after, researchers began exploring LNPs for the delivery of mRNA, a more complex but also more promising cargo. Unlike siRNA, which silences genes, mRNA acts as a temporary blueprint for protein production. This allows mRNA vaccines to instruct the body's own cells to produce a specific antigen, triggering a natural immune response without introducing the pathogen itself. It also opened the door for therapeutic cancer vaccines, where mRNA encoding tumor-specific neoantigens can be used to educate the immune system to recognize and attack malignant cells [5].

Before the COVID-19 pandemic, mRNA-LNP research was largely centered on therapeutic use cases. Academic institutions, biotechnology startups, and large pharmaceutical companies were investing in mRNA-based treatments for melanoma, non-small-cell lung cancer, and rare genetic disorders. Notable early studies by BioNTech, Moderna, and CureVac showed that these approaches in melanoma patients could generate robust immune responses and be manufactured rapidly and at scale [6].

However, when the SARS-CoV-2 virus began spreading globally in early 2020, the full potential of LNPs was thrust into the spotlight. Both Moderna and BioNTech pivoted rapidly, applying their LNP-mRNA platforms to develop COVID-19 vaccines. These vaccines, among the first to enter Phase I trials and the first to be authorized for emergency use, demonstrated not only high efficacy but also record-breaking speed of development. Within months, millions of doses were being administered worldwide, validating the LNP platform on an unprecedented scale [7,8].



LNP Development

2005 – 2015

Early LNP formulations for nucleic acid delivery

2018

First FDA-Approved LNP therapy (PMID: 29972753)

2021

LNP platform validated for mRNA delivery (PMID: 34841223)

2021 – 2023

Lipid composition tuning enables tissue targeting (PMID: 40927763)

2023 – 2025

Expansion of LNP use in oncology and inf dis trials (PMID: 40927763)

mRNA + LNP Overlap

2018 LNP + mRNA

Proof of nucleic delivery using LNP

2020 – 2021

mRNA + LNP applications: COVID-19 vaccines (PMID: 33378609)

2023

Intradermal mRNA-LNP (PMID: 36992242)

2023-2024

mRNA-LNP in therapeutic (PMID: 38246194)

2025

Personalized mRNA-LNP vaccines (PMID: 40700574)

mRNA Development

2014

Early mRNA cancer vaccine successes (PMID: 2523393)

2018

mRNA-vaccine platform technology (PMID: 29326426)

2020

First successful mRNA vaccine (PMID: 33301246)

2021

Global validation with moderna (PMID: 33378609)

2022

Intradermal mRNA potential (PMID: 34469811)

This global focus on COVID-19 had a significant side effect: many of the ongoing therapeutic applications of LNPs were temporarily put on hold as resources, manufacturing lines, and research teams were redirected toward pandemic response. Now, as the acute phase of the pandemic subsides, we are witnessing a renewed interest in the broader capabilities of LNPs, especially for therapeutic applications [2].

Clinical Development of LNP applications

The renewed interest in LNP technology has been accompanied by a surge in clinical trials targeting a wide range of diseases, including oncology, infectious diseases, and rare and autoimmune disorders. Some of the most advanced therapeutic trials focus on cancer immunotherapy, where LNPs are used to deliver mRNA encoding personalized neoantigens. These are tumor-specific mutations that, when translated into proteins by the host, elicit a targeted immune response against malignant cells [9].

At the forefront of this research are institutions like the Dana-Farber Cancer Institute, which developed a preclinical mRNA vaccine encapsulated in LNPs targeting BCMA (B-cell maturation antigen) for multiple myeloma. The formulation, particularly when combined with a TLR3 agonist (Poly(I:C)), elicited robust cytolytic CD8⁺ T cell responses and showed antitumor efficacy in mouse models [10].

Meanwhile, Memorial Sloan Kettering Cancer Center has been a key clinical site for autogene cevumeran (BNT122/RO7198457), a personalized mRNA-LNP vaccine developed by BioNTech and Genentech. In a Phase I trial in pancreatic cancer patients, the vaccine showed promising results, inducing strong neoantigen-specific immune responses. These findings have justified progression into Phase II studies, combining the vaccine with checkpoint inhibitors and chemotherapy to prevent recurrence after surgery [11].

Beyond these institutions, companies like Moderna are pursuing broader indications with mRNA-4157/V940, a personalized cancer

vaccine delivered via solid LNPs. In partnership with Merck, this formulation is being tested in Phase IIb trials as an adjuvant therapy in combination with pembrolizumab for melanoma and other solid tumors [12].

Ongoing monitoring of registries such as EUDRA CT and ClinicalTrials.gov shows a steady rise in LNP-enabled studies. These span multiple stages, from early safety evaluation to large-scale efficacy trials, and a diverse array of targets, including mpox (BioNTech's BNT166 candidate), RSV, influenza, and rare genetic conditions. As of 2024, over 50 active clinical trials worldwide are evaluating LNP-based delivery of nucleic acids, underlining widespread confidence in this platform.

Inflammation and Adjuvanticity

LNPs have shown great promise as delivery vehicles for nucleic acid-based vaccines, but their interaction with the immune system remains a key focus in ongoing research. Some components, particularly ionizable and PEG-lipids, are known to activate parts of the innate immune system. In some cases, this helps boost immune responses, acting as an adjuvant. For example, ionizable lipids can trigger endosomal escape, but may also activate inflammasome pathways like NLRP3, leading to inflammatory responses. Once protonated in acidic endosomal environments, they may disrupt membranes not only to release their cargo but also to activate inflammasomes. Similarly, PEG-lipids, designed to reduce aggregation and extend circulation time, may provoke anti-PEG antibody formation, especially upon repeated dosing. This immunogenicity could reduce efficacy over time or contribute to hypersensitivity reactions [13].

Consistent with this, Ndeupen et al. (2021) demonstrated that the lipid nanoparticle component used in preclinical mRNA-LNP vaccine studies is highly inflammatory, inducing neutrophil infiltration and inflammasome-associated innate immune activation. Nevertheless, the overall safety profile of mRNA-LNP formulations depend on both the lipid composition and the mRNA cargo used [14].

Inflammation and Adjuvanticity

One possible strategy to minimize unwanted inflammation could be to reduce the total LNP dose while maintaining vaccine efficacy. Intradermal (ID) delivery could support this approach, thanks to the skin's rich network of antigen-presenting cells. This suggests that ID administration of SARS-CoV-2 mRNA-LNP vaccines may enable dose-sparing strategies, an approach that has already been explored to enhance immune responses while reducing reactogenicity. Recent studies have shown that lower ID doses of these vaccines can achieve comparable immunogenicity to higher intramuscular doses [15,16].

While further clinical validation is needed, this line of research offers a promising direction for the next generation of mRNA-based vaccines, focusing not only on strong immune responses but also on optimizing patient tolerability [17].

Vaccination and Administration Routes

Most LNP-based vaccines to date have relied on mRNA as the active pharmaceutical ingredient. Unlike traditional vaccines that use inactivated pathogens or protein subunits, mRNA vaccines encode the antigen of interest, prompting cells to produce the target protein and initiate an immune response. This method avoids the need for live virus handling, allows for rapid development, and enables quick adaptation to emerging threats [18].

mRNA vaccines do not integrate into the genome and are rapidly degraded after protein translation, making them both safe and transient. They can be adapted across different disease areas simply by altering the mRNA template, while maintaining a consistent LNP delivery system [18].

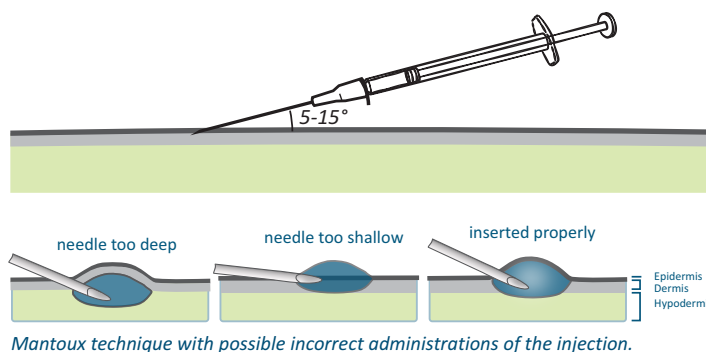
The route of administration critically affects vaccine performance. Most current mRNA vaccines, including COVID-19 vaccines, are administered intramuscularly due to established regulatory protocols and ease of use. However, muscle tissue has relatively few immune sentinel cells like dendritic cells, meaning higher doses of mRNA and LNPs may be required to achieve a sufficient immune response [19].

In contrast, the skin, specifically the dermis, is densely populated with antigen-presenting cells, including dendritic cells and Langerhans cells. This immune-rich environment enables effective antigen presentation at lower doses of both antigen and adjuvant. Several studies investigating SARS-CoV-2 mRNA-LNP vaccines have shown that intradermal administration can induce immune responses comparable to intramuscular injection while using substantially lower doses.

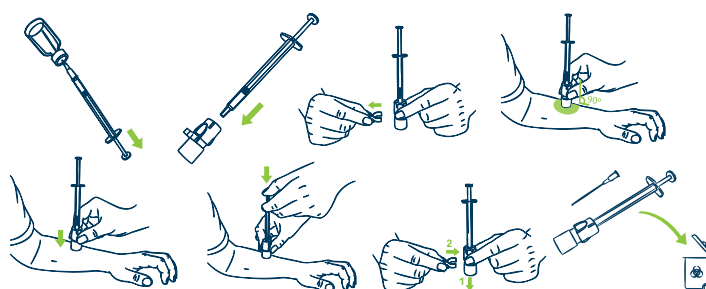
This dose-sparing effect is likely linked to the high density of antigen-presenting cells within the dermis, enabling efficient immune activation with reduced amounts of antigen and LNPs. Consequently, intradermal delivery may not only improve vaccine efficiency but also help reduce LNP-associated inflammation and reactogenicity [15-17,20].

VAX-ID®: A Tool for Precision Intradermal Delivery

One of the key challenges with ID administration has been ensuring consistent and reproducible delivery into the correct layer of the skin. Traditional intradermal injection with a syringe, using the Mantoux technique, requires advanced training, and even among skilled practitioners, variability in angle and depth can impact the immune response or cause patient discomfort. Micheels and Goodman [21] reported that up to 70% of intradermal administrations using the Mantoux technique may be performed incorrectly, underscoring the technical complexity and poor reproducibility of conventional ID injection methods.



VAX-ID® addresses these challenges by providing a standardized, easy-to-use, and minimally invasive intradermal injection device. The device is CE-marked and developed specifically to overcome variability in manual techniques. The device uses a fixed geometry and microneedle-based system to consistently place a vaccine formulation in the dermal layer, ensuring optimal contact with immune-responsive cells like Langerhans and dermal dendritic cells.





Because VAX-ID® delivers a consistent volume into the skin's immune-rich environment, it may support dose-sparing strategies that reduce the total amount of LNPs and antigen needed, aligning with the hypothesis that ID administration may lower inflammation and improve safety profiles. In addition, the device minimizes the need for extensive training, making it highly suitable for mass vaccination programs, clinical trials, and innovative delivery of nucleic acid-based therapies.

Its compatibility with acid-based therapies, including mRNA-LNP formulations, positions VAX-ID® as a promising bridge between formulation innovation and practical implementation in both high-resource and global health settings [22].

Conclusion

LNPs have reshaped the landscape of vaccine and therapeutic development. Initially developed as a solution to the delivery challenges of nucleic acids, LNPs have proven to be far more than just delivery vehicles. Their modular architecture, capacity for tissue targeting, and compatibility with multiple administration routes have enabled both rapid pandemic responses and exciting new therapeutic innovations.

From siRNA treatments and COVID-19 vaccines to cancer immunotherapies and personalized neoantigen vaccines, LNPs are at the center of a growing ecosystem of next-generation medicine. Yet challenges remain, particularly around inflammation, dose requirements, and the need for optimized administration routes. This is where new tools like VAX-ID® come into play, enabling precise, skin-targeted delivery that may not only improve tolerability and immunogenicity but also broaden access through simplified applications.

As LNP technology continues to evolve, so will its applications, redefining what is possible in preventive and therapeutic medicine. With continued collaboration between scientists, clinicians, engineers, and device innovators, the next chapter of LNP-based therapies promises to have an even greater impact.

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